

NEW HORIZONS IN HEALTH- PROMOTING: FROM METHODS TO IMPLEMENTATION SCIENCE

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NEW HORIZONS IN HEALTH-PROMOTING: FROM METHODS TO IMPLEMENTATION SCIENCE

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Editorial: New Horizons in Health-Promoting: From Methods to Implementation Science

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Editorial on the Research Topic

New Horizons in Health-Promoting: From Methods to Implementation Science

New technologies with the potential to improve population health are being continually introduced through research and innovation. To improve care with available resources, it is necessary to promote the most cost-effective technologies, respecting organizational, social and ethical issues. This can be a concern in recent years with the growth in pharmaceutical expenditure being driven by new medicines for complex diseases, including cancer and orphan diseases, often though with limited health gain (Cohen, 2017; Luzzatto et al., 2018; Godman et al., 2021c; Moreira et al., 2021). This calls for greater evidence-based approaches to healthcare especially in countries with universal healthcare systems faced with rising costs and continued unmet need (Camargo et al., 2016; Fulone et al., 2016; Godman et al., 2021b).

Health Technology Assessment (HTA) has become an indispensable tool to inform health decisions and contribute to best practices, whether in the clinical or management scope. Furthermore, it has been widely used to improve health policies. This Research Topic seeks to debate in way the current challenges for the application of health technology innovation - specifically the use of rational and evidence-based approaches.

Publications contained in this Research Topic (n = 23 studies) summarized information regarding to health technologies (medicines, pharmaceutical services, health litigation, medical devices, diagnostics test, and other health interventions) focusing on reporting of therapeutic risk management (adverse drug reactions - ADRs, drug-drug interactions - DDIs, non-responding to treatment and other adverse outcomes (n = 4); available evidence of effectiveness and/or safety of medicines (n = 5); drug utilization research (n = 1); effectiveness of other interventions (services pharmaceutical and community-based interventions) (n = 2); methodological studies (n = 2); health litigation (n = 3); implementation science (n = 4); cost-effectiveness analysis (n = 1); and digital technologies (n = 1).

ADRs are a predominant public health problem especially among the elderly, hospitalized and those patients on multiple medicines. Aspects related to safety regarding the use of medications among children were also studied (Calderon-Ospina et al.; Lima et al.) alongside the adults/elderly (Ferreira et al.). Another study analyzed adverse neonatal outcomes in adolescent pregnancy (Honorato et al.).

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One study collected information from the database of the Brazilian Surveillance Agency, known as Notivisa, where reports of suspected serious adverse drug reactions (SADR) mainly with IV dosage forms and off label drugs, were observed demonstrating the need for further drug research in this area including the use of better dosage forms among children (Calderon-Ospina et al.). Another study collected data from pediatric intensive care units (PICU) in a teaching hospital. The authors observed that most of children were exposed to at least one potential DDI during PICU stay and there was increased of length of stay in children with major or contraindicated DDIs (Lima et al.).

Another study analyzed the prevalence of ADRs in a population with Alzheimer's disease. Data were collected through interviews with patients and caregivers who obtained their medication for Alzheimer's at a public pharmacy in Brazil, complemented by the prescribing data system. Most patients had at least one ADR, mainly due to psychiatric disorders (Ferreira et al.).

The risks of adverse neonatal outcomes in younger pregnant adolescents properly followed through group prenatal care, delivered by specialized public services, were also analyzed. Data were obtained from medical records and interviews with a multidisciplinary team that treated these patients. The lower incidence of adverse outcomes was observed in younger pregnancy adolescents that followed the prenatal care model (Honorato et al.). We believe this provides guidance to others experiencing such concerns.

The effectiveness in the use of medicines was also addressed in studies of Vieira et al., Fulone et al., Pedrosa et al., Zhang et al., and Nascimento et al.

A systematic review compared the efficacy of five antiangiogenic drugs for the treatment of diabetic macular edema. The findings demonstrated the effectiveness of these medicines but there were differences between them for the outcomes evaluated. This study concludes that more randomized controlled trials are needed to confirm these findings Zhang et al.

Switching between second-generation antipsychotics (SGA) is a common clinical practice in the treatment of schizophrenia and schizoaffective disorders due to differences in the tolerability and safety profiles of the different anti-psychotics (Leucht et al., 2013; Huhn et al., 2019; Fulone et al., 2021b), as well as the challenge of obtaining an ideal response (Fulone et al., 2016; Mayer et al., 2021). Data were obtained from a pharmaceutical assistance program, by using an administrative database. The groups most susceptible to SGA switching were older individuals, women, and those living in the northeast region of Brazil (Fulone et al.). Risperidone was the antipsychotic associated with the highest risk of switching. Previous research conducted in Brazil has also shown greater effectiveness of olanzapine versus risperidone in routine clinical care (Barbosa et al., 2021).

De-escalation guided by blood cultures for patients with a diagnosis of sepsis, severe sepsis or septic shock were also analyzed to verify if blood cultures will reduce mortality and antimicrobial drug resistance in adults admitted to intensive care

units (ICU). Overall, the hospital mortality was lower in the group who received empirical broad-spectrum antibiotic therapy (EAT), although the antibiotic therapy guided by blood cultures (ATGBC) also reduced the mortality in these patients (Pedrosa et al.). Appropriate empiric use of antibiotics is important to reduce morbidity, mortality and costs associated with antimicrobial resistance (Godman et al., 2021).

Almost 30% of new antiepileptic drugs have drug-resistant forms of the disease. A cohort study assessed the impact of a number of genetic factors and their possible association with treatment response to phenytoin. Little more than half of the evaluated subjects were non-responding to phenytoin and the decreased function alleles of CYP2C9 were predictive of vestibular-cerebellar ADR to phenytoin (Vieira et al.). This is important to help guide future treatment approaches.

A 16-years cohort constructed by deterministic and probabilistic matching, through three databases of the Brazilian public health system, assessed the impact on liver graft survival with two different calcineurin inhibitors (tacrolimus or cyclosporine). Younger patients had a longer graft survival time than older ones. The use of tacrolimus was also more prevalent and had a better survival rate. Older age and the greater time ratio without using an immunosuppressant were identified risk factors for liver graft loss. White-skinned patients and tacrolimus-based regimens are factors for improved graft survival (Nascimento et al.).

The use of proton pump inhibitors (PPI) in ambulatory care was analyzed based on aggregated utilization data from the National Health Insurance database. Despite the tolerability and clinical benefits, potential long-term side effects have been observed with PPIs. There is a concern that patients receive PPIs in high doses and for a long period of time resulting in health authorities seeking to encourage rapid transfer from a healing to a maintenance dose. Overall, pantoprazole was the PPI most frequently used by hospitalized patients (Matuz et al.).

The DIATHEM observational study (type 2 DIAbetes: optimizing THERapy by Medication review in community pharmacies) evaluated the impact of medication reviews from community pharmacies in elderly patients with type 2 diabetes under real-life conditions. The study shows that medication reviews performed by community pharmacists reduced the frequency and number of drug-related problems even though the pharmacies had to face obstacles such as lack of cooperation by the prescriber or lack of reimbursement (Schindler et al.). This is important with the envisaged greater role of pharmacists to help with healthcare (Lima et al., 2008; Vieira et al., 2010; Yamauti et al., 2017).

Sustainable long-term interventions, such as health worker training and provision of health education to the patients, contribute to health improvements in patients with hypertension and diabetes from rural communities (Lemos Macedo et al.). This is important for the future especially if community pharmacists are the principal healthcare provider, and often the first point of contact for patients across countries (Marković-Peković et al., 2017).

Rosa et al. showed that using POC-A1c devices in primary care settings is a cost-effective alternative for monitoring glycated

hemoglobin A1c as a marker of blood glucose control in people living with type 2 diabetes (Rosa et al.). This is important given rising prevalence rates for diabetes across countries with an appreciable impact on morbidity, mortality and costs if not properly managed (Araujo et al., 2016; Barros et al., 2020; Lam et al., 2020; Chan et al., 2021; Chan et al., 2021).

Two methodological studies addressed a newly developed instrument (HM-PRO) to evaluate patients' health-related quality of life (HRQoL) with hematological malignancies and their symptom experience in daily clinical practice as well as in research (Goswami et al.; Goswami et al.). The findings can be used to improve the care of these patients in the future. Others initiatives can be used to increase knowledge translation and strengthening capacity core teams of health professionals (Tavares et al., 2019; Fulone et al., 2021a; Motter et al., 2021).

In Brazil, the Federal Constitution states that the right to health is a social right to be guaranteed by policies that promote and ensure universal and equal access to programs and services for the promotion, protection, and restoration of the health of citizens Yamauti et al. When policies do not guarantee these rights, the patients seek to the courts, characterizing the phenomenon known as the judicialization of health which can appreciable increase the cost of care. Three articles published in this research topic addressed this key issue. Silva et al. investigated the occurrence of serious adverse events related to medicines obtained by patients through health litigation and found that many of these medicines resulted in deaths and serious adverse events in expanded access and compassionate use programs in Brazil. Yamauti et al. summarized 78 strategies implemented by public institutions in Brazil to approach the judicialization of health care. Machado; Santos; Lopes et al. (2010) described the planning and implementation of strategies to approach medicines litigation at municipality level (Silva et al.; Yamauti et al.; Machado et al.). These papers are important to give guidance to the authorities in Brazil as they seek to tackle the increasing costs of litigation (Lopes et al., 2010).

Three qualitative studies emphasized the importance of considering patient preference for the development of guidelines and to develop strategies for behavioral change communication. Petrocchi et al. conducted a study with patients from Belgium and Italy undergoing treatment for lung cancer and found that aspects related to efficacy and safety, as well as psychological impact, are common areas of concern for patients regardless of origin cultural or country. Weller et al. contributed to understanding which factors

influence patients' adherence to venous leg ulcer treatment recommendations in primary care. Doke et al. studied the basic perceptions, knowledge, and behavior of women before the implementation of preconception care to reduce maternal and child mortality in India (Doke et al.; Petrocchi et al.; Weller et al.). Such approaches are essential to improve the health of patients.

The implementation of Clinical Practice Guidelines (CPGs) was also studied by Vasconcelos et al.. The authors concluded that even among high-quality CPGs, the implementation strategies report can be improved, especially concerning monitoring of implementation outcomes and selection of strategies based on relevant implementation barriers (Vasconcelos et al.). Studies have shown that multiple activities involved in the implementation and monitoring of adherence to guidelines helps enhance their use and impact (Godman et al., 2021b). In addition, the CPGs must be easy to use and regularly updated (Lopes et al., 2014; Silveira et al., 2014; Camargo et al., 2016; Niaz et al., 2020).

Digital health encompasses several technologies, which have the ability to monitor the human body continuously and uninterruptedly, collecting physiological data, and enabling the improvement of clinical practices. These technologies enable the integration of pharmacotherapies with self-care, lifestyle interventions and patient empowerment, while concurrently advancing patient-centered care, integrative medicine and digital health ecosystems (Bulaj et al.). This will be an increasing area of research as the use of technologies grows to monitor medicine use and outcomes across sectors.

In this Research Topic, a particular emphasis, was given to the technological development of new health care/services approaches describing processes regarding the introduction and implementation of technologies into health systems; the knowledge translation; evidence-based policy and its utility as a guide for implementation of health-promoting technologies; big data analytics for health policy in decisions making; and real-world cases. We will continue to monitor the situation to provide future guidance.

AUTHOR CONTRIBUTIONS

SB-F and CB contributed to the design and to the analysis of results. LL and BG made additional analysis. All authors contributed to the manuscript and approved the submitted version.

REFERENCES

- Araujo, J. L., Pereira, M. D., de Cássia Bergamaschi, C., de Sá Del Fiol, F., Lopes, L. C., De Toledo, M. I., et al. (2016). Access to Medicines for Diabetes Treatment in Brazil: Evaluation of "health Has No price" Program. *Diabetol. Metab. Syndr.* 8, 35. doi:10.1186/s13098-016-0150-8
- Barbosa, W. B., Gomes, R. M., Godman, B., Acúrcio, F. A., and Guerra Júnior, A. A. (2021). Real-world Effectiveness of Olanzapine and Risperidone in the Treatment of Schizophrenia in Brazil over a 16-year Follow-Up Period: Findings and Implications. *Expert Rev. Clin. Pharmacol.* 14, 269–279. doi:10.1080/17512433.2021.1865799
- Barros, C., Miranda, V., Cortellazzi, K., Lopes, L., Barberato-Filho, S., Ferreira, T., et al. (2020). *Efficacy of Pharmacotherapy Follow-Up Care in Brazilian Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Trial* (Sao Paulo: Rev Bras Farm Hosp Serv Saude). [Internet] 11.
- Chan, J. C. N., Lim, L. L., Wareham, N. J., Shaw, J. E., Orchard, T. J., Zhang, P., et al. (2021). The Lancet Commission on Diabetes: Using Data to Transform Diabetes Care and Patient Lives. *Lancet* 396, 2019–2082. doi:10.1016/S0140-6736(20)32374-6
- Cohen, D. (2017). Cancer Drugs: High price, Uncertain Value. *BMJ* 359, j4543. doi:10.1136/bmj.j4543
- de Camargo, I. A., Almeida Barros, B. C., do Nascimento Silveira, M. S., Osorio-De-Castro, C. G., Guyatt, G., and Lopes, L. C. (2016). Gap between Official

- Guidelines and Clinical Practice for the Treatment of Rheumatoid Arthritis in São Paulo, Brazil. *Clin. Ther.* 38, 1122–1133. doi:10.1016/j.clinthera.2016.02.020
- Fulone, I., Barberato-Filho, S., Dos Santos, M. F., Rossi, Cde. L., Guyatt, G., and Lopes, L. C. (2016). Essential Psychiatric Medicines: Wrong Selection, High Consumption and Social Problems. *BMC Public Health* 16, 52. doi:10.1186/s12889-015-2589-1
- Fulone, I., Silva, M. T., and Lopes, L. C. (2021b). Gender Differences in the Use of Atypical Antipsychotics in Early-Onset Schizophrenia: a Nationwide Population-Based Study in Brazil. *BMC Psychiatry* 21, 320. doi:10.1186/s12888-021-03327-7
- Fulone, I., Barreto, J. O. M., Barberato-Filho, S., Bergamaschi, C. D. C., Silva, M. T., and Lopes, L. C. (2021a). Improving Care for Deinstitutionalized People with Mental Disorders: Experiences of the Use of Knowledge Translation Tools. *Front. Psychiatr.* 12, 575108. doi:10.3389/fpsy.2021.575108
- Godman, B., Fadare, J., Kwon, H. Y., Dias, C. Z., Kurdi, A., Dias Godói, I. P., et al. (2021b). Evidence-based Public Policy Making for Medicines across Countries: Findings and Implications for the Future. *J. Comp. Eff. Res.* 10, 1019–1052. doi:10.2217/ce-2020-0273
- Godman, B., Hill, A., Simoens, S., Selke, G., Selke Krulichová, I., Zampiroli Dias, C., et al. (2021c). Potential Approaches for the Pricing of Cancer Medicines across Europe to Enhance the Sustainability of Healthcare Systems and the Implications. *Expert Rev. Pharmacoecon Outcomes Res.* 21, 527–540. doi:10.1080/14737167.2021.1884546
- Godman, B., Egwuenu, A., Haque, M., Malande, O. O., Schellack, N., Kumar, S., et al. (2021). Strategies to Improve Antimicrobial Utilization with a Special Focus on Developing Countries. *Life (Basel)* 11, 528. doi:10.3390/life11060528
- Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., et al. (2019). Comparative Efficacy and Tolerability of 32 Oral Antipsychotics for the Acute Treatment of Adults with Multi-Episode Schizophrenia: a Systematic Review and Network Meta-Analysis. *Lancet* 394, 939–951. doi:10.1016/S0140-6736(19)31135-3
- Lam, W. M. J., Al-Khalifah, R., Florez, I. D., Cruz-Lopes, L., Sekercioglu, M. F., Couban, R., et al. (2020). Management of Type 2 Diabetes Using Non-insulin Glucose-Lowering Therapies: a Critical Appraisal of Clinical Practice Guidelines with the AGREE II Instrument. *Diabet Med.* 37, 636–647. doi:10.1111/dme.14231
- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., et al. (2013). Comparative Efficacy and Tolerability of 15 Antipsychotic Drugs in Schizophrenia: a Multiple-Treatments Meta-Analysis. *Lancet* 382, 951–962. doi:10.1016/S0140-6736(13)60733-3
- Lima, A. P. C. S., Gallani, N. R., Toledo, M. I. d., and Lopes, L. C. (2008). Utilização de um sistema de gerenciamento de benefícios farmacêuticos (PBM) para a caracterização Do perfil de prescrição e aquisição de antibióticos. *Rev. Bras. Cienc. Farm.* 44, 215–223. doi:10.1590/s1516-93322008000200007
- Lopes, L. C., Barberato-Filho, S., Costa, A. C., and Osorio-de-Castro, C. G. (2010). Rational Use of Anticancer Drugs and Patient Lawsuits in the State of São Paulo, Southeastern Brazil. *Rev. Saude Publica* 44, 620–628. doi:10.1590/s0034-89102010000400005
- Lopes, L. C., Silveira, M. S., de Camargo, M. C., de Camargo, I. A., Luz, T. C., Osorio-De-Castro, C. G., et al. (2014). Patient Reports of the Frequency and Severity of Adverse Reactions Associated with Biological Agents Prescribed for Psoriasis in Brazil. *Expert Opin. Drug Saf.* 13, 1155–1163. doi:10.1517/14740338.2014.942219
- Luzzatto, L., Hyry, H. I., Schieppati, A., Costa, E., Simoens, S., Schaefer, F., et al. (2018). Outrageous Prices of Orphan Drugs: a Call for Collaboration. *Lancet* 392, 791–794. doi:10.1016/S0140-6736(18)31069-9
- Marković-Peković, V., Grubiša, N., Burger, J., Bojanić, L., and Godman, B. (2017). Initiatives to Reduce Nonprescription Sales and Dispensing of Antibiotics: Findings and Implications. *J. Res. Pharm. Pract.* 6, 120–125. doi:10.4103/jrpp.JRPP_17_12
- Mayer, R. C. F., Alves, M. R., Yamauti, S. M., Silva, M. T., and Lopes, L. C. (2021). Quality of Life and Functioning of People with Mental Disorders Who Underwent Deinstitutionalization Using Assisted Living Facilities: A Cross-Sectional Study. *Front. Psychol.* 12, 622973. doi:10.3389/fpsyg.2021.622973
- Moreira, S. S., Camargo, M. C., Caetano, R., Alves, M. R., Itria, A., Pereira, T. V., et al. (2021). Efficacy and Costs of Nanocrystalline Silver Dressings versus 1% Silver Sulfadiazine Dressings to Treat burns in Adults in the Outpatient Setting: A Randomized Clinical Trial. *Burns* S0305-4179, 00136. doi:10.1016/j.burns.2021.05.014
- Motter, F. R., Cantuaria, N. M., and Lopes, L. C. (2021). Healthcare Professionals' Knowledge, Attitudes and Practices toward Deprescribing: a Protocol of Cross-Sectional Study (Desmedica Study-Brazil). *BMJ Open* 11, e044312. doi:10.1136/bmjopen-2020-044312
- Niaz, Q., Godman, B., Campbell, S., and Kibuule, D. (2020). Compliance to Prescribing Guidelines Among Public Health Care Facilities in Namibia; Findings and Implications. *Int. J. Clin. Pharm.* 42, 1227–1236. doi:10.1007/s11096-020-01056-7
- Silveira, M. S., de Camargo, I. A., Osorio-de-Castro, C. G., Barberato-Filho, S., Del Fiol, Fde. S., Guyatt, G., et al. (2014). Adherence to Guidelines in the Use of Biological Agents to Treat Psoriasis in Brazil. *BMJ Open* 4, e004179. doi:10.1136/bmjopen-2013-004179
- Tavares, S. S., Cruz, L. N., Castro, J., and Lopes, L. C. (2019). Development and Validation of a Questionnaire for the Assessment of the Knowledge, Management and Reporting ADR in Paediatrics by Healthcare Teams (QUESA-P). *BMJ Open* 9, e028019. doi:10.1136/bmjopen-2018-028019
- Vieira, F. S., Lopes, L. C., Barberato-Filho, S., Marques, D. C., and Pepe, V. L. E. (2010). Pharmaceutical Services and Judicial Decisions: Proposals to Improve Access and Rational Use of Medicines. *RAS. Revista de Administração Em Saúde* 12, 79–86. doi:10.3895/rl.v12n12.2369
- Yamauti, S. M., Bonfim, J. R. d. A., Barberato-Filho, S., and Lopes, L. C. (2017). Essencialidade e racionalidade da relação nacional de medicamentos essenciais Do Brasil. *Ciênc. Saúde Coletiva* 22, 975–986. doi:10.1590/1413-81232017223.07742016

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Possible Genetic Determinants of Response to Phenytoin in a Group of Colombian Patients With Epilepsy

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Background: Epilepsy is a serious health problem worldwide. Despite the introduction of new antiepileptic drugs (AEDs) almost 30% of these patients have drug-resistant forms of the disease (DRE), with a significant increase in morbi-mortality.

Objective: Our objective was to assess the impact of some genetic factors and its possible association with treatment response and adverse drug reactions (ADRs) to phenytoin in 67 adult Colombian patients with epilepsy.

Methods: We conducted an analytical, observational, prospective cohort study to screen four polymorphisms in pharmacogenes: *CYP2C9**2-c.430C>T (rs1799853), *CYP2C9**3-c.1075A>C (rs1057910), *ABCB1*-c.3435T>C (rs1045642), and *SCN1A*-IVS5-91G>A (rs3812718), and their association with treatment response. Patients were followed for 1 year to confirm the existence of DRE (non-response) and ADRs using an active pharmacovigilance approach, followed by a consensus in order to classify ADRs according to causality, preventability, intensity and their relation with phenytoin dose, the duration of treatment, and susceptibility factors (DoTS methodology).

Results: A little more than half of evaluated subjects (52.2%) were non-responding to phenytoin. Regarding the genotype-phenotype correlation there was no association between polymorphisms of *SCN1A* and *ABCB1* and DRE (non-response) ($p = 0.34$), and neither with *CYP2C9* polymorphisms and the occurrence of ADRs ($p = 0.42$). We only found an association between polymorphic alleles of *CYP2C9* and vestibular-cerebellar ADRs (dizziness, ataxia, diplopia, and dysarthria) ($p = 0.001$). Alleles *CYP2C9**2-c.430C>T and *CYP2C9**3-c.1075A>C were identified as susceptibility factors to ADRs in 24% of patients.

Conclusions: Decreased function alleles of *CYP2C9* were highly predictive of vestibular-cerebellar ADRs to phenytoin in our study ($p = 0.001$). However, the genetic variants

*CYP2C9*2-c.430C>T*, *CYP2C9*3-c.1075A>C*, *ABCB1-c.3435T>C*, and *SCN1A-IVS5-91G>A*, were not associated with treatment response in our study.

Keywords: drug resistant epilepsy, phenytoin, drug-related side effects and adverse reactions, pharmacovigilance, pharmacogenetics

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders (Thurman et al., 2011). It affects around 65 million people around the world, and approximately 80% of these patients live in developing countries (Thurman et al., 2011; Ngugi et al., 2011). According to the World Health Organization (WHO), epilepsy represents 0.75% of the global burden of disease, particularly in children and young adults, with an estimated 23.4 million cases of active epilepsy in 2015 (Feigin et al., 2017). The most serious form of the disease, which is refractory to pharmacological treatment, represents approximately 30% of the cases (Cavalleri et al., 2011; Balestrini and Sisodiya, 2018).

Despite the introduction of new antiepileptic drugs (AEDs), more than 30% of patients with epilepsy have drug-resistant forms of the disease, which leads to a significant increase in the morbidity and mortality of epilepsy (Thurman et al., 2011).

This form of the disease, known as drug-resistant epilepsy (DRE), has been defined by the *International League Against Epilepsy* (ILAE) as “failure of adequate trials of two tolerated and appropriately chosen AED schedules (whether as monotherapies or in combination) to achieve seizure freedom” (Kwan et al., 2009). Although nowadays there are more than 30 different AEDs, there is no satisfactory treatment for DRE (Cavalleri et al., 2011). Therefore, patients with epilepsy tend to be difficult to treat due to the need for combination therapy and the high frequency of non-responding patients, drug interactions, and adverse drug reactions (ADRs), among other factors (Manford, 2017).

On the other hand, genetic factors have been involved as possible causes of variable responses to AEDs, including a lack of response to treatment, as well as the occurrence of ADRs (Balestrini and Sisodiya, 2018). This genotype-phenotype relationship is particularly well studied for phenytoin, which is one of the most widely used AEDs in the world (Cavalleri et al., 2011; Caudle et al., 2014; Balestrini and Sisodiya, 2018). However, the relationship between the therapeutic response and the most widely studied genetic variants, is mainly unknown (Balestrini and Sisodiya, 2018). It is the same case for some ADRs to phenytoin (e.g., cutaneous ADRs) (Balestrini and Sisodiya, 2018).

Likewise, among the most important pharmacogenes which influence the response to phenytoin are those related to the transport through the blood–brain barrier, such as the *ABCB1* gene, which encodes the glycoprotein P (P-gp); the *CYP2C9* gene and others that encode drug-metabolizing enzymes, and the genes that encode targets, such as *SCN1A*, which encodes the α -subunit of the voltage-gated sodium channel, which is a common target for phenytoin and other AEDs (McDonagh et al., 2011; Balestrini and Sisodiya, 2018).

In the new era of personalized medicine, it is essential to identify possible pharmacogenomic biomarkers as predictors of treatment response (El-Ibiary et al., 2008). Therefore, we evaluated the impact of the best-studied variants of the aforementioned genes as possible risk factors for non-response or ADRs to phenytoin.

Aim of the Study

The aim of the study was to assess the impact of genetic factors as causes of non-response and ADRs to phenytoin in a group of Colombian patients with epilepsy.

MATERIALS AND METHODS

Study Design

This was a cohort observational study that followed patients for 12 months, conducted jointly by treating physicians, and members of the study team, which was composed of a pharmacist, a pharmacologist, and doctors of other specialities (genetics, epidemiology, neurology).

Setting and Participants

Screening was carried out on patients who were treated at a center specializing in the treatment of patients with epilepsy and at the neurological service of a tertiary-level university hospital in Bogotá between October 2012 and February 2014.

Regarding the sample size calculation, we estimated a prevalence of 0.3% of DRE in Colombia according to what is reported in the literature (Pradilla et al., 2003). The value of sample proportion (p) was estimated according to the frequency of *ABCB1-c.3435T>C* (*rs1045642*) allele identified in gnomAD database (<https://gnomad.broadinstitute.org/>). Considering an alpha value of 0.05 and a power of 90% the sample size was equal to 68.

Patients with an established diagnosis of epilepsy, resident in Colombia, who had given written consent for their participation, and who were using at least one AED were included in the study. The patients were monitored for 12 months, with the aim of establishing the phenotypic response to treatment. Subjects who met the ILAE criteria were considered as non-responding patients (DRE) (Kwan et al., 2009), while those that did not suffer any epileptic seizure during the treatment period were deemed to be responsive (Kwan and Brodie, 2000). Patients with impaired hepatic and/or renal function, as well as those who did not adhere to the treatment, were excluded from the study. Ninety-six patients were included in the study. However, only 77 patients were evaluated since 19 of them were lost during the follow-up, so the phenotype could not be adequately assessed. Of

these 77 patients, ten more were excluded because they were not receiving phenytoin, for a final sample size of 67 patients. The study protocol was approved by the Ethics Committees of the participating institutions and was carried out in accordance with the Helsinki Declaration, in addition to local and international regulations regarding research on human subjects.

Research Procedure

ABCB1, *SCN1A*, and *CYP2C9* Genotyping

Genomic DNA was obtained from patient's peripheral blood samples using the standard salting-out procedure. Genomic regions encompassing *CYP2C9**2-*c.430C>T* (rs1799853), *CYP2C9**3-*c.1075A>C* (rs1057910), *ABCB1*-*c.3435T>C* (rs1045642), and *SCN1A*-*IVS5-91G>A* (rs3812718) polymorphisms were amplified by PCR. Specific primers for PCR reactions were designed using Primer Blastn (<https://www.ncbi.nlm.nih.gov/tools/primer-blast/>) and Primer3 software (<https://primer3plus.com/cgi-bin/dev/primer3plus.cgi>). For sequencing reactions we used an internal primer designed by Primer3 software. Primer sequences are available upon request. For each PCR reaction, 200 ng of DNA was using, 12.5 µl of the GoTaq Green Master Mix (Promega M-712) and 2 µl of each primers (forward and reverse at 10 µM) were added to each sample. Thereafter PCR was performed and consisted of initial denaturation for 10 min at 95°C, then 35 amplification cycles, (95°C for 40 s, 60°C (for *ABCB1*, *SCN1A*, and *CYP2C9* *3), or 55°C (for *CYP2C9**2) for 40 s and 72°C for 1 min), followed by a 10-min incubation at 72°C. The amplified products were visualized on ethidium bromide stained agarose gels.

PCR products were purified with conventional procedures (using shrimp alkaline phosphatase and exonuclease I). Direct Sequencing was performed with the same primers used in PCR reaction. Sequencing was made using the 3130xl Genetic Analyzer (Applied Biosystems). We analyzed the sequences in ab1.file by using FinchTV software (<http://www.digitalworldbiology.com/finchtv>). Wild-type sequences are listed in the Ensembl database (<https://finchtv.software.informer.com>): ENST00000260682.7 (*CYP2C9*), ENST00000622132.4 (*ABCB1*), ENSG00000144285 (*SCN1A*). Alignments of sequences were realized by using of ClustalW software.

Outcome Measures

Patients were prospectively evaluated to establish the phenotypic response to treatment. This evaluation was carried out by means of a monthly telephone call and the completion of a monitoring form for each patient included in the study. As an additional endpoint ADRs were assessed by a checklist (**Supplementary Data Sheet 1**) designed for the study and applied by a pharmacologist with extensive experience in pharmacovigilance, who systematically checked for possible ADRs in each telephone call. Each time that an ADR was suspected, we obtained additional information from the patient's medical records and data provided by the treating physician.

Each ADR was subsequently evaluated in terms of its causality using the Naranjo algorithm (Naranjo et al., 1981), preventability by the Schumock and Thornton criteria

(Schumock and Thornton, 1992), the Aronson and Ferner intensity criteria (Aronson and Ferner, 2005), and the DoTS (dose, time, and susceptibility) criteria from the same authors (Aronson and Ferner, 2003).

The Naranjo algorithm is a questionnaire proposed by Naranjo et al. for determining the likelihood of whether an ADR was caused by the suspect drug (phenytoin in our study) rather than concomitant factors (e.g., comorbidities). Probability was assigned using a score named definite, probable, possible, or doubtful. Whenever the answer to any of the Naranjo algorithm questions was unknown, a score of "0" was assigned to the corresponding question, as it's established in the algorithm (Naranjo et al., 1981). Schumock and Thornton criteria are a set of seven questions widely used in pharmacovigilance studies which are useful in determining the preventability of ADRs. Anytime that the answer to one or more of the seven questions was "yes" the ADR was classified as preventable (Schumock and Thornton, 1992). The intensity criteria of Aronson and Ferner evaluate the severity of ADRs based on the need to change the dosage regimen of the offending drug (phenytoin in our study): grade 1 (no change in dosage regimen was required), grade 2 (altered dosage regimen was required or desirable), and grade 3 (withdrawal was required or desirable) (Aronson and Ferner, 2005). Finally, the DoTS criteria are a classification system for ADRs based on dose responsiveness, time course, and susceptibility (Aronson and Ferner, 2003). Regarding the dose, ADRs may have occurred at supratherapeutic doses (toxic effects); standard therapeutic doses (collateral effects); or subtherapeutic doses in susceptible patients (hypersusceptibility reactions). We defined standard therapeutic doses in our study as the defined daily dose (DDD) of phenytoin set by the WHO which is 300 mg. In relation to time, ADRs can be time-independent which occurred at any time during treatment, independent of the duration of therapy, or time-dependent ADRs. In turn, time dependent ADRs were classified as rapid, first dose reactions, early, intermediate, late, or delayed depending on their temporal relationship with the administration of phenytoin. At last, the DoTS system include six susceptibility factors that could increase the risk of ADRs in certain populations (e.g., malnourished elderly patients). In our study these factors were: age (patients 60 years or older), sex (female gender), genetic variation (*CYP2C9**2-*c.430C>T* and *CYP2C9**3-*c.1075A>C* genetic polymorphisms), exogenous factors (drug interactions), and disease (comorbidities that, according to the researchers' criteria, could predispose to ADR) (Aronson and Ferner, 2003). Genetic susceptibility for ADRs was carried out considering the presence of decreased function alleles in *CYP2C9* that confer the intermediate/poor metabolizer phenotype, and its association with certain ADRs that have been associated with supra-therapeutic concentrations of phenytoin (Cavalleri et al., 2011). Physiological factors (e.g., pregnancy), which is defined by Aronson and Ferner as an additional susceptibility factor, were not assessed because pregnant women were not included in our study.

Each case of ADR or non-response was detected by a pharmacologist and subsequently double-checked by a

pharmacist. Two independent teams consisting of an epidemiologist, a clinical neurologist and a geneticist assessed the cases separately, and any discrepancies were resolved by consensus with a third author (pharmacologist).

Statistical Analysis

The categorical variables were presented as frequencies with percentages, using 95% confidence intervals (CI 95%).

The allelic and genotypic frequencies for *CYP2C9**2-*c.430C>T*, *CYP2C9**3-*c.1075A>C*, *ABCB1*-*c.3435T>C*, and *SCN1A*-*IVS5-91G>A* were determined using the SNP-Stats software (<https://www.snpsstats.net/>). Hardy-Weinberg equilibrium (HWE) was evaluated using chi-square test. We correlated *ABCB1* and *SCN1A* genotypes with the treatment response (phenotype) and the *CYP2C9* genotypes with ADRs (phenotype) using SPSS V25. Pre-specified analyses were performed for the different genotypes and ADRs by organs and systems affected. The result was deemed statistically significant when $p < 0.017$ (Bonferroni correction).

RESULTS

Table 1 presents the general characteristics of the 67 patients included, who had a mean age of 60 years. Approximately 51% of the patients were men, the majority of whom came from the Andean region of Colombia. In around 50% of cases, the epilepsy had an unknown cause and 90% of patients had no family history of epilepsy. Fifty-two percent of the subjects were classified as

patients with DRE (non-responding patients). Sixty-four percent of the patients received antiepileptic treatment as monotherapy with phenytoin.

Prevalence of the Studied Genotypes

Table 2 presents the allelic and genotypic frequencies of the polymorphisms analyzed.

Pharmacovigilance Analysis of the Studied Patients

We identified 53 patients with ADRs. Considering that some patients had more than one ADR the total number of ADRs was 143.

Regarding the systems/organs affected by ADRs, the nervous system was most affected, with 50.3% of the cases, followed by vestibular-cerebellar ADRs (18.2%) and gastrointestinal system (11.9%). The skin and the respiratory system were affected in 5.6% of ADR cases each of them. Reactions involving the endocrine/metabolic, hematological, genitourinary systems, and constitutional symptoms make up the remaining cases (8.4%).

Table 3 presents the ADRs to phenytoin in the study patients.

Regarding causality, 53.9% of the ADRs were classified as having a “possible” relationship, 45.5% were “probable” and only the 0.7% was considered “definite.”

Of the 143 ADRs, 68.5% were considered “preventable,” while the remaining 31.5% were classified as “non-preventable.”

Regarding the intensity of the evaluated ADRs, 46.9% were considered as “grade 1,” 44.1% were considered as “grade 2,” and the remaining 9.1% of ADRs were defined as “grade 3.”

Using the DoTS system, we found that 41.3% of the ADRs were “collateral,” 32.2% were classified as “hypersusceptibility” reactions and the remaining 26.6% were classified as “toxic effects.” However, it is important to mention that there was only objective evidence of supra-therapeutic plasma levels associated with phenytoin toxicity in a single patient (Calderon-Ospina et al., 2018).

According to the temporal relationship of ADRs established by the DoTS system, 86.7% of the ADRs were time-independent regarding the drug administration. The remaining 13.3% had a temporal relationship with drug administration as follows: 9.1% were “late” and 4.2% were “intermediate.” There were no documented “rapid,” “first dose,” “early,” or “delayed” ADRs.

TABLE 1 | Description of the population evaluated (n = 67).

Variable	n	%	CI 95%
Sex			
Female	33	49.3	37.7–60.9
Male	34	50.7	39.1–62.4
Age (years)			
18–64	35	52.2	40.5–63.8
65–79	22	32.8	22.8–44.8
≥80	10	14.9	8.3–25.4
BMI (kg/m ²)			
< 18.5	8	11.9	6.2–21.8
18.5–24.9	22	32.8	22.8–44.8
25–29.9	33	49.3	37.7–60.9
≥30	4	6.0	2.4–14.4
Etiology of epilepsy			
Structural	31	46.2	3.5–58.1
Genetic	3	4.5	1.6–12.4
Unknown	33	49.3	37.7–60.9
Family history of epilepsy			
Yes	7	10.5	5.2–20.0
No	60	89.6	80.0–94.8
Response to antiepileptic treatment			
DRE (non-responding patients)	35	52.2	40.5–63.8
Controlled epilepsy	32	47.8	36.3–59.5
Drug treatment			
Monotherapy	43	64.2	52.2–74.6
Combination therapy	24	35.8	25.4–47.8

CI 95%, confidence interval 95%; BMI, body mass index; DRE, drug-resistant epilepsy.

TABLE 2 | Allelic and genotypic frequencies of the studied genotypes.

Gene	Allelic frequency (%)		Genotypic frequency (%)	
<i>CYP2C9</i>	*1	86.4	*1/*1	74
	*2	9.1	*1/*2	18.2
	*3	4.5	*1/*3	6.5
			*3/*3	1.3
<i>ABCB1</i>	A	60	AA	36.4
	G	40	GA	44.2
<i>SCN1A</i>			GG	19.5
	C	39	CC	16.9
	T	61	TC	44.2
			TT	39

TABLE 3 | Description of adverse reactions to phenytoin (n = 143).

ADR	Number of cases	Percentage of total % (CI 95%)
Nervous system		
Somnolence	22	15.4 (10.4–22.2)
Blurred vision	11	7.7 (4.4–13.3)
Tremor	10	7.0 (3.8–12.4)
Lethargy	10	7.0 (3.8–12.4)
Headache	7	4.9 (2.4–9.8)
Nervousness	4	2.8 (1.1–7.0)
Loss of vision	4	2.8 (1.1–7.0)
Confusion	2	1.4 (0.4–5.0)
Cognitive impairment	2	1.4 (0.4–5.0)
Vestibular-cerebellar		
Dizziness	16	11.2 (7.0–17.4)
Dysarthria	4	2.8 (1.1–7.0)
Diplopia	3	2.1 (0.7–6.0)
Ataxia	3	2.1 (0.7–6.0)
Respiratory		
Bronchorrhea	8	5.6 (2.9–10.7)
Digestive		
Nausea	6	4.2 (1.9–8.9)
Vomiting	5	3.5 (0.2–7.9)
Gingival enlargement	3	2.1 (0.7–6.0)
Anorexy	2	1.4 (0.4–5.0)
Sialorrhea	1	0.7 (0.1–3.9)
Dermatological		
Acne	4	2.8 (1.1–7.0)
Rash	3	2.1 (0.7–6.0)
Hypertrichosis	1	0.7 (0.1–3.9)
Endocrine/metabolic		
Weight gain	3	2.1 (0.7–6.0)
Osteoporosis	1	0.7 (0.1–3.9)
Hematological		
Anemia	2	1.4 (0.4–5.0)
Leucopenia	1	0.7 (0.1–3.9)
Genitourinary		
Kidney stones	1	0.7 (0.1–3.9)
Increased urinary frequency	1	0.7 (0.1–3.9)
Constitutional symptoms		
Fatigue	3	2.1 (0.7–6.0)

ADR, adverse drug reaction; CI 95%, confidence interval 95%.

Only in 5.6% of the ADRs it was not possible to identify a susceptibility factor predisposing the patient to ADRs. However, the remaining 94.4% of the ADRs had different susceptibility factors as follows: genetics (23.8%), age (43.4%), sex (53.2%), exogenous factors (55.2%), and disease (19.6%).

Table 4 presents the classification of the ADRs found in the study.

Genotype—Phenotype Correlation

No significant differences were observed between the genetic variants *ABCB1-c.3435T>C* (rs1045642) and *SCN1A-IVS5-91G>A* (rs3812718) and the presence of DRE (non-response to antiepileptic treatment) ($p=0.34$) (**Table 5**). We also found no association between the genetic variants *CYP2C9*2-c.430C>T* and *CYP2C9*3-c.1075A>C* and ADRs ($p=0.42$) (**Table 6**).

However, performing specific analyses of affected systems/organs using the one sample chi-square test with the Bonferroni

TABLE 4 | Classification of adverse reactions to phenytoin (n = 143).

Variable	n	%	IC 95%
Causality			
Definitive	1	0.7	0.1–3.9
Probable	65	45.5	37.5–53.6
Possible	77	53.9	45.7–61.8
Preventability			
Preventable	98	68.5	60.5–75.6
Non-preventable	45	31.5	24.4–39.5
Intensity			
Grade 1	67	46.9	60.5–75.6
Grade 2	63	44.1	36.2–52.3
Grade 3	13	9.1	5.4–14.9
DoTS system (dose)			
Hypersusceptibility	46	32.2	25.1–40.2
Collateral	59	41.3	33.5–49.5
Toxic effects	38	26.6	20.0–34.4
DoTS system (time)			
Not related	124	86.7	80.2–91.3
Intermediate	6	4.2	1.9–8.9
Late	13	9.1	5.4–14.9
DoTS system (susceptibility)			
Genetic	34	23.8	17.6–31.4
Age	62	43.4	35.5–51.6
Sex	76	53.2	45.0–61.1
Exogenous factors	79	55.2	47.1–63.2
Disease	28	19.6	13.9–26.8

CI 95%, confidence interval 95%; DoTS, dose, time, and susceptibility.

TABLE 5 | Genotype-phenotype correlation for the outcome of response to antiepileptic treatment with phenytoin.

	DRE (non-responding patients)	Responding patients
Patients homozygous for allele A of the <i>SCN1A</i> gene or patients homozygous for allele C of the <i>ABCB1</i> gene	16	13
Heterozygous and homozygous patients for the G allele of the <i>SCN1A</i> gene or heterozygous or homozygous patients for the T allele of the <i>ABCB1</i> gene	19	19

DRE, drug-resistant epilepsy; *SCN1A*, sodium voltage-gated channel alpha subunit 1; *ABCB1*, ATP binding cassette subfamily B member 1.

correction, we found an association between decreased function alleles of *CYP2C9* and vestibular-cerebellar ADRs (dizziness, ataxia, diplopia, and dysarthria) ($p=0.001$). Regarding the other systems/organs affected by ADRs, we did not find a significant association: neurological ADRs ($p=0.075$), respiratory ($p=0.186$), digestive ($p=0.017$), dermatological (0.15), endocrine/metabolic ($p=0.456$), hematological ($p=0.352$), genitourinary ($p=0.238$), and constitutional symptoms ($p=0.075$).

DISCUSSION

This was an exploratory study with the aim to evaluate possible genetic determinants of response to anticonvulsant treatment with

TABLE 6 | Genotype-phenotype correlation for the outcome of adverse drug reactions to phenytoin.

	Patients with ADRs	Patients without ADRs
Intermediate/poor metabolizers for <i>CYP2C9</i> (homozygous or heterozygous for the allele <i>CYP2C9*2</i> and the allele <i>CYP2C9*3</i>)	13	3
Normal metabolizers for <i>CYP2C9</i> (homozygous for the allele <i>CYP2C9*1</i>)	40	11

CYP2C9, cytochrome P450 family 2 subfamily C member 9; ADR, adverse drug reaction.

phenytoin in a group of Colombian patients with epilepsy. The three studied pharmacogenes provided valuable information on three critical points of the pharmacokinetic/pharmacodynamic pathways of this drug. Allelic and genotypic frequencies of *CYP2C9* were very similar to those found in another study carried out by our research group aimed at designing a pharmacogenetic algorithm, which involved 152 Colombian patients using warfarin (Galvez et al., 2018). However, the frequency of intermediate metabolizers in the present study was three times greater than the overall frequency of this phenotype reported in the literature (Caudle et al., 2014).

With respect to the *ABCB1-c.3435T>C* variant, results were similar to the overall frequency (Genome Reference Consortium, n.d). However, these results differ from those found by Velasco-Parra et al. in a case (n = 111) and control (n = 91) study on the relationship between this same variant and refractory epilepsy in a sample of 202 Colombian patients with epilepsy, in whom the frequency of the TT genotype was considerably lower (Velasco-Parra et al., n.d). It is possible that this can be explained by methodological differences such as the definition of DRE in both studies.

Finally, for the *SCN1A* gene, frequencies were similar to that reported in the literature (Genome Reference Consortium, n.d). As far as we know, no published studies have systematically evaluated the relationship between *SCN1A-IVS5-91G>A* polymorphism (rs3812718) and DRE in Colombian patients. However, the presence of heterozygosity for this polymorphism has been reported in a Colombian family affected by generalized epilepsy with febrile seizures (Pineda-Trujillo et al., 2005).

We did not find an association between *ABCB1-c.3435T>C* polymorphism and DRE. These results are consistent with different meta-analyses, which have yielded contradictory results (Bournissen et al., 2009; Haerian et al., 2010; Balan et al., 2014; Lv et al., 2014; Chouchi et al., 2017). This could be explained by the high degree of heterogeneity of the included studies, due to the varying definitions of DRE, the use of different AEDs, and the inclusion of different types and syndromes of epilepsy. Although some evidence from animal studies, clinical cases and genetic studies supports the hypothesis of overexpression of P-gp in the BBB as a cause of resistance to pharmacological treatment of epilepsy (Wang et al., 2016), the true implications of *ABCB1-c.3435T>C* polymorphism of the *ABCB1* gene have not yet been explained.

ABCB1-c.3435T>C polymorphism corresponds to a synonymous SNP in exon 26, which has been associated with an alteration in P-gp activity (Hoffmeyer et al., 2000; Drescher et al., 2002) and, when it appears in a haplotype, with reduced functionality (Salama et al., 2006). However, it has also been proposed that changes in phenotypic activity of P-gp expression can depend on the type and number of AEDs used, as well as the duration of treatment for each patient. This theory provide another biologically plausible explanation of the differences obtained in the studies (and meta-analyses) performed to evaluate the impact of *ABCB1-c.3435T>C* polymorphism on the therapeutic response to AEDs (Sisodiya and Goldstein, 2007).

Probably the most important result of this study was the association between the intermediate/poor metabolizer phenotype for *CYP2C9* and vestibular-cerebellar ADRs (dizziness, ataxia, diplopia, and dysarthria) ($p=0.001$). Due to the non-linear pharmacokinetics of phenytoin, consistent with a change in elimination kinetics from first to zero order (more evident in poor metabolizers) the role of the *CYP2C9* enzyme and its polymorphisms is critical for the generation of this type of ADRs (Silvado et al., 2018). Recently the FDA has recently adjusted the clinical pharmacology section of the phenytoin label to warn about the possibility of unusually high levels in patients with certain allelic variants in *CYP2C9* and *CYP2C19* (Research C for DE and. Science & Research (Drugs), n.d).

The pharmacovigilance results of this study coincide with previous reports (Chmielewska et al., 2013), with approximately 70% of ADRs being preventable, and the most frequent cause of adverse effects (and possibly non-response cases) being insufficient monitoring of plasma concentrations of phenytoin. This result is evident in the fact that according to DoTS evaluation almost three out of 10 ADRs were related to supra-therapeutic doses in our study. These figures highlight the necessary inclusion of non-genetic factors in pharmacogenetic studies.

As far as we know, this is the first clinical study with a pharmacogenomic and pharmacovigilance approach aimed at investigating the impact of three pharmacogenes and four distinct genetic polymorphisms in the therapeutic response to phenytoin, all of which were identified by an exhaustive literature review. This study used the ILAE criteria in order to have an objective, up-to-date and comprehensive definition of pharmacoresistance. Likewise, the ADRs were evaluated exhaustively with an active pharmacovigilance approach.

One of the limitations of the research project is that this was observational in nature, and plasma levels of phenytoin were only available in less than 20% of patients evaluated. The availability of this information for all patients would have allowed an accurate correlation between *CYP2C9* genotypes, plasmatic levels of phenytoin and therapeutic response, as well as a more precise attribution of causal relationship in ADRs according to the Naranjo algorithm, which includes supratherapeutic plasma levels of the suspect drug as one of the items to be evaluated. While phenytoin has a narrow therapeutic range, there is evidence to suggest that this drug should not be freely interchangeable (Gidal, 2009; Rediguieri and Zeredo, 2014). Therefore, the lack of control over which specific

brand of phenytoin used by each patient may have introduced an additional bias into the study. Finally, the lack of statistical significance for many of the evaluated genotype-phenotype correlations, could be explained by the relatively small sample size or by the evaluation of a reduced number of polymorphisms within many hundreds of possible genetic variants. In addition, the analysis of the two other common *ABCB1* variants (c.1236C>T and c.2677G>T/A) in order to generate the corresponding haplotype would have been more relevant than the study of a unique *ABCB1* variant (Chouchi et al., 2017).

It has been hypothesized that synchronized neuronal hyperactivity (e.g., epileptic seizures) induces deep shifts in the epigenome and the expression of downstream genes. Epigenetic changes including DNA methylation, histone modifications, and microRNAs may be responsible for functional and structural changes within neural networks, as well as at the beginning of epilepsy and its progression to DRE (Kobow and Blümcke, 2018). In this way, the complexity of the problem to be studied (DRE) along with the limitations of the available data (e.g., lack of epigenetic data) may have limited the scope of this study.

Considering that the study was carried out in care centers specializing in the treatment of epilepsy could explain the higher frequency of patients with DRE, compared to what has been reported (Kwan et al., 2011; Balestrini and Sisodiya, 2018). Furthermore, the great majority of patients had epilepsy of unknown or structural/metabolic origin, and all of them received phenytoin to treat the condition, so the results obtained could not be extrapolated to other populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

REFERENCES

- Aronson, J. K., and Ferner, R. E. (2003). Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 327, 1222–1225. doi: 10.1136/bmj.327.7425.1222
- Aronson, J. K., and Ferner, R. E. (2005). Clarification of terminology in drug safety. *Drug Saf.* 28, 851–870. doi: 10.2165/00002018-200528100-00003
- Balan, S., Bharathan, S. P., Vellichiraman, N. N., Sathyan, S., Joseph, V., Radhakrishnan, K., et al. (2014). Genetic Association Analysis of ATP Binding Cassette Protein Family Reveals a Novel Association of *ABCB1* Genetic Variants with Epilepsy Risk, but Not with Drug-Resistance. *PloS One* 9, e89253. doi: 10.1371/journal.pone.0089253
- Balestrini, S., and Sisodiya, S. M. (2018). Pharmacogenomics in epilepsy. *Neurosci. Lett.* 667, 27–39. doi: 10.1016/j.neulet.2017.01.014
- Bourmisen, F. G., Moretti, M. E., Juurlink, D. N., Koren, G., Walker, M., and Finkelstein, Y. (2009). Polymorphism of the *MDR1/ABCB1* C3435T drug-transporter and resistance to anticonvulsant drugs: A meta-analysis. *Epilepsia* 50, 898–903. doi: 10.1111/j.1528-1167.2008.01858.x
- Calderon-Ospina, C. A., Dominguez-Dominguez, C. A., and Aristizabal-Gutierrez, F. A. (2018). Neurological toxicity associated with phenytoin in an intermediate metabolizer patient for CYP2C9 enzyme. *Pharm. Care (Esp)* 20, 228–235.
- Caudle, K. E., Rettie, A. E., Whirl-Carrillo, M., Smith, L. H., Mintzer, S., Lee, M. T. M., et al. (2014). Clinical Pharmacogenetics Implementation Consortium Guidelines

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética en Investigación de la Universidad del Rosario. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly to the preparation of the manuscript, are in agreement with the content of the manuscript and agree to submission to the journal.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2020.00555/full#supplementary-material>

SUPPLEMENTARY DATA SHEET 1 | Checklist for the evaluation of adverse reactions to phenytoin in the study patients.

- for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing. *Clin. Pharmacol. Ther.* 96, 542–548. doi: 10.1038/clpt.2014.159
- Cavalleri, G. L., McCormack, M., Alhusaini, S., Chaila, E., and Delanty, N. (2011). Pharmacogenomics and epilepsy: the road ahead. *Pharmacogenomics* 12, 1429–1447. doi: 10.2217/pgs.11.85
- Chmielewska, B., Lis, K., Rejdak, K., Balcerzak, M., and Steinborn, B. (2013). Pattern of adverse events of antiepileptic drugs: results of the aESCAPE study in Poland. *Arch. Med. Sci. AMS* 9, 858–864. doi: 10.5114/aoms.2013.38679
- Chouchi, M., Kaabachi, W., Klau, H., Tizaoui, K., Turki, I. B.-Y., and Hila, L. (2017). Relationship between *ABCB1* 3435TT genotype and antiepileptic drugs resistance in Epilepsy: updated systematic review and meta-analysis. *BMC Neurol.* 17, 1–14. doi: 10.1186/s12883-017-0801-x
- Drescher, S., Schaeffeler, E., Hitzl, M., Hofmann, U., Schwab, M., Brinkmann, U., et al. (2002). *MDR1* gene polymorphisms and disposition of the P-glycoprotein substrate fexofenadine. *Br. J. Clin. Pharmacol.* 53, 526–534. doi: 10.1046/j.1365-2125.2002.01591.x
- El-Ibiary, S. Y., Cheng, C., and Alldredge, B. (2008). Potential roles for pharmacists in pharmacogenetics. *J. Am. Pharm. Assoc.* 48, e21–e32. doi: 10.1331/JAPhA.2008.07050
- Feigin, V. L., Abajobir, A. A., Abate, K. H., Abd-Allah, F., Abdulle, A. M., Abera, S. F., et al. (2017). Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 16, 877–897. doi: 10.1016/S1474-4422(17)30299-5

- Galvez, J. M., Restrepo, C. M., Contreras, N. C., Alvarado, C., Calderón-Ospina, C.-A., Peña, N., et al. (2018). Creating and validating a warfarin pharmacogenetic dosing algorithm for Colombian patients. *Pharmacogenom. Pers. Med.* 11, 169–178. doi: 10.2147/PGPM.S170515
- Genome Reference Consortium (n.d). *The NCBI Handbook - NCBI Bookshelf*, <https://www.ncbi.nlm.nih.gov/books/NBK153600/> (accessed November 12, 2018).
- Gidal, B. E. (2009). Bioequivalence of antiepileptic drugs: how close is close enough? *Curr. Neurol. Neurosci. Rep.* 9, 333–337. doi: 10.1007/s11910-009-0050-5
- Haerian, B. S., Roslan, H., Raymond, A. A., Tan, C. T., Lim, K. S., Zulkifli, S. Z., et al. (2010). ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: A systematic review and meta-analysis. *Seizure* 19, 339–346. doi: 10.1016/j.seizure.2010.05.004
- Hoffmeyer, S., Burk, O., von Richter, O., Arnold, H. P., Brockmöller, J., John, A., et al. (2000). Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc. Natl. Acad. Sci. U. S. A.* 97, 3473–3478. doi: 10.1073/pnas.050585397
- Kobow, K., and Blümcke, I. (2018). Epigenetics in epilepsy. *Neurosci. Lett.* 667, 40–46. doi: 10.1016/j.neulet.2017.01.012
- Kwan, P., and Brodie, M. J. (2000). Early Identification of Refractory Epilepsy. *N Engl. J. Med.* 342, 314–319. doi: 10.1056/NEJM200002033420503
- Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., Mathern, G., et al. (2009). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies: Definition of Drug Resistant Epilepsy. *Epilepsia* 51, 1069–1077. doi: 10.1111/j.1528-1167.2009.02397.x
- Kwan, P., Schachter, S. C., and Brodie, M. J. (2011). Drug-Resistant Epilepsy. *N Engl. J. Med.* 365, 919–926. doi: 10.1056/NEJMra1004418
- Lv, W. P., Han, R. F., and Shu, Z. R. (2014d). Associations between the C3435T polymorphism of the ABCB1 gene and drug resistance in epilepsy: a meta-analysis. *Int. J. Clin. Exp.* 7 (11), 3924–3932.
- Manford, M. (2017). Recent advances in epilepsy. *J. Neurol.* 264, 1811–1824. doi: 10.1007/s00415-017-8394-2
- McDonagh, E. M., Whirl-Carrillo, M., Garten, Y., Altman, R. B., and Klein, T. E. (2011). From pharmacogenomic knowledge acquisition to clinical applications: the PharmGKB as a clinical pharmacogenomic biomarker resource. *Biomark. Med.* 5, 795–806. doi: 10.2217/bmm.11.94
- Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., et al. (1981). A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* 30, 239–245. doi: 10.1038/clpt.1981.154
- Ngugi, A. K., Kariuki, S. M., Bottomley, C., Kleinschmidt, I., Sander, J. W., and Newton, C. R. (2011). Incidence of epilepsy: A systematic review and meta-analysis. *Neurology* 77, 1005–1012. doi: 10.1212/WNL.0b013e31822cfc90
- Pineda-Trujillo, N., Carrizosa, J., Cornejo, W., Arias, W., Franco, C., Cabrera, D., et al. (2005). A novel SCN1A mutation associated with severe GEFS+ in a large South American pedigree. *Seizure* 14, 123–128. doi: 10.1016/j.seizure.2004.12.007
- Pradilla, A. G., Vesga, A. B. E., and León-Sarmiento, F. E. (2003). Estudio neuroepidemiológico nacional (EPINEURO) colombiano. *Rev. Panam. Salud. Pública* 14, 104–111. doi: 10.1590/S1020-49892003000700005
- Rediguieri, C. F., and Zeredo, J. L. (2014). Assessing bioequivalence of antiepileptic drugs: are the current requirements too permissive? *J. Pharm. Pharm. Sci. Publ. Can. Soc. Pharm. Sci. Soc. Can. Sci. Pharm.* 17, 220–228. doi: 10.18433/J3659Z
- Research C for DE and Science & Research (Drugs) (n.d). Table of Pharmacogenomic Biomarkers in Drug Labeling. <https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm> (accessed December 21, 2018).
- Salama, N. N., Yang, Z., Bui, T., and Ho, R. J. (2006). MDR1 haplotypes significantly minimize intracellular uptake and transcellular P-gp substrate transport in recombinant LLC-PK1 cells. *J. Pharm. Sci.* 95 (10), 2293–2308.
- Schumock, G. T., and Thornton, J. P. (1992). Focusing on the preventability of adverse drug reactions. *Hosp. Pharm.* 27, 538.
- Silvado, C. E., Terra, V. C., and Twardowsky, C. A. (2018). CYP2C9 polymorphisms in epilepsy: influence on phenytoin treatment. *Pharmacogenom. Pers. Med.* 11, 51–58. doi: 10.2147/PGPM.S108113
- Sisodiya, S. M., and Goldstein, D. B. (2007). Drug resistance in epilepsy: more twists in the tale. *Epilepsia* 48, 2369–2370. doi: 10.1111/j.1528-1167.2007.01260_1.x
- Thurman, D. J., Beghi, E., Begley, C. E., Berg, A. T., Buchhalter, J. R., Ding, D., et al. (2011). Standards for epidemiologic studies and surveillance of epilepsy: Standards for Epidemiologic Studies and Surveillance of Epilepsy. *Epilepsia* 52, 2–26. doi: 10.1111/j.1528-1167.2011.03121.x
- Velasco-Parra, H., Rodríguez, L., González, C., Zambrano, V., Espinosa, E., and Izquierdo, Ávaro (n.d). Polimorfismo C3435T del Gen ABCB1 (MDR1) en pacientes con Epilepsia refractaria en tres centros de referencia Nacional en Colombia. *Med. (Bogotá)* 33, 249–259.
- Wang, G.-X., Wang, D.-W., Liu, Y., and Ma, Y.-H. (2016). Intractable epilepsy and the P-glycoprotein hypothesis. *Int. J. Neurosci.* 126, 385–392. doi: 10.3109/00207454.2015.1038710

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The High “Cost” of Experimental Drugs Obtained Through Health Litigation in Brazil

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Background: Brazilian patients have legal right to access unlicensed medicines undergoing clinical research, if there is evidence of efficacy and safety. This study investigated the occurrence of serious adverse events related to very high-cost medicines from clinical studies, expanded access and compassionate use programs, obtained by patients through health litigation.

Methods: A descriptive study using secondary data investigated unlicensed medicines obtained through lawsuits from 2010 to 2017, costing more than 1 million Brazilian reais (BRL), adjusted by the Brazilian Consumer Index to July 2017. Data sources were the Brazilian Health Surveillance Agency Registry (DATAVISA) and Adverse Events in Clinical Studies (NotivisaEC) Databases. Medicines were categorized by the Anatomical Therapeutic Chemical classification to level 03 and events by the WHO Adverse Drug Reaction Terminology. The study received ethical approval by the University of Brasília Institutional Research Board.

Results: In the period, 812 drugs were obtained through litigation, and of these, 78 exceeded cost of 1 million BRL; 44 of them presented reports of 1,248 serious adverse events. Total Brazilian Government expenditure with these drugs was 3.2 billion BRL. Class L04A (n=7) showed greater expenditures (over 1.8 billion BRL). One hundred ninety-six deaths occurred and L01X was the most involved category (49.5%). Most other serious events (n=419) and sequelae (n=10) were related to L01X.

Conclusion: Very high-cost drugs paid for by the government and obtained through health litigation presented deaths and serious adverse events in expanded access and compassionate use programs in Brazil.

Keywords: litigation, clinical trials, compassionate use, expanded access, adverse drug event

INTRODUCTION

Serious and/or rare conditions with high social impact and risk of death are usually treated with high-cost drugs either recently brought to market or still in trial for later licensing (OPAS, 2009). However, these products may worsen a patient's condition if their efficacy and safety are not known or acceptable.

In Brazil, as in other countries, patients with serious clinical conditions with no therapeutic alternative may have access to unlicensed products that are still under development through compassionate use and expanded access programs (Mosegui and Antoñanzas, 2019). Authorizations for the expanded access program are given to groups of patients and the drugs must necessarily be in a phase III clinical trial (Brasil, 2013a). On the other hand, entry into the compassionate use program, which is individualized, may be authorized when the medicine is at any phase of clinical development (Brasil, 2013a). Since 2012, sponsors of clinical trials are further obligated to provide participants with the medicine under investigation free of charge, even after the study's conclusion, for as long as there is a clinical benefit (Brasil, 2012).

Patients included in clinical trials and in compassionate use and expanded access programs must be monitored (Brasil, 2013a; Brasil, 2015) for the occurrence of serious adverse events (Brasil, 2015). Unexpected events under suspicion of cause by the experimental drug must be notified to the *Agência Nacional de Vigilância Sanitária* (Brazilian Health Regulatory Agency, Anvisa). Data from these notifications are important when evaluating the health profile of the medicines under investigation, especially those used for rare conditions, for which there is relatively little evidence available.

However, patients also access unlicensed medicines—whether or not they are included into the programs discussed above—through litigation. Lawsuits have been filed in Brazilian courts to force the provision of experimental treatments, based on medical prescriptions issued to the plaintiffs (Diniz et al., 2014). In Brazil, judicialization has encompassed not only medicines, but also health products and other technologies (Diniz et al., 2014), with increasingly higher expenses (Ministério da Saúde do Brasil, 2018a; Ministério da Saúde do Brasil, 2018b; Ministério da Saúde do Brasil, 2018c).

Despite the dissemination of Brazilian studies on the provision of medicines through court rulings, there is scarce literature on the risks and clinical outcomes of this type of provision (Teodoro et al., 2017). This study analyzed serious adverse events notified during clinical trials, compassionate use, expanded access, and post-trial provision of experimental drugs that were the object of lawsuits filed against the Ministry of Health (MoH), with an adjusted cost of over one million reais, in the period from 2010 to 2017.

METHODS

We carried out a descriptive study based on independent secondary databases.

We obtained, from the *Sistema Eletrônico do Serviço de Informação ao Cidadão* (Citizen Information Service Electronic

System, e-SIC) (Brasil, 2019), a list of materials (medicines, health products, foods and others) acquired by the MoH, in the period from January 2010 to July 2017.

Following this step, we proceeded to identify which purchases involved drugs demanded through litigation but which had also been used in clinical trials (including post-trial provision), expanded access or compassionate use programs, made at any point during the study period with a contract value equal to or greater than 1 million BRL. The medicine prices listed in the purchase were adjusted for July 2017 by the *Índice Nacional de Preços ao Consumidor Amplo*—IPCA (National Broad Consumer Price Index) (IPCA, 2019). Expenses were calculated for all purchases of the same medicine and added.

The resulting list of costly medicines obtained through litigation was then screened for their safety profile during use in clinical trials, expanded and compassionate use programs in Brazil through both the *Sistema de Controle de Pesquisa Clínica* (Clinical Trial Control System, SCPC) and the *Sistema de Notificação de Eventos Adversos Graves em Ensaios Clínicos* (Adverse Events in Clinical Trials Notification System, NotivisaEC) to verify existence of adverse events reports (Anvisa, 2018). Drugs for which there were no reports of serious adverse events were excluded.

Drugs were then screened by the *Sistema de Produtos e Serviços sob Vigilância Sanitária* (Products and Services under Health Surveillance System, Datavisa) to verify the existence of a valid license.

We consulted the *Denominação Comum Brasileira* (Brazilian Non-proprietary Drug Name, DCB) and the commercial names of all drugs that had been licensed as medicines. For drugs not included in the DCB, synonyms were obtained from a commercial platform (Cortellis, Clarivate Analytics) (Clarivate Analytics, 2018), which works with updated data regarding pharmaceutical products, clinical trials and patents, and is used by Anvisa. For each drug we also verified its recommended clinical use based on the current International Classification of Diseases (ICD-10) (WHO, 2016).

Drugs were then classified according to the Anatomical Therapeutic Chemical classification (WHO, 2019). In order to maintain confidentiality of the drug and of commercial names of medicines, as is required by Anvisa, we chose to aggregate them at the ATC 3rd level category.

Quantitative adverse events data from clinical trials, expanded and compassionate use programs were retrieved from SCPC and from NotivisaEC. Adverse events with the same WHO Adverse Drug Reaction Terminology (WHOART) (WHO, 2018a), same beginning and end dates and on the same patient were considered only once. We compiled the recorded causality data between the adverse event and the suspected drug or medicine, which was evaluated by the clinical trial's investigator or the program physician, in accordance with the International Conference on Harmonisation—ICH (ICH, 2003) and the World Health Organization (WHO, 2018b).

Microsoft Excel (version 2016) was employed to produce a database with the following information: drug name, DCB, synonyms, commercial name (if applicable), medicine license, use in clinical trial (and phase)/programs, recommended clinical

use (ICD-10), adverse event notification, seriousness and type of event (expected and unexpected) and event outcome.

Results were described by sums (number of medicines, ATC 3rd level, total expenditure from litigation in the period, deaths, sequelae, and number of serious adverse events).

This study was approved by the Ethics Review Board of the School of Health Sciences of the University of Brasília (CAAE: 55035116.6.0000.0030).

RESULTS

From January 2010 to July 2017, the MoH acquired 812 medicines in compliance with court orders, of which 78 were responsible for purchases that exceeded 1 million BRL. At July 2017 prices, these expenses totaled 5,522,033,488.00 BRL. Of these, 20 were not included in clinical trials or compassionate use and expanded access programs and 14 were not associated with adverse events. The final sample included 44 medicines (56.4%) distributed according to ATC 3rd level (**Table 1**), which together cost, approximately, 3.2 billion BRL in the period (or around 58% of the expenses).

In the study period, class L04A was associated with the highest expenses, at more than 1.8 billion BRL, followed by classed A16A (1.7 billion) and L01X (134 million).

The 44 drugs caused 1,248 serious adverse events. Of these, 861 (69%) took place in clinical trials, 250 (20%) in expanded access programs, 100 (8%) in compassionate use programs, and 37 (6%) were associated with post-trial drug provision (non-tabulated data).

The most numerous class was L01X (other antineoplastic agents), with 20 different drugs. This class was further represented by an association with an immunosuppressant drug (class L04A). Class L04A had seven drugs (in addition to the one in combination with L01X).

The highest number of total reported outcomes (n=526; 42.2%) contained drugs classified as L01X. L01X + L04A was second in number (n = 272; 21.8%); the medicine formed by the association had 235 (23.3%) notified serious events. L04A alone accounted for 127 (10.2%) of outcomes. Events with sequelae (n=42) were more present among users of the associated L01X/L04A medicine (16), followed by users of L01X (10) and L04A (7).

With regard to type of event, 661 (53%) were considered unexpected (data not presented in **Table 1**). The 44 medicines were suspected of causing 196 deaths (16% of the total of adverse events). The class most involved with this event was L01X (n=97; 49.5%), followed by two unique medicines from class L02B and by the association L01X and L04A. Each was suspected of causing 21 deaths. Class A16A, the second in expenses and represented by three medicines, was associated with 16 deaths (8.5%).

DISCUSSION

This study showed that 44 medicines involved in trials and expanded access or compassionate use programs and bought by the Federal Government in compliance with court orders represented 3.2 billion BRL in expenses with individual purchases between January 2010 and July 2017. These medicines had serious adverse event notifications, including 196 deaths. Unexpected events corresponded to more than 50% of observed events.

There are no accessible and transparent databases that characterize the benefit of expanded access and compassionate use of experimental drugs in South American countries (Mosegui and Antónanzas, 2019). In Brazil, clinical trials and expanded access and compassionate use programs are regulated by Anvisa to guarantee enrolled patients' safety. They undergo prior assessment and authorization depends on the accrual of medical

TABLE 1 | Number of experimental drugs demanded through litigation, ATC 3rd level classification, incurred expenditures (BRL) and related outcomes.

n	ATC 3rd level (class name)	Total expenditures with litigation* (BRL)	Outcomes from clinical trials, expanded access and compassionate use programs [#]		
			Deaths	Sequelae	Other serious adverse events
7	L04A (Immunosuppressants)	1,829,315,680.96	12	7	108
3	A16A (Other Alimentary Tract and Metabolism Products)	1,174,512,692.82	16	1	58
20	L01X (Other Antineoplastic Agents)	134,340,122.74	97	10	419
1	C10A (Lipid Modifying Agents, Plain)	21,471,959.74	0	0	2
1	L02B (Hormone Antagonists and related Agents)	14,074,500.68	21	6	85
1	B06A (Other Hematological Agents)	6,804,103.46	0	0	1
1	R03D (Other Systemic Drugs for Obstructive Airway Diseases)	4,098,056.66	0	0	5
2	L01B (Antimetabolites)	3,418,587.19	12	0	20
2	J05A (Direct Acting Antivirals)	3,132,467.77	3	0	8
1	L01X (Other Antineoplastic Agents) and L04A (Immunosuppressants)	2,531,431.68	21	16	235
1	H05A (Parathyroid Hormones and Analogues)	2,460,970.36	3	1	5
1	S01L (Ocular Vascular Disorder Agents)	2,355,940.47	2	0	8
1	B02B (Vitamin K and other hemostatics)	2,169,034.39	4	1	11
1	A10A (Insulins and Analogues)	1,782,023.30	5	0	44
1	H01A (Anterior Pituitary Lobe Hormones and Analogues)	1,100,605.97	0	0	1
44		3,203,568,178.21	196	42	1010

Brazilian Ministry of Health and Anvisa, 2010–2017.

Source: *Litigation expenditures provided by the Brazilian Ministry of Health; [#]Serious adverse events reported data provided by Anvisa.

reports and drug safety and efficacy information which supports its prescription (Teodoro and Caetano, 2016). One of the criteria supposedly taken into consideration is the risk/benefit analysis of the demanded medicine. To participate, patients or their legal representatives must sign an informed consent document which must present the justification for product use, possible discomfort and risks, including adverse events, and expected benefits (Brasil, 2013a; Darrow et al., 2015; Teodoro and Caetano, 2016). These patients are monitored for adverse events.

However, despite the precautions taken by the regulatory agency, expanded access presumes the use of a drug of which little is known, and additionally, outside the investigative domain, which generates great uncertainty (Goldim, 2008). In these programs and trials, the availability of information and the evidence regarding the drug's safety and efficacy are limited. Phase I and II clinical trials, for example, may not show clinical benefits, with little knowledge available for decision-making. Often, the only assessment that is possible is whether or not the experimental drug poses a greater risk than the disease itself. When access results from litigation, the situation is even more complex. It is possible that the structure for patient support and monitoring present in clinical trials may not be available. Additionally, it is not possible to guarantee that the available information will be offered to patients, or that they or their legal representatives will have a clear understanding of potential risks and harms based on a consent form.

Patients who demand to participate in expanded access and compassionate use programs are especially vulnerable because they have serious diseases, with no therapeutic alternatives, and their capacity to perceive treatment risks is compromised. These patients are far more compelled to obtain access to an experimental treatment than to take into consideration the unpredictable risks of an unlicensed drug (Darrow et al., 2015).

Despite this situation, the occurrence of serious events seems only rarely to affect the development of expanded access programs. An analysis of 11,000 requests received by the FDA to include patients into expanded access programs over the course of 10 years showed that only two programs were temporarily interrupted due to the occurrence of adverse events (Jarow et al., 2016).

There is considerable pressure on health professionals and regulatory agencies to incorporate new products, a situation which is not exclusive to Brazil. The speed with which evidence is produced and the pressure for incorporation discourage a conservative approach to the use of technologies. Rapid- and slow-acting insulins, for example, which are leading objects of lawsuits against SUS, were incorporated, even after several studies that showed the lack of gains in effectiveness from the system's perspective (De Souza et al., 2014; Laranjeira et al., 2016; Chieffi et al., 2017; CONITEC, 2019a; CONITEC, 2019b).

In the face of health litigation, the health system has at times been called upon to provide technologies with no scientific evidence in support of the proposed use, or with fragile evidence of benefits amid a context of growing costs (Figueiredo et al., 2010). According to the MoH, between 2010 and 2016, the costs of litigation for the federal government increased more than 10-fold. In 2016, the expenses with judicial health demands consumed 1.3 billion BRL

of the federal budget. The list with the ten most expensive medicines was responsible for 90% of that sum (Conselho Nacional de Justiça, 2019). The expenses resulting from litigation have an impact on the medicines policy budget, with a reduction in the offer of other listed medicines, exams, and consultations to the general population (Paim et al., 2017). On the other hand, there seem to be inconsistencies and information failures even in the application of the *SUS Protocolos Clínicos e Diretrizes Terapêuticas* (Clinical Protocols and Therapeutic Guidelines, PCDT) (Figueiredo et al., 2013; Dias and da Silva, 2016) when regarding litigated medicines. In 2017, an audit of 414 judicial demands for medicines in Brazil showed that around half did not even include a diagnosis of the disease to be treated (Ministério da Saúde do Brasil, 2018d).

Many medicines demanded through litigation are generally prescribed for the treatment of chronic diseases, such as cancer and rare diseases (Chagas and Santos, 2018). In this study, a large portion of the medicines was classified as antineoplastic agents (L01X, for example). In fact, this subjacent risk profile, related either to the seriousness or to lack of knowledge as to the underlying disease also draws attention to the safety problems surrounding treatment.

In 2019, the Brazilian Supreme Court decided that States cannot be compelled to provide experimental drugs. However, in exceptional cases, it is possible for courts to award access to unlicensed drugs if there is an unreasonable delay in Anvisa's appreciation of the licensing documentation (Brasil, 2016) and when three criteria are met: i) existence of a licensing request (excepting orphan drugs for rare and ultra-rare diseases); ii) existence of a license for the medicine from a renowned foreign regulatory agency; and iii) non-existence of a licensed therapeutic substitute in Brazil (STF, 2019). In any case, it is worth noting that licensing requirements in Brazil became more flexible in 2013 (Decree 8.077) (Brasil, 2013b). Furthermore, there is pressure in favor of accepting licenses from foreign agencies, which are also under pressure from the pharmaceutical industry (Osorio-de-Castro et al., 2015), weakening safety requirements for licensing.

Licensing, as a country's first medicines selection process, would be considered an initial filter to the entry of safe and effective new technologies. However, it is worth noting that lack of safety information is also a problem for medicines that have undergone the licensing stage. This has to do with the quality of the process. In France, a 2017 analysis showed that 45 out of 92 new licensed medicines were products with no therapeutic advantage and 15 new medicines were classified as unacceptable (Prescrire International, 2018). In Brazil, an analysis that employed the same criteria concluded that 82% of new medicines approved for licensing by Anvisa between 2004 and 2016 were not innovative and had low therapeutic value (Hoefler et al., 2019).

This study showed that of the 44 medicines that were used by litigants, 81% were associated with serious adverse events other than sequelae (3.4%) or death (15.7%). However, there is no way to establish if litigants suffered these same effects, and with the same severity. Nonetheless, of all outcomes 83.2% were associated with the following medicine classes: L01B (antimetabolites), L01X (other antineoplastic agents), L02B (hormonal antagonists and other related agents), L04A (immunosuppressants). We must consider

that these events may have been influenced by the patients' serious clinical conditions, in addition to their comorbidities, since the drugs in these classes are potentially the last available therapeutic alternative. However, we should consider that beyond the medicine and the patient's intrinsic safety issues, the use of experimental drugs outside the research setting and as a result of litigation without the necessary controls considerably increases risks (Vidal et al., 2017).

If, on the one hand, these medicines have an inconclusive risk/benefit profile, on the other, they represent considerable expenses for the system. The medicines in classes L01 (antineoplastic agents), L02 (hormones), and L04 (immunosuppressants) are among the most expensive and most often incorporated since 2012. An analysis of expenses with medicines incorporation showed that class L corresponded to a greater variation in expenses between 2006 and 2013, with a 20-fold increase, while class L04 increased 250 times in the Brazilian federal government expenses (Luz et al., 2017). This medicine class was also responsible for high expenses in the United States, United Kingdom, Australia and Canada (Alves et al., 2018).

Class A16A (other alimentary tract and metabolism products) encompasses countless enzymes and biological medicines, many of which have been incorporated since 2014 (CONITEC, 2019c), with high added costs. Once a medicine is incorporated—and, therefore, a channel for government funding is established—new uses start to be suggested. Thus, we may assume that some of the recently incorporated A16A medicines are targets for prescriptions of new, unlicensed uses. The presence of this class shows the potential of experimental uses driving the costs of public provision.

A substantial, though unintentional, limitation of the study is the impossibility of defining exactly which litigated medicines were responsible for serious adverse events, including deaths. This barrier, imposed by Anvisa, interferes to some extent with regulatory activities (though Anvisa has the means to extract this information independently), but mainly compromises the transparency of information regarding safety of litigated medicines for assessment by the population, by patients, by health workers and by the law. This is new information which, to our knowledge, has not been previously published.

Otherwise we did not mean to establish a direct correlation between the use of drugs and the effect on individual patients. We worked with aggregated data and were not able to access patient-level data. Another possible limitation concerns the data collection strategy, since the databases were not linked. A study that used linked information, with patient-level data, would give greater robustness to the analysis.

But we do have a blueprint of adverse effects caused by these drugs. Litigation is actively supplying drugs without careful review and judges only adhere to the plaintiff's clinician. This has been demonstrated over the years, as a process that does not favor evidence-based use of medicines in clinical practice (Lopes et al., 2010; Chieffi et al., 2017).

It is important to consider that these are mostly drugs used in severe clinical conditions with a low benefit-risk ratio but in many situations, they are needed by the patient. Clinicians acknowledge the potential safety problems in view of the dire need for treatment

in many cases. Despite this, we highlight these are dangerous drugs and follow-up, through litigation is, at present, non-existent. This constitutes a paradox, since monitoring is mandatory in clinical trials, expanded and compassionate use programs in Brazil (Brasil, 2013a; Brasil, 2015).

CONCLUSION

The study showed the existence of serious adverse events, including deaths, related to litigated medicines in the country, from 2010 to 2017. These medicines, grouped at the 3rd level ATC, represent considerable expenses for the Ministry of Health. It is estimated that, given the reach of health litigation in the country, serious events and deaths may also be happening in connection to medicines purchased by other Federal Government institutions and at other government levels.

We point to the important implications related to the lack of transparency of data regarding the safety—or lack thereof—of experimental, unlicensed drugs, which may be obtained through litigation, which, as is known, is a fast, potentially uncritical and considerably widespread practice for accessing new medicines or new medicine uses in the country. As several countries in Latin America are also going through health litigation for access to medicines, the results presented in this paper may be useful for further discussion on drug safety issues.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Board of the School of Health Sciences of the University of Brasília. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RS, EL, MN, and CO-D-C made substantial contributions to conception, design and acquisition of data. In addition, RS, EL, and CO-D-C analyzed and interpreted the data. All authors read and approved the final manuscript.

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REFERENCES

- Alves, J. C., Osorio-de-Castro, C. G. S., Wettermark, B., and Luz, T. C. B. (2018). Immunosuppressants in Brazil: underlying drivers of spending trends 2010–2015. *Expert Rev. Pharmacoeconom. Outcomes Res.* 18, 565–572. doi: 10.1080/14737167.2018.1485098
- Anvisa (2018). Agência Nacional de Vigilância Sanitária. Sistema de Produtos e Serviços sob Vigilância Sanitária (Datavisa), para verificar a existência do registro, e tanto no Sistema de Controle de Pesquisa Clínica (SCPC) como no Sistema de Notificação de Eventos Adversos Graves em Ensaios Clínicos (NotivisaEC) para verificação dos eventos adversos. Acesso em maio de 2018.
- Brasil (2012). Resolução do Conselho Nacional de Saúde n. 466 de 12 de dezembro de 2012, que aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Disponível online em: <https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf> (Acessado em 04 junho, 2019).
- Brasil (2013a). Agência Nacional de Vigilância Sanitária. Resolução RDC n. 38/2013, que aprova o regulamento para os programas de acesso expandido, uso compassivo e fornecimento de medicamento pós-estudo. Disponível online em: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/rdc0038_12_08_2013.html (Acessado em 28 maio, 2019).
- Brasil (2013b). Decreto N. 8.077, de 14 de agosto de 2013. Regulamenta as condições para o funcionamento de empresas sujeitas ao licenciamento sanitário, e o registro, controle e monitoramento, no âmbito da vigilância sanitária, dos produtos de que trata a Lei nº 6.360, de 23 de setembro de 1976, e dá outras providências.
- Brasil (2015). Agência Nacional de Vigilância Sanitária (Anvisa). Resolução RDC n. 9 de 20 de fevereiro de 2015. Dispõe sobre o Regulamento para a realização de ensaios clínicos com medicamentos no Brasil. Disponível online em: http://portal.anvisa.gov.br/documents/10181/3503972/RDC_09_2015_.pdf/843a88bd-3381-489e-8711-aca256cb4360 (Acessado em 24 junho, 2019).
- Brasil (2016). LEI Nº 13.411, DE 28 DE DEZEMBRO DE 2016. Altera a Lei n. 6.360, de 23 de setembro de 1976, que dispõe sobre a vigilância sanitária a que ficam sujeitos os medicamentos, as drogas, os insumos farmacêuticos e correlatos, cosméticos, saneantes e outros produtos, e dá outras providências, e a Lei nº 9.782, de 26 de janeiro de 1999, que define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária, e dá outras providências, para dar transparência e previsibilidade ao processo de concessão e renovação de registro de medicamento e de alteração pós-registro.
- Brasil (2019). Governo Federal. Sistema Eletrônico do Serviço de Informação ao Cidadão. Versão 3.1.15. Disponível em <https://esic.cgu.gov.br/sistema/site/index.aspx>.
- Chagas, C. P., and Santos, F. P. (2018). Efeitos do gasto com a judicialização da saúde no orçamento da Secretaria Estadual de Saúde do Distrito Federal entre 2013 e 2017. *Cad. Ibero-Amer. Dir. Sanit.* 7, 147–172. doi: 10.17566/ciads.v7i2.496.
- Chieffi, A. L., Barradas, R. C. B., and Golbaum, M. (2017). Legal access to medications: a threat to Brazil's public health system? *BMC Health Serv. Res.* 17, 499. doi: 10.1186/s12913-017-2430-x
- Clarivate Analytics (2018). The Intellectual Property and Science business of Thomson Reuters. Available at: <https://www.cortellis.com/intelligence/login>. Do Accessed on 21 March 2018.
- CONITEC (2019a). Insulinas análogas de ação rápida para Diabetes Mellitus Tipo 1. Relatório de Recomendação. No245, Fevereiro/2017. Disponível online em http://conitec.gov.br/images/Relatorios/2017/Relatorio_Insulinas_DiabetesTipo1_final.pdf. (Acessado em 03 outubro, 2019).
- CONITEC (2019b). Insulinas análogas de ação prolongada para o tratamento de diabetes mellitus tipo II. Relatório de Recomendação Nº 434 Fevereiro/2019. Disponível online em http://conitec.gov.br/images/Relatorios/2019/Relatorio_InsulinasAnalogas_AcaoProlongada_DM2.pdf. (Acessado em 03 outubro, 2019).
- CONITEC (2019c). Recomendações sobre as tecnologias avaliadas em 2014. Relatório Técnico Alfaliglicerasa para o tratamento da doença de Gaucher. Disponível online em: <http://conitec.gov.br/index.php/decisoes-sobre-a-incorporacao-de-tecnologias-no-sus-2014> (Acessado em 20 outubro, 2019).
- Conselho Nacional de Justiça (2019). Judicialização da Saúde no Brasil: Perfil das demandas, causas e propostas de solução. Relatório Analítico Propositivo. Série Justiça Pesquisa. Realização: Instituto de Ensino e Pesquisa – Insper. Brasília.
- Darrow, J. J., Sarpatwari, A., Avorn, J., and Kesselheim, A. S. (2015). Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs. *N. Engl. J. Med.* 372, 279–286. doi: 10.1056/NEJMh1409465
- De Souza, A. L. C., Acúrcio, F. A., Guerra, A. A., Do Nascimento, R. C. R. M., Godman, B., and Diniz, L. M. (2014). Insulin Glargine in a Brazilian State: Should the Government Disinvest? An Assessment Based on a Systematic Review. *Appl. Health Econ. Health Policy* 12, 19–32. doi: 10.1007/s40258-013-0073-6
- Dias, E. R., and da Silva, G. B. (2016). Evidence-Based Medicine in judicial decisions concerning right to healthcare. *Einstein* 14, 1–5. doi: 10.1590/S1679-45082016AO3363
- Diniz, D., Machado, T. R., and Penalva, J. (2014). A judicialização da saúde no Distrito Federal. *Cien. Saude Colet.* 19, 591–598. doi: 10.1590/1413-81232014192
- Figueiredo, T. A., Pepe, V. L. E., and Osorio-de-Castro, C. G. S. (2010). Um enfoque sanitário sobre a demanda judicial de medicamentos. *Physis: Rev. Saúde Coletiva* 20, 101–118. doi: 10.1590/S0103-73312010000100007
- Figueiredo, T. A., Osorio-de-Castro, C. G. S., and Pepe, V. L. E. (2013). Evidence-based process for decision-making in the analysis of legal demands for medicines in Brazil. *Cad. Saúde Pública* 29, S159–S166. doi: 10.1590/0102-311X00161812
- Goldim, J. R. (2008). O uso de drogas ainda experimentais em assistência: extensão de pesquisa, uso compassivo e acesso expandido. *Rev. Panam. Salud. Publica/Pan Am. J. Public Health* 23, 198–206. doi: 10.1590/S1020-49892008000300007
- Hoefler, R., Alves, T. L., Leufkens, H. G., and Naves, J. O. S. (2019). Added therapeutic value of new drugs approved in Brazil from 2004 to 2016. *Cad. Saúde Pública* 35, e00070018. doi: 10.1590/0102-311X00070018
- ICH (2003). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH HARMONISED TRIPARTITE GUIDELINE. POST-APPROVAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING E2D.
- IPCA (2019). Índice Nacional de Preços ao Consumidor Amplo. Instituto Brasileiro de Geografia e Estatística – IBGE. Disponível em <https://www.portalbrasil.net/ipca.htm> Acesso em 15/03/2019.
- Jarow, J. P., Lemery, S., Bugin, K., Khozin, S., and Moscicki, R. (2016). Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period. *Ther. Innov. Regul. Sci.* 50, 705–709. doi: 10.1177/2168479016656030
- Laranjeira, F. O., da Silva, E. N., and Pereira, M. G. (2016). Budget Impact of Long-Acting Insulin Analogues: The Case in Brazil. *PloS One* 11, e0167039. doi: 10.1371/journal.pone.0167039
- Lopes, L. C., Barberato-Filho, S., Costa, A. C., and Osorio-de-Castro, C. G. S. (2010). Rational use of anticancer drugs and patient lawsuits in the state of São Paulo, Southeastern Brazil. *Rev. Saúde Pública* 44 (4), 620–628. doi: 10.1590/S0034-89102010000400005
- Luz, T. C. B., Osorio-de-Castro, C. G. S., and Wettermark, B. (2017). Trends in medicines procurement by the Brazilian federal government from 2006 to 2013. *PloS One* 12, e0174616. doi: 10.1371/journal.pone.0174616
- Ministério da Saúde do Brasil (2018a). Fundo Nacional de Saúde. Ministério da Saúde vai disponibilizar software para controlar ações judiciais em saúde. Disponível online em: <http://portalms.saude.gov.br/ultimas-noticias/1677-ministerio-da-saude-vai-disponibilizar-software-para-controlar-acoes-judiciais-em-saude> (Acessado em 06 março, 2018).
- Ministério da Saúde do Brasil (2018b). Ministro da Saúde discute acesso da população à saúde pública. Disponível online em: <http://portalms.saude.gov.br/noticias/agencia-saude/28563-ministro-da-saude-discute-acesso-da-populacao-a-saude-publica> (Acessado em 06 março, 2018).
- Ministério da Saúde do Brasil (2018c). Ministério da Saúde adota medidas para garantir oferta de medicamentos para doenças raras. Disponível online em: <http://portalms.saude.gov.br/noticias/agencia-saude/42719-ministerio-da-saude-adota-medidas-para-garantir-oferta-de-medicamentos-para-doencas-raras> (Acessado em 08 março, 2018).
- Ministério da Saúde do Brasil (2018d). Liminar aponta “afronta a concorrência” em compra para doenças raras. Disponível em: <http://www.saude.gov.br/noticias/agencia-saude/42669-liminar-aponta-afronta-a-concorrenca-em-compra-para-doencas-raras> (Acessado em 25 maio, 2019).
- Mosegui, G., and Antofianzas, F. (2019). Normatização de programas de acesso expandido e uso compassivo de medicamentos na América do Sul [Regulations on expanded access and compassionate use of medicines in South

- America [Regulación de los programas de acceso ampliado y uso compasivo de medicamentos en América del Sur]. *Rev. Panameric. Salud Publica Pan Am. J. Public Health* 43, e57. doi: 10.26633/RPSP.2019.57
- OPAS (2009). Organização Pan-Americana da Saúde. Acesso aos medicamentos de alto custo nas Américas. Contexto, desafios e perspectivas. Disponível online em: http://bvsms.saude.gov.br/bvs/publicacoes/acesso_medicamentos_alto_custo_americas.pdf (Acessado em 20 maio, 2019).
- Osorio-de-Castro, C. G. S., Caetano, R., and Pepe, V. L. E. (2015). The 21st Century Cures Act: can the regulatory framework survive the “cures”? *Cad. Saúde Pública* 31, 1807–1810. doi: 10.1590/0102-311XPE010915
- Paim, L. F. N. A., Batt, C. R., Saccani, G., and e Guerreiro, I. C. K. (2017). Qual é o custo da prescrição pelo nome de marca na judicialização do acesso aos medicamentos? *Cad. Saúde Colet.* 25, 201–209. doi: 10.1590/1414-462X201700020022
- Prescrire International (2018). Drugs in 2017: a brief review. *Rev. Prescrire* 38, 145–146.
- STF (2019). Supremo Tribunal Federal. Decisão do STF desobriga Estado de fornecer medicamento sem registro na Anvisa. Disponível online em: <http://www.stf.jus.br/portal/cms/verNoticiaDetalhe.asp?idConteudo=411857&caixaBusca=N> (Acessado em 23 setembro, 2019).
- Teodoro, C. R. S., and Caetano, R. (2016). O caso da fosfoetanolamina sintética e a preocupante flexibilização das normas sanitárias no Brasil. *Physis: Rev. Saúde Coletiva* 26, 741–746. doi: 10.1590/s0103-73312016000300002
- Teodoro, C. R. S., Caetano, R., Godman, B., Reis, A. L. A., Maia, A. A., Ramos, M. C. B., et al. (2017). Federal procurement of unlicensed medicines in Brazil: findings and implications. *Expert Rev. Pharmacoecon. Outcomes Res.* 17, 607–613. doi: 10.1080/14737167.2017.1311209
- Vidal, T. J., Moraes, E. L., Retto, M. P. F., and Da Silva, M. J. S. (2017). The lawsuits to antineoplastic drugs: the tip of an iceberg? *Cien. Saude Colet.* 22, 2539–2548. doi: 10.1590/1413-81232017228.07982017
- WHO (2016). World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Available online at: <http://apps.who.int/classifications/icd10/browse/2016/en> (Accessed October, 10, 2016).
- WHO (2018a). World Health Organization. Adverse Reaction Terminology WHO-ART (Uppsala (Sweden): The Uppsala Monitoring Center). Accessed on March 29, 2018.
- WHO (2018b). World Health Organization. The WHO-UMC system for standardised case causality assessment. World Health Organization. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf Accessed on March 10, 2018.
- WHO (2019). World Health Organization. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). Available at: <https://www.who.int/classifications/atcddd/en/> (Accessed June, 11, 2019).

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Strategies Implemented by Public Institutions to Approach the Judicialization of Health Care in Brazil: A Systematic Scoping Review

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Background: The judicialization of health care is a social claim concerning the right to the access to health care. It usually occurs due to gaps in public policy or failures in its application. In Brazil, several public institutions have implemented strategies to approach this phenomenon. However, these strategies have not yet been systematized into functional categories.

Objective: To categorize and analyze the strategies implemented by public institutions in Brazil to approach the judicialization of health care.

Method: A systematic scoping review was developed following the method proposed by the Joanna Briggs Institute. The descriptor 'judicialization of health' was used to conduct the searches for studies in 18 electronic databases and other types of documents in the gray literature until March 2019. Documents containing the reports of strategies implemented in public institutions to approach the judicialization of health care in Brazil were included. Two independent reviewers assessed the eligibility of the documents and extracted the data. The strategies identified were categorized using definitions from the World Health Organization and existing Brazilian legislation.

Results: Seventy eight implemented strategies were identified and organized into nine categories: i. Technical support to the judiciary; ii. State health committees; iii. Organization of assistance; iv. Compliance with court orders, v. Computerized information systems; vi. Administrative proceeding; vii. Defense of the public authority; viii. Pharmacy and therapeutics committee; ix. Alternative dispute resolution. These categories are not mutually exclusive and often act in concert or complement each other's activities. They represent services either existing or provided for in legal provisions by the public administration to meet various types of demands.

Conclusions: The categories proposed to approach the judicialization of health care represent some of the recommendations for qualifying public administration or are provided

for in Brazilian legislation, or both. The existence of recommendations and legislation facilitate, but do not guarantee, the implementation of strategies by public institutions.

Keywords: Brazil, judicialization of health care, organization and administration, public health, lawsuits and litigation, justice administration system, delivery of health care, health systems

INTRODUCTION

The judicialization of health care, mainly in Latin America and the Caribbean, can be considered as a social claim to a pressing need: access to adequate health care, whether services or medical supplies, is currently not being met due to various reasons. Among these reasons are the lack of, or inadequacy of, health coverage; limitations or inequality in access to health care; and the poor quality of service delivery (Pinzón-Flórez et al., 2016).

In Brazil, the judicialization of health emerged with the activism of people who live with the HIV virus who demanded drug treatment (Tribunal de Contas da União, 2017). This happened shortly after the promulgation of the Federal Constitution in 1988 and the creation of the Unified Health System (SUS in Portuguese) in 1990, where for the first time, the Brazilian government considered health as a fundamental right of those who live in the country (Brasil, 1988; Brasil, 1990).

SUS is its main health policy and one of the largest social inclusion policies in the world. It provides universal and comprehensive care to all people without distinction in order to guarantee access to health care. Social participation is an important factor for the construction of SUS and for reducing inequities (Vieira et al., 2014; Ministério da Saúde, 2019b).

However, in Brazil, the claim of these rights through judicialization of health care can deepen the inequalities in access to health care (Chieffi and Barata, 2009).

The judicialization, especially when instigation factors are avoidable, has a negative functional and financial impact on both public health care and legal institutions. Their results often bring an increase in the number of services that must be offered, health technology expenditures when health care needs could be more efficiently met using other products that existing in the public health care system, and significant costs associated with lawsuits. Furthermore, it can also lead to fines, seizing of funds, and even imprisonment of managers for noncompliance with court order (Vieira and Zucchi, 2007; Delduque et al., 2013; Tribunal de Contas da União, 2017; Vargas-Pelaez et al., 2019).

The effect of increase in the number of lawsuits is alterations in the health care delivery that public institutions are able to provide to the public, in that these institutions now need to prioritize compliance with court orders to the detriment of systemic rationality in the provision of access to health care (Chieffi and Barata, 2009; Tribunal de Contas da União, 2017; Vargas-Pelaez et al., 2019).

Public Administration driven by pressures to expand services and health care technologies, is being institutionally reorganized to meet these demands (Vargas-Pelaez et al., 2019). However, the strategies used to approach the judicialization in Brazil, in both the legal and health areas, have not yet been categorized as to their organization and operation.

The purpose of this review is to categorize and analyze the institutional strategies used by the public sector to approach the judicialization of health care in Brazil.

METHOD

This scoping review used the following guidelines: the Joanna Briggs Institute guidelines for conducting systematic scoping reviews (Levac et al., 2010; Peters et al., 2015); the elaboration of narrative syntheses for systematic reviews produced by Popay et al. (2006); and the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018) (Appendix 1).

Eligibility Criteria

Inclusion and Exclusion Criteria

Both primary and secondary studies were analyzed, regardless of their study design or publication status. Abstracts and presentations given at scientific events, newsletters and administrative reports, as well as news published on the internet were also scrutinized.

Documents were included concerning any type of institutional strategy that has been implemented to approach the judicialization of health care in Brazil, both in the areas of health care management and legal¹.

Documents were excluded from the analysis when merely: i. described or characterized the judicialization of health, according to the type of action, the characteristics of the actors involved, number of lawsuits, etc.; ii. analyzed specific lawsuits from the point of view of the plaintiffs' needs; iii. suggested strategies that were not in fact implemented; iv. cited the name of an implemented strategy without providing sufficient information to characterize it; v. reported strategies that were used by lawyers, the public defender's office or the public prosecution office to judicialize health care demands.

Concepts

Considering the objectives of this review, the following concepts were employed:

¹ In Brazil, the legal area or the justice system is composed primarily of judges and courts of law belonging to the Judiciary Power which are responsible for judging lawsuits, and the essential functions of justice which are composed of the Public Prosecution Office, Public Defender's Office and Attorney Office which are responsible for the defense of public patrimony, the most vulnerable citizens and the public institutions, respectively. (In: Campos AG. Sistema de justiça no Brasil: problemas de equidade e efetividade. Brasília: IPEA; 2008.).

Judicialization of health care: A multifaceted phenomenon, present in Latin America and the Caribbean in a similar way, where a lawsuit is filed against an institution of the public health care sector due to gaps in health policy or health care delivery failures (Perlingeiro, 2014). The purpose of the lawsuit is to guarantee the person's, individually or collectively, constitutional right to health care. The term covers all solicitations related to the provision of health care, including medicines, equipment and procedures, materials, hospitalizations, medical care, care programs, protocols (Vieira, 2016), and any materials deemed necessary for providing health care to the population in order to minimize or resolve diseases or health problems (Panerai and Peña-Mohr, 1989). However, it does not include litigation for medical act or medical malpractice, for rights of the dying or judicialization of end of life medical decision-making, for reproductive rights of women or abortion rights and lawsuits for compulsory hospitalization. In Brazil, the court's decision is almost always in favor of the plaintiff (Advocacia-Geral da União et al., 2017).

Strategy, regarding health care systems: as defined by the World Health Organization, is "a series of broad lines of action intended to achieve a set of goals and targets set out within a policy or programme" (World Health Organization, 2019). It differs from 'intervention', which is defined as "an activity or set of activities aimed at modifying a process, course of action or sequence of events, in order to change one or several of their characteristics such as performance or expected outcome" (World Health Organization, 2019). Although strategy and intervention are distinct activities, in the health policy literature, there is a prevalence of the use of the word strategy, and the studies on the topic generally use 'strategy' to the detriment of 'intervention'.

Therefore, this scoping review adopted the term 'strategy' to define any activity, action, service, experience or practice, professional or otherwise, implemented in public institutions in order to approach the judicialization of health care.

Context and Institutions Involved

Public sector institutions, both health and legal, that are affected by the judicialization of health care have as a consequence an increase in the demand for services which in turn results in an increased need for public spending (Asensi and Pinheiro, 2015; Advocacia-Geral da União et al., 2017; Conselho Nacional de Justiça, 2017; Schulze, 2017). This can compromise the health care and legal services provided for all users and can also serve to disrupt these institutions, both administratively and financially (Siqueira, 2015; Tribunal de Contas da União, 2017). Consequently, these institutions are required to reorganize and reallocate resources earmarked for other purposes in order to comply with court orders for health care technologies (Tribunal de Contas da União, 2017; Vargas-Pelaez et al., 2019).

To circumvent such situation, several public institutions have created their own strategies to avoid or minimize the judicialization of health care in the provision of public services. However, yet there is no categorization of these strategies that can be used to conduct further studies on the subject.

Search Strategy

The terms of the Brazilian descriptor "judicialization of health" (judicialização da saúde, in Portuguese) (Descritores em Ciência da Saúde (DeCS), 2017) were used both alone and in combination for this search strategy (Appendix 2).

Information Sources

The search was performed from between data inceptions databases until March 2019, without limits on language. The search was limited to documents from Brazil. The following electronic information bases were used:

1. OneFile, Scopus, Social Sciences Citation Index, Expanded Sciences Citation Index (Web of Science), Directory of Open Access Journals (DOAJ), Sociological Abstracts, MEDLINE/PubMed, Scientific Electronic Library Online (SciELO), SciELO Brazil, JSTOR Archival Journals, NDLTD Union Catalog, SAGE Journals and Publications, Science Direct Journals and Books, Elsevier, Oxford Journals, Materials Science & Engineering Database, Cambridge Journals, and Dialnet. The searches in these databases were carried out *via* the Digital Library of Scientific Journals of the Brazilian Federal Agency for the Improvement of Higher Education (Portal CAPES, in Portuguese)².
2. Gray literature websites: CAPES Thesis Bank and Digital Library of Theses and Dissertations (BDTD) *via* Portal CAPES; Federal Pharmacy Council; Innovare Institute; National School of Public Administration; National Council of Health Secretaries; National Council of Justice; and websites of public agencies promoting awards in order to increase the dissemination of successful practices in the areas of public health, law and administration.

Other Search Resources

In documents reporting the implementation of strategies, a lack of specifics about the strategies themselves is a fact that was predicted and described by Popay et al., (2006). Therefore, to circumvent this problem, a manual search was performed using the references and citations in the selected documents in order to locate strategies unidentified in the original search and to complement the information of documents with insufficient data for data extraction.

The webpages of courts, municipal or state health departments, attorney offices, public prosecutor's offices, public defender's offices, the Brazilian ministry of health, and other institutions that have implemented strategies of interest for this study were also scrutinized.

Study Selection Process

The selection of titles and abstracts was performed by two independent reviewers (SY and LL) based upon the eligibility

²Portal CAPES has free access to journals and databases from different areas of knowledge, acts as a meta-researcher and is available in <http://www.periodicos.capes.gov.br/>.

criteria. Any disagreements between the reviewers were resolved by consensus.

Data Extraction

Reviewer's calibration was performed in screening full documents by extracting at least three articles until consensus was reached. This procedure occurred until the reviewers could extract the data they identified:

- Article (authors, year of publication, title, and type of publication);
- Study (city/state, year of implementation and name of strategy adopted by the institution responsible for its implementation);
- Strategy (objectives, how it functioned in practice and results).

Categorization of Findings, Analysis and Synthesis of Results

The implemented strategies identified in this scoping review were grouped according to their stated objectives and the similarity of activities developed and described in the included documents. They were categorized according to concepts used by the Pan American Health Organization/World Health Organization regarding existing services or activities in health care (Holloway and Green, 2003; Ribeiro et al., 2004; WHO Regional Office for the Western Pacific, 2004; Health Metrics Network and World Health Organization, 2008). For strategies related to Public Administration or the legal area, definitions based on Brazilian legislation were used (Brasil, 1999; Brasil, 2010; Conselho Nacional de Justiça, 2010a; Conselho Nacional de Justiça, 2010b; Brasil, 2015; Conselho Nacional de Justiça, 2016b).

Explanatory tables and figures were then elaborated about the proposed categories, along with a narrative synthesis about each category's characteristics.

RESULTS

Document Selection and Composition of the Identified Strategies

The initial search for this study retrieved 2,377 documents, of which 2,225 documents were removed during the screening of titles and abstracts and 111 documents were excluded after a reading of the full text. Sixty one documents were found by manual search in other search resources. The final selection included 102 documents containing 78 strategies implemented by Brazilian public institutions to approach the health care judicialization (**Figure 1**).

Categorization of Institutional Strategies

Seventy eight implemented institutional strategies were identified in this review. After being grouped, they resulted in the proposition of nine categories of strategies to approach the judicialization of health care (**Table 1** and **Figure 2**).

Four strategies were allocated into two categories at the same time: 'Special Requests Review Board' (Perin et al., 2008; Boldrin, 2014), 'Araguaína Municipal Technical Support Center' (Henrique et al., 2013; Asensi and Pinheiro, 2015; Farias, 2016; CEMAS, 2019), 'Interinstitutional Center for Health Judicialization' (Secretaria de Estado da Saúde de Alagoas, 2013; Macêdo et al., 2015) and 'Pharmaceutical and Nutrition Screening and Guidance Services' (Núcleo de Comunicação Social, 2017; Reis, 2018; Ministério Público do Estado de São Paulo, 2019).

Lists containing information about the characteristics of the strategies and the documents included in this scoping review can be found in **Appendix 3** and **Appendix 4**.

Characteristics of the Proposed Categories

Alternative Dispute Resolution

The implemented strategies focused on alternative dispute resolution methods are the most documented (19.5%). This is partly due to the fact that there exist laws that encourage their use, regardless of the material nature of the matter (Brasil, 1988; Brasil, 2015).

The 16 strategies that make up this category (Pinheiro, 2010; Reis, 2011; Yoshinaga, 2011; Triagem farmacêutica no juizado especial da fazenda pública de São Paulo, 2013; Tribunal de Justiça do Estado do Pará, 2013; Boldrin, 2014; Orsatto, 2014; Asensi and Pinheiro, 2015; Assis, 2015; Galliez, 2015; Macedo, 2016; Nunes, 2016; Souza, 2016; Júnior, 2017; Núcleo de Comunicação Social, 2017; Sant'Ana, 2017) provide for negotiation or inter-institutional dialogue in order to meet health care demands. They also provide for inter-institutional agreements and allow for action without an appeal to the courts. Five of these strategies can also be implemented when there are current legal actions pending (Advocacia Geral da União, 2009; Pinheiro, 2010; Henrique et al., 2013; Queiroz, 2013; Orsatto, 2014; Tavares et al., 2014; Asensi and Pinheiro, 2015; Guimarães and Palheiro, 2015; Paim et al., 2015; Prefeitura Municipal de Lages, 2015; Vasconcellos, 2015; Farias, 2016; Souza, 2016; Cotrim, 2017; Sant'Ana, 2017; CEMAS, 2019). However, the strategies in this category can only be implemented when the matter at hand does not involve an urgency or an emergency.

The meetings for mediation, conciliation or negotiation take place mainly in legal environments (11/15) (Reis, 2011; Yoshinaga, 2011; Triagem farmacêutica no juizado especial da fazenda pública de São Paulo, 2013; Tribunal de Justiça do Estado do Pará, 2013; Queiroz, 2013; Orsatto, 2014; Assis, 2015; Galliez, 2015; Guimarães and Palheiro, 2015; Macedo, 2016; Ringeisen, 2016) with the physical presence of interested parties. Only one of the strategies conducts mediation or conciliation by electronic means (Galliez, 2015).

The public defender is one of the most representative actors in the implementation of these strategies, with the exception of cases which fall into the specialized areas of 'Health Mediation'—Belo Horizonte (Assis, 2015) and the 'Pharmaceutical Screening at the Small Claims Courts' (Triagem farmacêutica no juizado especial da fazenda pública de São Paulo, 2013;

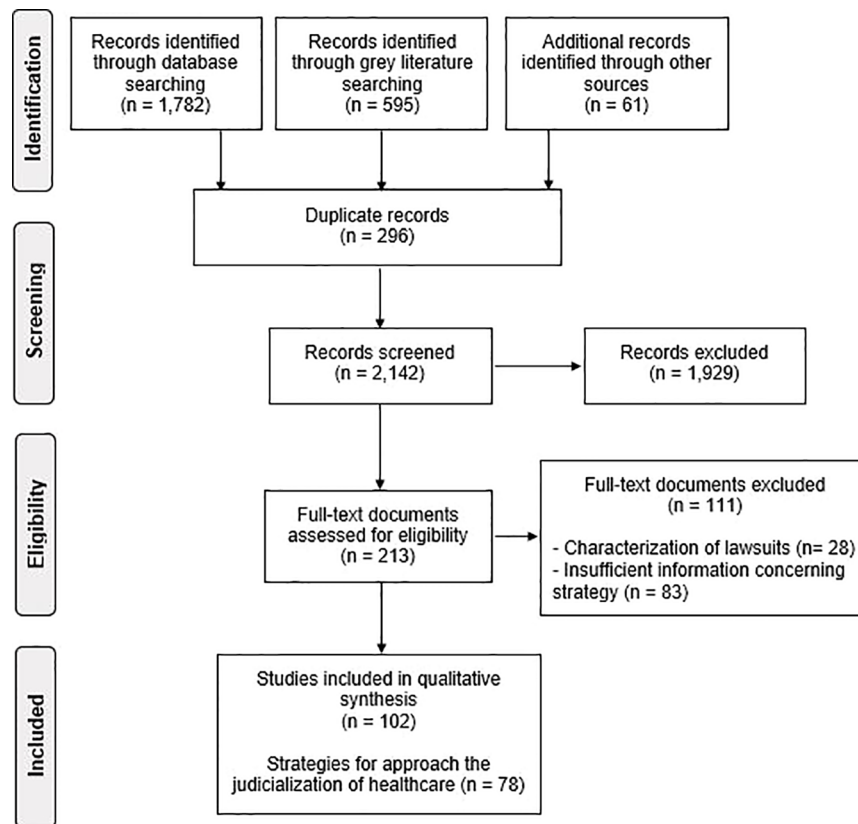


FIGURE 1 | Flow diagram for the scoping review process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Toma et al., 2017). Of the at least six implementations of Alternative dispute resolution strategies found where the public defender's office is present, it acts as a mediator (Reis, 2011; Pereira, 2012; Assis, 2015; Galliez, 2015; Secretaria de Estado da Saúde do Estado do Maranhão, 2015; Nunes, 2016; Ringeisen, 2016; Secretaria Estadual de Saúde, 2016; Bittencourt, 2017; Cotrim, 2017; Júnior, 2017; Sant'Ana, 2017; Imprensa da DPE/RN, 2019).

Conflict mediation is a dispute resolution strategy that utilizes negotiation facilitated or instigated by a qualified practitioner, intended to reduce or avoid litigation in general (Conselho Nacional de Justiça, 2016a). This process has recently been adapted to better suit the demands for health care technologies and is currently recommended by the Civil Procedure Code, updated in 2015 (Brasil, 2015). It is also presented as one of the options for approach health care judicialization in a synthesis of evidence for health policy (Ministério da Saúde, 2019a). This measure, when it results in agreements between the stakeholders, reduces the costs and expenses associated with the judicialization of health care (Conselho Nacional de Justiça, 2016a).

Some of the reports argue that inter-institutional dialogue facilitates an out-of-court settlement as well as being a cheap,

effective and swift strategy (Asensi and Pinheiro, 2015; Instituto de Ensino e Pesquisa, 2019). According to the reported data, the percentage of claims resolved using alternative dispute resolution methods ranged from 26% (Imprensa da DPE/RN, 2019) to 90% (Yoshinaga, 2011; Henrique et al., 2013; Vasconcellos, 2015), but no evidence was found on exactly which method has the best overall effectiveness in resolving health care conflicts.

Technical Support to the Judiciary

Strategies based upon the use of technical support centers in support of the judiciary seem to have arisen from Rio de Janeiro's experience in 2009 with the 'Technical Advisory Center' (Silva, 2012). Subsequently, the National Council of Justice (CNJ, in Portuguese) recommended that such centers be established in all courts which deal with health care demands. The establishment of these centers rapidly expanded across the country in two waves: in 2012, after the CNJ Recommendation No. 31 of March 30, 2010 (Conselho Nacional de Justiça, 2010a), and in 2016, following CNJ Resolution No. 238 of September 6, 2016 (Conselho Nacional de Justiça, 2016b).

Centers that provide such technical support to the judiciary are usually denominated with one of two common names:

TABLE 1 | Categorization of institutional strategies implemented to approach the judicialization of health care.

Category	Explanation
Legislation	
Alternative Dispute Resolution	The consensual settlement of conflicts is provided for in Law No. 13,105 of March 16, 2015 (WHO Regional Office for the Western Pacific, 2004) of the Brazilian Civil Procedure Code, which decrees in its paragraphs 2 and 3 of article 3 that conciliation, mediation and other methods of consensual dispute resolution should be encouraged by judges, lawyers, public defenders and prosecutors, including during the course of the judicial process, and should also be promoted by the State whenever possible.
Technical support to the judiciary	This category encompasses the technical support centers for the judiciary and services that provide technical reports on health care technologies. It is based on the Resolution of the National Council of Justice (CNJ) No. 238 of September 6, 2016 (Health Metrics Network & World Health Organization, 2008), which establishes the creation of Technical Support Centers for the Judiciary, > made up of health professionals, to prepare opinions based upon the best available evidence; and, CNJ Recommendation No. 31 of March 30, 2010 (Ribeiro et al., 2004), which recommends that courts take steps to better support judges and other legal operators to ensure greater efficiency in resolving legal claims involving health care.
Compliance with court orders	Category based on Law No. 13,105, of March 16, 2015, of the Civil Procedure Code (WHO Regional Office for the Western Pacific, 2004), explains in its paragraphs 1, 2 and 3 of Article 203 that the pronouncements or declarations of the resolutions taken by the Judge shall consist of: sentence—ends the cognitive phase of the common procedure and extinguishes the execution; interlocutory decision—is any judicial pronouncement of a decisional nature that does not fall as a sentence; or orders—other pronouncements practiced in the process, of office or at the request of the party. These resolutions must be enforced by the judicialized institutions under penalty of fines, seizing of funds or imprisonment of the institutional representative.
Administrative proceeding	This category is based on Law No. 9,784, of January 29, 1999 (Conselho Nacional de Justiça, 2016b), which regulates the administrative proceeding within the Federal Public Administration, in its articles 5, 6 and 7, defines that the administrative proceeding must be carried out subsequent to a request from the interested party by means of a letter or standardized form with the following data: I—administrative body or authority to which it is addressed; II—identification of the person concerned or who represents him; III—domicile of the applicant or place to receive communications; IV—formulation of the request, with statement of the facts and their grounds; V—date and signature of the applicant or his representative. The public servant should advise the interested party of any problems and may not unreasonably refuse to receive the documents. The administrative proceeding is also present at the state and municipal levels.
Defense of the public authority	Presidential Decree No. 7,392, of December 13, 2010 (Conselho Nacional de Justiça, 2010a), which approves the regimental structure and the organization of commission positions of the Attorney General of the Union (AGU); defines in its annex I that the AGU is the institution that represents and defends the Union, judicially and extra judicially, through legal advice and legal processing in service to the Executive Power. The Federal Attorney General's Office performs such functions over federal autarchies and foundations, the State Attorney General's Office and the Municipal Attorney General's Office act within the State and municipal governments, respectively.
State Health Committee	State health committees are provided for in CNJ Resolution No. 238 of September 6, 2016 (Health Metrics Network and World Health Organization, 2008), which provides for the establishment and maintenance of State Health Committees by the Federal Courts and Regional Courts; and, CNJ Resolution 107, of April 6, 2010 (Brasil, 2015), which states that these committees have the same duties as those for the National Executive Committee. It is noteworthy that such committees should propose concrete and normative measures aimed at the prevention of judicial conflicts, define strategies on health law issues and assist the courts in the creation of Judiciary Technical Support Centers. In addition, each committee should have multi-professional representation which, at a minimum, includes of Magistrates, health care managers, and other participants in the Health and Judicial System.
Recommendations for qualifying health services	
Organization of Assistance	"The organization of care is based on the ordering of health care management, informed by local situations as well as municipality as a whole, responding to the needs of the population, either within the scope of Primary Health Care/Family Health or specialized attention at all levels of resolution" (Siqueira, 2015). This category includes any and all strategies implemented with a primary focus on the planning, organization and management of services provided to the population and the pharmaceutical care cycle (selection, procurement, distribution, storage, dispensing).
Computerized Information System	Information and communication technology are a set of instruments consisting of computers, software, data capture devices, wireless communication devices, and local and long-distance networks that move information. It also includes the people who design, implement and support these tools and the information system (Descritores em Ciência da Saúde (DeCS), 2017). An information system is a tool that provides information support for the decision-making process at each level of an organization (Holloway and Green, 2003). In this context, a computerized information system is a system that provides information about the citizen and the provision of services and/or to manage health and/or legal demands using information and communication technology.
Pharmacy and Therapeutics Committee	The Pharmacy and Therapeutic Committees (Asensi and Pinheiro, 2015) are forums that bring together everyone involved in drug-use decisions at any level within a healthcare system. Its role is to develop drug policies, in addition to having a technical-advisory character to the health and administrative teams for issues related to the Drug Policy and pharmaceutical assistance. It is responsible for the evaluation and selection of products which compose drug formularies and also for the development of clinical protocols and therapeutic guidelines.

'Technical Health Chamber' (Costa, 2014; Tribunal de Justiça do Estado de Alagoas, 2016) and 'Judiciary Technical Support Center (NAT-Jus, in Portuguese)' (Tribunal de Justiça do Estado do Pará, 2013; Costa, 2014; Barros, 2016; Comitê Estadual das Demandas da Saúde do Rio Grande do Norte, 2016; Farias, 2016; Tribunal de Justiça do Estado da Bahia, 2017a; Tribunal de Justiça do Estado da Bahia, 2017b; Tribunal de Justiça do Estado do Ceará, 2017c; Ascom, 2018; Henrique et al., 2018; Mariano et al., 2018; CEMAS, 2019). However,

there are centers with other names (Castro, 2012; Boldrin, 2014) that also provide advice or technical reports on health care technologies to the judiciary (Departamento de Informática, 2015; Duarte, 2017).

The judiciary support services identified in this review were implemented in courts at the state level, with the exception that two of these centers were located within teaching hospitals (Perin et al., 2008; Boldrin, 2014; Duarte, 2017) and one at a municipal health department (CEMAS, 2019).

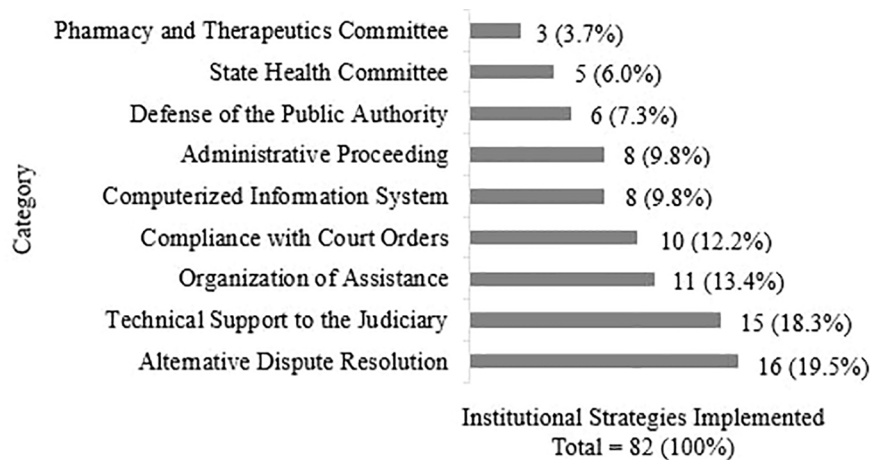


FIGURE 2 | Number of institutional strategies implemented to approach the judicialization of health care by category.

These centers usually have technical cooperation agreements with the health departments, which provide full-time or part-time health professionals for the purpose of preparing advises or technical reports. There are three exceptions to the above: two of the services studied used internal human resources from the court itself (Departamento de Informática, 2015; Tribunal de Justiça do Estado de Alagoas, 2016), and a technical advisory center was hired by the Minas Gerais State Department of Health to clarify the judges' doubts (Duarte, 2017).

Most of the strategies in this category involve a multi-professional team, with some centers open during all hours that the court is functioning, while others use an 'on duty' or 'on-call' scheme (Castro, 2012; Silva, 2012; Costa, 2014; Guimarães and Palheiro, 2015; Souza, 2016; Tribunal de Justiça do Estado de Alagoas, 2016; Tribunal de Justiça do Estado da Bahia, 2017a; Tribunal de Justiça do Estado da Bahia, 2017b; Ascom, 2018).

For this purpose, these centers are equipped with standardized documents and technical reports for use, as well as an electronic communication infrastructure and online systems allowing them to respond to requests within 24 h (regardless of the day of the week) or up to five business days.

Its *modus operandi* resembles the existing rapid response services that are available in some countries, where the request for information is processed and answered in a short time (Haby et al., 2016).

Although there exist comparative studies between different NAT-Jus models (Duarte, 2017) and publications describing their history, activities, and service provision (Arruda, 2017; Mariano et al., 2018), there are few studies that have measured the effectiveness of these efforts (Silva, 2012; Instituto de Ensino e Pesquisa, 2019). In addition, some studies and documents reported poor demand for services offered by NAT-Jus (Silva, 2012; Barros, 2016; Tribunal de Contas da União, 2017; Instituto de Ensino e Pesquisa, 2019).

Organization of Assistance

The way health service delivery is organized is a determining factor in access to health services goods and services. For this reason, the organizational structure is the focus of attention of the Pan American Health Organization (Pan American Health Organization, 2017), World Health Organization (World Health Organization, 2010a; World Health Organization, 2010b); and the Brazilian Ministry of Health (Ministério da Saúde, 2009; Ministério da Saúde, 2016a; Ministério da Saúde, 2016b).

In this scoping review, it was found that 13.4% of the strategies had as their main objective the reorganization of the care provided: improving service (Mauad et al., 2009; Tavares et al., 2010; Conselho Federal de Farmácia, 2013; Conselho Federal de Farmácia, 2016; Secretaria da Saúde do Município de Ribeirão Preto, 2017); implementing specialized services (Tavares et al., 2009; Tavares et al., 2010; Ungaro, 2011; Secretaria da Saúde do Município de Ribeirão Preto, 2017; Chayamiti, 2018); investing in training and capacity building (Governo do Estado do Espírito Santo, 2007; Tavares et al., 2009; Tavares et al., 2010; Oliveira, 2018); and/or organizing existing services (Bahia et al., 2005; Pontarolli et al., 2015; Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça, 2015; Simões, 2015; Schulze, 2018).

Reports and data from the National Council of Justice from the State of Espírito Santo indicate that these strategies resulted in more agile and effective procedures, reducing the number of active lawsuits, and resolving the cases of unmet court orders (Oliveira, 2018; Instituto de Ensino e Pesquisa, 2019). In addition, savings have been generated through the rational use of high-cost medications resulting from dose sharing and medical supervision in patients with atorvastatin prescription or indication for atorvastatin use (Tavares et al., 2009; Tavares et al., 2010).

In the other Brazilian states, the implementation of strategies focused on the organization of assistance generated important results, such as: i. the detection and arrest of a group of people

who were profiting from the sale of biological medicines through lawsuits against public institutions (Sanchez et al., 2008) by monitoring, evaluating and detecting possible frauds in lawsuits (Ungaro, 2011); ii. the decrease in the number of judicial penalties, imposed on both the State government and individual managers (Araújo, 2014), resulting from the restructuring and reallocation of services and professionals from the technical, legal, administrative and assistance sectors in the same physical space (Assis, 2015); and iii. more efficient communication between the actors involved and faster service delivery, using integrated computer systems (data and information control) to guide the reorganization of health service demand response flows (Bahia et al., 2005; Pontarolli et al., 2015; Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça, 2015; Schulze, 2018).

These results suggest that the institutional organization probably helps minimize the judicialization of health care. However, as of 2015, no strategy specifically focused on the organization of assistance was detected, although at that time several Brazilian municipalities experienced institutional disorganization in their health services, especially in the area of pharmaceutical care (Costa E. A. et al., 2017; Costa K. S. et al., 2017; Gerlack et al., 2017; Leite et al., 2017).

Compliance With Court Orders

All 10 of the strategies in this category were implemented by health care departments using the existing human resources already available within the service itself. These departments centralized the control and monitoring of court proceedings, including information about plaintiffs and inventories, and the dispensing of medicines, special diets and pharmaceutical materials. They have set protocols and procedures of attendance, usually performing both the initial screening of judicial process to verify the existence of, and the possibility of referral of the complainant to, an already existing service within Brazilian Unified Health System (SUS, in Portuguese) and verifying the need to prepare a technical report for the defense of the public authority.

There exist other services that also assist with extrajudicial demands (Junior, 2008; Tavares et al., 2010; Secretaria de Estado da Saúde de Alagoas, 2013; Macêdo et al., 2015; Guimarães and Palheiro, 2015) and computerized services (Junior, 2008; Tavares et al., 2010; Garofalo et al., 2012; Conselho Federal de Farmácia, 2013; Tribunal de Justiça de Mato Grosso do Sul, 2013; Guimarães and Palheiro, 2015; Pontarolli et al., 2015; Nantes and Dobashi, 2015; Barros, 2016; Secretaria de Estado de Saúde do Mato Grosso do Sul, 2018).

The reports of these strategies indicate that management planning and the structure and organization of both informational and operational activities have led to a more rapid service (Bahia et al., 2005; Junior, 2008; Secretaria de Estado da Saúde do Paraná, 2008; Tavares et al., 2010; Garofalo et al., 2012; Conselho Federal de Farmácia, 2013; Guimarães and Palheiro, 2015; Pontarolli et al., 2015) and in some cases have decreased the expenses associated with

judicialization (Junior, 2008; Tavares et al., 2010; Garofalo et al., 2012; Guimarães and Palheiro, 2015).

Two strategies in this category used financing arrangements in order to comply with budgetary burden of court orders. These strategies, however, proved to be insufficient to meet all demands quickly (Pereira, 2012; Tribunal de Justiça de Mato Grosso do Sul, 2013; Simões, 2015; Secretaria de Estado de Saúde do Mato Grosso do Sul, 2018).

Computerized Information Systems

The use of computerized information systems integrated with inventory controls intensified in 2005 (Sanchez et al., 2008; Pontarolli et al., 2015).

Some institutions have chosen to adapt their medication control systems, using the specialized component of pharmaceutical care, in order to use these systems concurrently with their control of court demands: 'Medication Administration System' (Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça, 2015; Defensoria Pública do Estado do Rio Grande do Sul, 2019); 'High Cost Drug Management System' (Conselho Federal de Farmácia, 2013; Pontarolli et al., 2015); 'National Pharmaceutical Assistance System (Hórus System)' (Reis, 2011; Ministério da Saúde, Assistência Farmacêutica, 2013). This practice of adaptation has been shown to be more efficient than the development of in-house controls or systems (Garofalo et al., 2012; Pontarolli et al., 2015).

Other institutions have opted to set up systems to standardize processes, reduce miscommunication, and streamline actions and compliance with court orders. The systems that have been developed, such as 'Coordination of SUS Strategic Demands System' (Naffah-Filho et al., 2010; Siqueira et al., 2018) and 'National Register of Opinions, Notes and Technical Information (e-NAT-Jus, in Portuguese)' (Secretaria-Geral e Departamento de Gestão Estratégica, 2017) contain records of legal opinions and technical information concerning various health technologies. This information is available to the registered user. The 'Legal Control System' (Sanchez et al., 2008; Yoshinaga, 2011), 'Coordination of SUS Strategic Demands System' (Naffah-Filho et al., 2010; Siqueira et al., 2018) and the 'Health Chamber System' (Guimarães and Palheiro, 2015) store information pertinent to court proceedings, such as the plaintiff's data, dispensations made, tracking information for the entire process and the monitoring of judicial process.

Through the 'Electronic Portal of Judicial Subpoena' or 'Online Judicial Order' (Tribunal de Justiça do Estado do Espírito Santo, 2018; Secretaria de Estado da Saúde do Espírito Santo, 2018), the judiciary electronically forwards any and all documents related to public health care actions in order to promote compliance by the health department. The 'Extrajudicial Health Procedure' (Bittencourt, 2017) is an online system used for health care mediation, technical clarifications, and administrative analysis of extrajudicial requests.

Computerized information technologies are now indispensable tools in institutional management, as they simplify many administrative tasks, help control inventories, track user data along with their consumption history, facilitate

communication, provide evidence, support decision-making, and aid in the rationalization of available resources (Conselho Nacional de Secretários de Saúde, 2011). These technologies are both recommended and incentivized by the World Health Organization (WHO Regional Office for the Western Pacific, 2004; Health Metrics Network and World Health Organization, 2008) and the Ministry of Health (Brasil, 2016).

Both the Ministry of Health and the National Council of Justice provide computerized information systems free of charge to interested institutions: 'Coordination of SUS Strategic Demands System' (Siqueira et al., 2018) and 'Hórus system' (Ministério da Saúde, Assistência Farmacêutica, 2013), and 'e-NAT-Jus' (Secretaria-Geral e Departamento de Gestão Estratégica, 2017), respectively. Other control systems may also be obtained in the same way, upon request and contract with the health departments (Guimarães and Palheiro, 2015; Pontarolli et al., 2015).

Administrative Proceeding

In the strategies involving an Administrative proceeding, the service provision is performed upon request using a standardized form, along with a prescription, medical report and complementary exams. The request can be registered in a computerized system or as a hard copy, and the applicant receives a protocol document for tracking the process. The request may be evaluated by a committee of experts, or merely analyzed as to the feasibility of the service. The response time can vary from 24 h to 45 days (Teixeira, 2011; Yoshinaga, 2011; Conti, 2013; Henrique et al., 2013; Secretaria de Estado da Saúde de Alagoas, 2013; Asensi and Pinheiro, 2015; Guimarães and Palheiro, 2015; Macêdo et al., 2015; Toma et al., 2015; Farias, 2016; Souza, 2016; Núcleo de Comunicação Social, 2017; Secretaria da Saúde do Estado do Amapá, 2017; Toma et al., 2017; Reis, 2018; CEMAS, 2019; Ministério Público do Estado de São Paulo, 2019; Secretaria de Estado da Saúde do Estado de São Paulo, 2019).

Typically, health care services also provide information and clarification on access to medicines within the SUS, and requests for products or services on the SUS funding list are forwarded to the individual units responsible for that specific type of care. They are managed by the health departments, except the 'Judicial Demand Response Center' (Teixeira, 2011) which is under the responsibility of the Public Defender's office.

Addressing health care demands through Administrative proceedings enables the detection of failures in access to SUS and health care technologies which should be evaluated for possible incorporation into SUS. This strategy also helps identify legitimate and just demands for health care technologies, where the individual has exhausted all the existing therapeutic possibilities within SUS to treat their disease or injury (Siqueira, 2015).

The reports of these strategies show that there have been annual increases in health care technology request as well as increases in administrative resolutions (Yoshinaga, 2011; Conti, 2013; Macêdo et al., 2015). All the strategies in this category have reported a decreasing number of health care disputes. However, these data should be analyzed with caution, as what was

calculated was based upon the number of administrative proceeding that actually turned into legal proceedings, so it is not possible to know from these reports if all those who applied for administrative proceeding would file a lawsuit if the strategy did not exist.

Thus, there is a need for studies that analyze whether this strategy has actually reduced the number of health care disputes and reduced inequalities in access. Studies are also needed to determine if these strategies are cost-effective and rational, because in Administrative proceedings, it is the manager who determines the items to be offered by the institution, and the manager's decision is partially based upon purchase volume to decrease per-unit costs (Siqueira, 2015) and is not necessarily based upon the effectiveness of a product (Santos-Pinto, 2013).

Defense of the Public Authority

When a public health institution is the defendant in a lawsuit, it is defended in court by attorneys general (Brasil, 2010; Advocacia-Geral da União, 2012), supported by the associated services which provide the necessary technical information (Bandeira et al., 2009; Yoshinaga, 2011; Pereira, 2012).

According to the reports of the strategies in this category, the specialization of attorneys general in health or health law, or of health professionals in the area of law, has generated speed and competence in the defense of the public authority (Sanchez et al., 2008; Yoshinaga, 2011; Pontarolli et al., 2015; Secretaria de Estado da Saúde do Estado de Alagoas, 2015; Toma et al., 2017; Faglioni and Castelo, 2018).

State attorneys who are specialized in health law and who act directly in defense of the state department of health were identified the municipalities of Curitiba/PR, São Paulo/SP and Maceió/AL (Sanchez et al., 2008; Yoshinaga, 2011; Pontarolli et al., 2015; Secretaria de Estado da Saúde do Estado de Alagoas, 2015; Toma et al., 2017; Faglioni and Castelo, 2018). In addition, some reports identified others who perform the administrative function of evaluating public contracts and tenders (Secretaria de Estado da Saúde do Estado de Alagoas, 2015). State prosecutors have entered into partnerships with health secretariats to form integrated teams, supplemented by the use of technical reports prepared by the technical health areas (Sanchez et al., 2008; Yoshinaga, 2011; Secretaria de Estado da Saúde do Estado de Alagoas, 2015; Toma et al., 2017).

These attorney offices also have implemented computerized, standardized and less bureaucratic procedures (Sanchez et al., 2008; Yoshinaga, 2011; Pontarolli et al., 2015; Toma et al., 2017; Faglioni and Castelo, 2018) which facilitate the detection of fraud involving the judicialization of health care (Ungaro, 2011) and the identification of lawsuits where state defense is most likely to succeed (Pontarolli et al., 2015; Faglioni and Castelo, 2018).

Like state prosecutors, those in technical health areas have also sought to specialize in the legal arena, in order to issue better-prepared reports and technical advice in a language accessible to magistrates and prosecutors. Three support services that issue this type of document were detected and all have at least 10 years of existence: 'Technical Advisory Center of Minas Gerais State Department of Health' (Pereira, 2012; Pereira and Carneiro, 2012), 'Technical Report prepared by the

Coordination of SUS Strategic Demands' (Sanchez et al., 2008; Naffah-Filho et al., 2010; Yoshinaga, 2011; Siqueira et al., 2018), and 'Technical Support Center in Health for the Attorney Office' (Bandeira et al., 2009; Costa, 2019).

These services are located in health departments and have standardized routines and procedures. They have multi-professional teams including doctors and pharmacists, and work in conjunction with the attorney office. They also use computerized and integrated systems that manage both inventories and lawsuits, helping to avoid duplicate care among health care institutions (Sanchez et al., 2008; Bandeira et al., 2009; Naffah-Filho et al., 2010; Yoshinaga, 2011; Pereira, 2012; Pereira and Carneiro, 2012; Siqueira et al., 2018; Costa, 2019).

Such measures have reduced bureaucracy, streamlined responses to judicial demands, and virtually extinguished punitive measures against the health department due to judicial noncompliance (Sanchez et al., 2008; Bandeira et al., 2009; Naffah-Filho et al., 2010; Yoshinaga, 2011; Costa, 2019). One exception is in the State of Minas Gerais, where managerial, structural and behavioral problems increased the number of health claims and needed to be resolved separately (Pereira, 2012).

State Health Committee

The Health Forum, established by Resolution CNJ No. 107/2010 and coordinated by the National Executive Committee, aim to monitor and resolve demands for health care technologies (Conselho Nacional de Justiça, 2010b). The National Committee is composed of the State health committees belonging to the Courts of Justice of the individual States.

Of the 27 State Committees allotted for by legislation, only seven committees are listed on the CNJ website³. Sant'Ana (2017) identified six acting committees, three of which differ from those listed on the CNJ website (Sant'Ana, 2017).

However, this scoping review found data sufficient to characterize only five of them: Rio Grande do Sul (Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça, 2015; Schulze, 2018), Paraná (Pontarolli et al., 2015), Tocantins (Farias, 2016; Farias et al., 2016; CEMAS, 2019), Mato Grosso do Sul (Tribunal de Justiça de Mato Grosso do Sul, 2013; Nantes and Dobashi, 2015) and Maranhão (Diniz, 2015; Tribunal de Justiça do Maranhão, 2018).

These committees, composed of at least 12 members, make inter-institutional agreements and are multi-professional, with representatives from the areas of health care, law and the public at large. Except for the Maranhão Committee, the reports indicate that they also promote educational lectures and training to their members, and issue statements and recommendations to the legal area. Only three committees hold monthly meetings, regional meetings and offer training (Tribunal de Justiça de Mato Grosso do Sul, 2013; Pontarolli et al., 2015; Comitê Executivo do Fórum Nacional do Judiciário

para Saúde do Conselho Nacional de Justiça, 2015; Nantes and Dobashi, 2015; Schulze, 2018).

Three committees have reports on their activities: i. Rio Grande do Sul, which implemented systemic planning and management actions in order to organize health care in the state. Through these actions, Rio Grande do Sul was able to reduce the number of both new and active judicial actions, as well as to reduce the amount of funds blocked by the judiciary (Schulze, 2018); ii. Mato Grosso do Sul encouraged the implementation of specialized health services and the production of clinical protocols and discovered that meetings and regional training programs produced better results than other strategies used (Tribunal de Justiça de Mato Grosso do Sul, 2013); iii. According to Diniz (2015), between 2012 and 2015 the committee in Maranhão was without human resources to manage it and did not generate any approximation between the Judiciary and the Executive Powers, to the point that most of the magistrates of the state were unaware of the committee's duties (Diniz, 2015).

The State health committees, when they have active members, appear to improve communication among the various stakeholders involved in health care judicialization, in addition to monitoring and qualifying health services (Tribunal de Justiça de Mato Grosso do Sul, 2013; Pontarolli et al., 2015; Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça, 2015; Nantes and Dobashi, 2015; Farias, 2016; Farias et al., 2016; Schulze, 2018; CEMAS, 2019).

Pharmacy and Therapeutic Committee

The use of Pharmacy and therapeutics committees is a strategy that has been recommended by the World Health Organization (Holloway and Green, 2003) since 2003. These committees exist in hospitals, in various municipalities, and at the state and the federal level in Brazil.

The Pharmacy and therapeutics committee is a support body directly linked to the management board of health care institutions. It is responsible for the elaboration and updating of reigning protocols and therapeutic guidelines for clinical practice within the institution, and for the selection, standardization and incorporation of health care technologies and medication. It is made up of a multi-professional team and avails itself to the expertise of *ad hoc* consultants for specific or specialized topics. It has regular meetings at the health departments headquarters and takes an evidence-based approach to the assessment of health care technology (Tavares et al., 2009; Tavares et al., 2010; Secretaria da Saúde do Estado de São Paulo, 2012; Toma et al., 2015; Simabuku et al., 2015; Secretaria de Estado da Saúde do Estado de São Paulo, 2019).

In addition to these activities, the committees also prepare technical reports by legal (Simabuku et al., 2015) and health professionals and provide information on health care technologies upon request, *via* e-mail or official letter. This service can be available to the public (Secretaria da Saúde do Estado de São Paulo, 2012; Toma et al., 2015; Secretaria de Estado da Saúde do Estado de São Paulo, 2019), but in some cases is available only to the pharmacy responsible for dispensing specialty medication (Tavares et al., 2009; Tavares et al., 2010).

³ Available form: <http://www.cnj.jus.br/programas-e-acoeforum-da-saude/iniciativas-dos-comites-estaduais>

These technical reports are provided for the clarification of the author, as well as for the defense of the public power, either as an extrajudicial strategy or in the course of judicial proceedings.

Some reports indicate that the judicialization of health care has resulted in the incorporation of new technology and in the reduction of judicial processes related to such incorporation (Tavares et al., 2009; Tavares et al., 2010; Yoshinaga, 2011; Simabuku et al., 2015), a fact also found in the study by Messeder et al. (2005). However, in Brazil the incorporation of new technologies is still a slow process and with a limited impact on the judicialization of health care (Siqueira, 2015).

Interrelationship and Interdependence Between Categories

Some categories have activities in common with other categories, such as: extrajudicial (prevention of judicial conflicts) and/or judicial (action based on the filing of the lawsuit); production and provision of technical information to assist in judging health care technology applications; provision of health care products, namely medicines, pharmaceuticals and diets; health care management (service monitoring, standardization of health care technologies, improvements in infrastructure, health care delivery and computerization of services) (Table 2).

It was observed that there are strategies which involve, in a harmonious and shared manner, services originating from different sectors working in a single physical space, such as the 'Health Dispute Resolution Chamber' (Tavares et al., 2014; Guimarães and Palheiro, 2015; Souza, 2016; Sant'Ana, 2017) and the 'Judicialization of Health Care Assistance Center' (Assis, 2015; Simões, 2015), in order to reduce bureaucracy and provide faster and more resolute services.

A deeper analysis of the categorized strategies allows us to verify activities interrelate between some of them: i. complementary activities: the provision of technical advice, provided by the Pharmacy and therapeutics committee, to the

services that act with Administrative proceeding and defense of the public authority; ii. services resulting from a cause-effect relationship: compliance with court decisions favorable to the plaintiff due to the complainant's rejection of the proposals resulting from Administrative proceeding and/or Alternative dispute resolution methods; iii. synergistic strategies: use of computerized information systems across all categories, whether shared or not, as a management tool (Figure 3).

DISCUSSION

Main Findings

The 78 institutional strategies implemented to approach the judicialization of health care in Brazil were divided into nine categories with extrajudicial or judicial action, or both, interrelated in a complementary or synergistic manner.

The proposed categories correspond to the activities provided for in both legislation (Brasil, 1999; Brasil, 2010; Conselho Nacional de Justiça, 2010a; Conselho Nacional de Justiça, 2010b; Brasil, 2015; Conselho Nacional de Justiça, 2016b) and in recommendations to improve health care services (Holloway and Green, 2003; World Bank, 2007; Health Metrics Network and World Health Organization, 2008; Ministério da Saúde, 2009; Brasil, 2016; Ministério da Saúde, 2016b). The application of these legal provisions and recommendations are not restricted to a specific area of activity covered, in that any manager can, regardless of their sector of involvement (legal or health), appeal to these provisions.

It was observed that the categories which represent the prevention of conflict appear to be balanced by those categories that represent actions taken after the process of judicialization; the categories of Alternative dispute resolution, Technical support to the judiciary, Organization of assistance and Compliance with court order are those with the greatest number of strategies implemented.

TABLE 2 | Characteristics of categories of institutional strategies implemented to approach the judicialization of health care in Brazil.

Category	Created and implemented according to legislation	Extrajudicial approach	Judicial approach	Production and supply of technical information	Health Products Supply	Health Care Management
Technical support to the judiciary	✓		✓	✓		
Alternative dispute resolution	✓	✓	✓			
Administrative proceeding	✓	✓			✓	✓
Compliance with court orders	✓		✓		✓	✓
State health committee	✓	✓				✓
Defense of the public sector	✓		✓	✓		
Pharmacy and therapeutics committee		✓	✓	✓		✓
Organization of assistance		✓	✓		✓	✓
Computerized information system		✓	✓	✓		✓

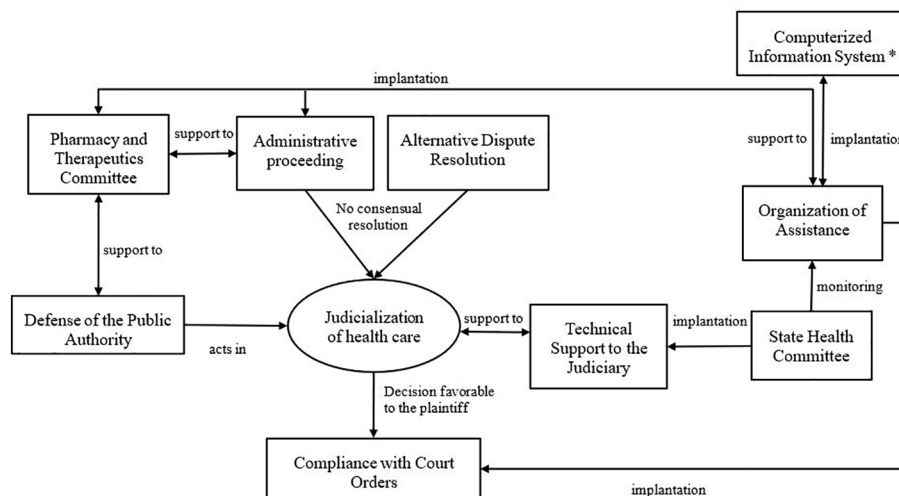


FIGURE 3 | Simplified schematic of the interrelationships existing among categories of strategies for approach the judicialization of health care. *The computerized information system can provide support for all categories of strategies.

The findings of this review show that public institutions have only implemented those strategies governed within the public management policies and guidelines (Ministério do Planejamento Orçamento e Gestão, Secretaria de Gestão Pública, 2007; Ministério do Planejamento Orçamento e Gestão, Secretaria de Gestão Pública, 2014). This is because the failure of a public administration manager to comply with these precepts is considered as administrative misconduct (Brasil, 1992).

The Relationship Between the Categories of Strategies With the Feasibility of Legal and Health Systems

It was found that the strategies implemented in public institutions to approach the judicialization of health care in Brazil are strongly linked to the existence of national legal provisions that recommend their implementation and provide them with legal support.

The legal framework is an important factor that facilitates the implementation of these strategies, because it allows the existing services of the public sector to meet various types of demands while permitting that these services be expanded to approach the judicialization of health care, as verified by the strategies in the categories of Administrative proceeding, Defense of the public authority and Alternative dispute resolution.

The findings of this scoping review indicate that, although Brazil is not yet a member of the Organisation for Economic Co-operation and Development (OECD), the Brazilian Public Administration is adopting several OECD recommendations to improve the quality of public service delivery (Organisation for Economic Co-operation and Development, 2018) in order to align with international policies. As well as the Brazilian legal area that is adapting to World Bank recommendations to

improve judicial operations in the court system (World Bank, 2004).

These actions can contribute to minimize or solve the existing problems in Public Administration, evidenced by the judicialization of health care. This includes the citizen's difficulty in accessing goods and health care due to health technologies that do not exist or are not available in the health system, delays in the time required to serve the user, excessive bureaucracy and inefficient communication; the need to generate information and control judicial demands to avoid fraud and duplication of service.

However, not all institutions appear to be able to implement strategies stemming from legal norms, such as NAT-Jus and the State health committee, as there are likely to be unidentified barriers that prevent their implementation, despite the threat of legal enforcement.

In the area of health care, the alignment of the categories with the recommendations concerning adequacy and best practices in public management (Ministério do Planejamento Orçamento e Gestão, Secretaria de Gestão Pública, 2014) and health care systems (World Health Organization, 2010a; Pan American Health Organization, 2017), elaborated by Pan American Health Organization (Pan American Health Organization, 2017), World Health Organization (World Health Organization, 2010a; World Health Organization, 2010b), Ministry of Health (Ministério da Saúde, 2009; Ministério da Saúde, 2016a; Ministério da Saúde, 2016b) and the National Council of State Health Secretaries (Conselho Nacional de Secretários de Saúde, 2011), is useful in assisting in the implementation of strategies focused on the structure of services and the improvement of human resources.

Although strategies in the categories of the Organization of assistance and Computerized information system originate from

the recommendations of health institutions, they have universal characteristics and can be used in any field.

The categories of strategies include a combination of strategies and activities implemented simultaneously to approach the judicialization of health care. This is because public institutions are integrated in the same socio-cultural, legal and political context, where one action affects the other (Handtke et al., 2019) inside and outside the institution.

The simultaneous implementation of a series of practices to organize and improve the provision of services are international recommendations (World Bank, 2004; Organisation for Economic Co-operation and Development, 2018), as one activity acts to complement the other and the change in organizational culture must occur throughout the institution.

Thus, it is possible to affirm that, in order to approach the judicialization of health care, systemic planning is necessary in order to both evaluate the vulnerable aspects in Public Administration that should be prioritized for the implementation of strategies, and identify which strategies are most likely to succeed within the local context.

Otherwise, strategies that are destined to fail may be implemented due to lack of supporting services, a fact which could have been identified if a more systematic perspective had been taken. For example, defense of the public sector has a poor chance of being successful if there are no support services to provide the necessary technical information. Likewise, the implementation of services using costly technologies may prove impossible if efficient inventory control is not present.

Strengths and Limitations of the Study

This study is the first to categorize, describe and analyze feasible and effectively implemented strategies in public institutions to approach the judicialization of health care in Brazil. The proposed categories are based on Brazilian legislation and both international and national recommendations for improving health services.

The Brazilian legislation used in this scoping review is in line with the OECD recommendations on the performance of public services (Organisation for Economic Co-operation and Development, 2018) and the World Bank on the performance of the courts system (World Bank, 2004). It is believed that the alignment of the strategies implemented in Brazil with the recommendations of the OECD and the World Bank facilitates and improves their understanding by various stakeholders.

Although this study used international recommendations strongly based on the best institutional practices, there was little data available on the effectiveness of the strategies implemented, therefore, it was not possible to analyze the impact of these strategies on the Brazilian judicial and health systems.

In addition, it was not possible to compare the strategies implemented in Brazil with those of other countries, as no comparable strategies were found because the subject adopted in this scoping review is rarely published in indexed journals.

Despite these limitations, this scoping review contributes to the systematization of knowledge by facilitating its incorporation into actual management practice and enabling decision makers to properly assess the implementation of one, several or all strategy categories.

Thus, it is expected that countries with governmental systems and with judicialization of health care like Brazil, especially those belonging to Latin America and the Caribbean, can benefit from the proposed categorization.

It is known that the number of strategies presented in this review does not represent all strategies that have been implemented; many strategies encountered did not meet the criteria of inclusion due to the incompleteness of data concerning these strategies. However, it is unlikely that there are institutional strategies which do not fit in one of the proposed categories, as Public Administration is governed by the same principles and guidelines contemplated in the proposed categories, and any variance from these principles and guidelines would be construed as administrative misconduct.

Finally, some of the implemented strategies identified names, given by the institution, that did not indicate the actual activities performed. In these cases, the objectives and various supporting documents were analyzed in order to categorize them.

CONCLUSIONS

The nine categories of strategies proposed to approach health care judicialization interrelate in a complementary or synergistic way. These act both in the prevention of health care conflicts and after the filing of a lawsuit. These also can be used by any type of institution, regardless of the area of expertise.

The existence of legal provisions and recommendations facilitate the implementation of these strategies and services in public institutions, as they guide their structuring and execution. However, this legal support does not guarantee either implementation or success.

Implications for Public Officials

It is likely that managers in the areas of health care and law already have notions about some of the categories proposed in this review, as some of them are services that originally were used in Public Administration to meet various types of demands and only later were adapted to approach the judicialization of health care.

In addition, public officials interested in implementing such strategies should identify the areas where institutional management is most vulnerable; these areas may prove to be among the main causes of health disputes. Public officials should also analyze whether there is sufficient infrastructure to implement a given strategy.

The consideration of the above aspects may facilitate the choice, or prioritization, of feasible strategies to be implemented in the local context.

Implications for Researchers

There is a need for studies that better and more fully describe the strategies identified in this scoping review and that are able to assess their respective effectiveness.

The proposed categorization may be useful for further research on the strategies implemented in public institutions to approach the judicialization of health care.

Finally, the development of systematic reviews or policy briefs specific to each of the proposed categories may provide managers with important evidence and help identify those strategies which are most likely to succeed given the local context.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

SY, JB, and LL contributed conception and design of the study. SY and LL planned the study, performed data extraction and

analysis. SY wrote the first draft of the manuscript. SY, JB, SB-F, and LL wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2020.01128/full#supplementary-material>

REFERENCES

- Advocacia Geral da União (2009). *CIRADS*. Available at: http://www.agu.gov.br/page/content/detail/id_conteudo/97046 (Accessed April 6, 2019).
- Advocacia-Geral da União, Consultoria-Geral da União and Consultoria Jurídica junto ao Ministério da Saúde (2017). *Judicialização da saúde no âmbito da União em números: recursos extraordinários 566471 e 657718* (Brasília: Advocacia-Geral da União).
- Advocacia-Geral da União (2012). *Histórico da AGU Brasília*. Available at: https://www.agu.gov.br/page/content/detail/id_conteudo/200644 (Accessed June 26, 2019).
- Araújo, A. F. S. (2014). Judicialização da saúde em Minas Gerais: novas estratégias de enfrentamento: a criação do Núcleo de Atendimento à Judicialização da Saúde. *Cad Ibero-Amer Dir Sanit* 3 (2), 7. doi: 10.1590/1413-81232014195.17242013
- Arruda, S. C. (2017). Análise sobre a judicialização da saúde no Estado de Mato Grosso no período de 2011-2012. *Rev. Cadernos Ibero-Americanos Direito Sanitário* 6 (1), 25. doi: 10.17566/ciads.v6i1.308
- Ascom, T. J. B. A. (2018). *Núcleo de apoio técnico do judiciário: NAT-JUS reúne-se na assessoria especial da presidência II*. Available at: <http://www5.tjba.jus.br/portal/mais-uma-reuniao-do-nucleo-de-apoio-tecnico-do-judiciario-nat-jusfoi-realizada-na-assessoria-especial-da-presidencia-aep-ii-na-ultima-terceira-25-06-18/> (Accessed April 2, 2019).
- Asensi, F. D., and Pinheiro, R. (2015). *Judicialização da saúde no Brasil: dados e experiências* (Brasília: Conselho Nacional de Justiça).
- Assis, G. (2015). "Mediação sanitária: direito, saúde e cidadania," in *Conselho Nacional dos Secretários de Saúde. Direito à saúde. Para Entender a Gestão do SUS*, 1^ª ed. (Brasília/BR: CONASS).
- Bahia, G. O. M., Lamb, L., Nicoletti, R. H. A., Cataneli, R. C. B., and Luiz, V. R. (2005). "A política de medicamentos no Estado do Paraná," in *Conselho Nacional dos Secretários de Saúde. Relatório final do I encontro do CONASS para troca de experiências*. CONASS Documenta (Brasília/BR: CONASS).
- Bandeira, L. M., Bandeira, R. C., Costa, C. A., Santos, JBFMS, Silva, H. A., and Furtado, E. A. V. (2009). *A atuação do Núcleo de Apoio à Procuradoria Adjunta de Suporte à Saúde no município de Três Rios como um norte para a contenção saudável da judicialização em saúde*. Available at: <http://www.ideiasus.fiocruz.br/portal/index.php/banco-de-praticas> (Accessed April 6, 2019).
- Barros, L. D. (2016). *Judicialização do direito à saúde: uma análise acerca do fornecimento judicial de medicamentos no Estado de Pernambuco (dissertation/master's thesis)* (Recife: Universidade Federal de Pernambuco).
- Bittencourt, F. R. (2017). "Sistema PES: Procedimento Extrajudicial de Saúde," in *14ª edição do Prêmio Inovare; 2017 Dec 5, Supremo Tribunal Federal, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Boldrin, P. H. M. (2014). *A efetividade da Comissão de Análise de Solicitações Especiais da judicialização das políticas de saúde referentes às demandas*
- ajuizadas pela Defensoria Pública do Estado de São Paulo - Regional Ribeirão Preto (graduation monograph)* (Ribeirão Preto: Universidade de São Paulo).
- Brasil (1988). *Constituição da República Federativa do Brasil. Texto promulgado em 05 de outubro de 1988* (Brasília: Diário Oficial da União).
- Brasil (1990). *Lei nº 8.080, de 19 de Setembro de 1990* (Brasília: Diário Oficial da União).
- Brasil (1992). *Lei nº 8.429, de 2 de junho de 1992. Dispõe sobre as sanções aplicáveis aos agentes públicos nos casos de enriquecimento ilícito no exercício de mandato, cargo, emprego ou função na administração pública direta, indireta ou fundacional e dá outras providências* (Brasília: Diário Oficial da União).
- Brasil (1999). *Lei nº 9.784, de 29 de janeiro de 1999. Regula o processo administrativo no âmbito da Administração Pública Federal* (Brasília: Diário Oficial da União).
- Brasil (2010). *Decreto nº 7.392, de 13 de dezembro de 2010. Aprova a Estrutura Regimental e o Quadro Demonstrativo dos Cargos em Comissão da Advocacia-Geral da União, aprova o Quadro Demonstrativo dos Cargos em Comissão da Procuradoria-Geral Federal e remaneja cargos em comissão para a Advocacia-Geral da União e para a Procuradoria-Geral Federal* (Brasília: Diário Oficial da União).
- Brasil (2015). *Lei nº 13.105, de 16 de março de 2015. Código de processo civil* (Brasília: Diário Oficial da União).
- Brasil (2016). *Política Nacional de Informação e Informática em Saúde / Ministério da Saúde, Secretaria-Executiva, Departamento de Monitoramento e Avaliação do SUS* (Brasília: Ministério da Saúde).
- Castro, K. R. T. R. (2012). *Os juízes diante da judicialização da saúde: o NAT como instrumento de aperfeiçoamento das decisões judiciais na área da saúde* (Rio de Janeiro: Fundação Getúlio Vargas).
- CEMAS (2019). *Comitê Executivo para Monitoramento das Ações da Saúde no Estado do Tocantins*. Available at: <http://www.tjto.jus.br/saude/> (Accessed April 6, 2019).
- Chayamiti, E. M. P. C. (2018). *Coordenadora. Manual do serviço de atenção domiciliar. 2ª revisão* (Ribeirão Preto: Secretaria Municipal da Saúde de Ribeirão Preto).
- Chieffi, A. L., and Barata, R. B. (2009). "Judicialization" of public health policy for distribution of medicines [Judicialização da política pública de assistência farmacêutica e equidade, in Portuguese]. *Cadernos saúde Publica* 25, 1839–1849. doi: 10.1590/S0102-311X2009000800020
- Comitê Estadual das Demandas da Saúde do Rio Grande do Norte (2016). *Comitê da Saúde do RN Natal: Secretaria de Comunicação do Tribunal de Justiça do Estado do Rio Grande do Norte*. Available at: <http://comite.tjrj.jus.br/index.php> (Accessed April 6, 2019).
- Comitê Executivo do Fórum Nacional do Judiciário para Saúde do Conselho Nacional de Justiça (2015). *Ação de planejamento e de gestão sistêmicos com foco na saúde* (Porto Alegre: Comitê Executivo do Rio Grande do Sul).

- Conselho Federal de Farmácia (2013). *Experiências exitosas de farmacêuticos no SUS. CFF*, ano I(1):82. Available at: <https://cff.org.br/pagina.php?id=768&menu=768&titulo=Experi%C3%Aancias+Exitosas> (Accessed July 24, 2020).
- Conselho Federal de Farmácia (2016). *Experiências exitosas de farmacêuticos no SUS. CFF*, Ano IV(4):192. Available at: <https://cff.org.br/pagina.php?id=768&menu=768&titulo=Experi%C3%Aancias+Exitosas> (Accessed July 24, 2020).
- Conselho Nacional de Justiça (2010a). *Recomendação nº. 31, de 30 de março de 2010. Recomenda aos Tribunais a adoção de medidas visando a melhor subsidiar os magistrados e demais operadores do direito, para assegurar maior eficiência na solução das demandas judiciais envolvendo a assistência à saúde* (Brasília: Diário da Justiça Eletrônico).
- Conselho Nacional de Justiça (2010b). *Resolução nº 107, de 06 de abril de 2010. Institui o Fórum Nacional do Judiciário para monitoramento e resolução das demandas de assistência à saúde* (Brasília: Conselho Nacional de Justiça).
- Conselho Nacional de Justiça (2016a). *Manual de Mediação Judicial. 6ª ed.* (Brasília: CNJ).
- Conselho Nacional de Justiça (2016b). *Resolução nº 238, de 6 de setembro de 2016. Dispõe sobre a criação e manutenção, pelos Tribunais de Justiça e Regionais Federais de Comitês Estaduais da Saúde, bem como a especialização de vara em comarcas com mais de uma vara de fazenda Pública* (Brasília: CNJ).
- Conselho Nacional de Justiça (2017). *Justiça em números Brasília: CNJ*. Available at: <http://www.cnj.jus.br/programas-e-acoess/pj-justica-em-numeros> (Accessed February 21, 2018).
- Conselho Nacional de Secretários de Saúde (2011). *Assistência Farmacêutica no SUS* (Brasília/BR: CONASS).
- Conti, M. A. (2013). *Avaliação das demandas judiciais por acesso a medicamentos no Distrito Federal (dissertation/master's thesis)* (Brasília: Universidade de Brasília, Faculdade de Ciências da Saúde).
- Costa, E. A., Araújo, P. S., Pereira, M. T., Souto, A. C., Souza, G. S., Guerra Junior, A. A., et al. (2017). Technical issues and conservation conditions of medicines in the primary health care of the Brazilian Unified Health System. *Rev. Saúde Pública* 51 (Suppl 2), 12s. doi: 10.11606/S1518-8787.2017051007106
- Costa, K. S., Tavares, N. U. L., Nascimento Júnior, J. M. D., Mengue, S. S., Álvares, J., Guerra Junior, A. A., et al. (2017). Pharmaceutical services in the primary health care of the Brazilian Unified Health System: advances and challenges. *Rev. Saúde Pública* 51 (Suppl 2), 3s. doi: 10.11606/s1518-8787.2017051007146
- Costa, I. C. (2014). *Judicialização da saúde e a Câmara Técnica de Saúde no tribunal de justiça da Paraíba (graduation monograph)* (Guabira/BR: Centro de Humanidades da Universidade Estadual da Paraíba).
- Costa, C. A. (2019). *Gestão de pessoal e educação permanente em saúde pública como viés para redução do ativismo judicial*. Available at: <http://www.ideiasus.fiocruz.br/portal/index.php/banco-de-praticas/busca-avancada> (Accessed April 6, 2019).
- Cotrim, T. P. (2017). *Mediação como instrumento de ação pública: estudo de caso sobre a CAMEDIS (DF) e o SUS Mediado (RN) (graduation monograph)* (Brasília/BR: Faculdade de Administração, Contabilidade, Economia e Gestão de Políticas Públicas da Universidade de Brasília).
- Defensoria Pública do Estado do Rio Grande do Sul (2019). *A Defensoria*. Available at: <http://www.defensoria.rs.def.br/apresentacao> (Accessed April 6, 2019).
- Delduque, M. C., Marques, S. B., and Ciarlini, Á. (2013). "Judicialização das Políticas de Saúde no Brasil," in *Direito Sanitário em Perspectiva 2*. Eds. S. M. C. Alves, M. C. Delduque and N. D. Neto (Brasília: Escola Superior do Ministério Público da União).
- Departamento de Informática (2015). *Departamento Médico Judiciário*. Available at: <https://www.tjrs.jus.br/novo/institucional/estrutura-do-judiciario/tribunal-de-justica/setores/departamento-medico-judiciario/> (Accessed April 6, 2019).
- Descritores em Ciência da Saúde (DeCS) (2017). *Judicialização da saúde São Paulo: Biblioteca Virtual em Saúde*. Available at: <http://decs.bvs.br/> (Accessed February 20, 2018).
- Diniz, I. M. (2015). *Direito à saúde e judicialização: uma análise da atuação do Conselho Nacional de Justiça no aprimoramento da prestação jurisdicional nas demandas de saúde (dissertation/master's thesis)* (São Luís: Universidade Federal do Maranhão).
- Duarte, V. G. (2017). *Arranjos e diálogos institucionais para enfrentamento da judicialização da saúde: uma análise dos modelos de assessoramento técnico (NAT's) (dissertation/master's thesis)* (Limeira: Universidade Estadual de Campinas).
- Fagioni, A. F., and Castelo, F. A. (2018). "A especialização das procuradorias dos estados nas questões relativas ao direito à saúde como instrumento eficaz na defesa dos entes estaduais: a experiência da PGE/PR," in *Boas Práticas e Diálogos Institucionais. Coletânea Direito à Saúde. 3, 1ª ed.* Eds. A. O. Santos and L. T. Lopes (Brasília: CONASS).
- Farias, D. R., Silva, M. V. C., Santos, A. S. S., and Perez, K. N. (2016). Os desafios e as estratégias do poder judiciário no Tocantins para a minimização da judicialização da saúde. *Rev. ESMAT* 8 (11), 29–56.
- Farias, D. R. (2016). *Judicialização da saúde: aspectos processuais e institucionais na efetivação do direito à saúde pública no Estado do Tocantins (dissertation/master's thesis)* (Palmas: Universidade Federal do Tocantins).
- Galliez, M. S. (2015). "Atuação extrajudicial na Saúde Pública: garantia de acesso e qualidade aos serviços," in *XII edição do Prêmio Inovare; 2015 Dec 1, Supremo Tribunal Federal, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Garofalo, G., Baseio, C., Campos, L., and Alonso, M. S. (2012). *Atenção farmacêutica na diminuição da prescrição e do uso irracional de medicamentos na judicialização do SUS. Prêmio Nacional de Incentivo à Promoção do Uso Racional de Medicamentos – 2011/Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia* (Brasília: Ministério da Saúde).
- Gerlack, L. F., Karnikowski, M. G. O., Areda, C. A., Galato, D., Oliveira, A. G., Álvares, J., et al. (2017). Management of pharmaceutical services in the Brazilian primary health care. *Rev. Saúde Pública* 51 (Suppl 2), 15s. doi: 10.11606/S1518-8787.2017051007063
- Governo do Estado do Espírito Santo (2007). *Decreto nº 1956-R, de 07 de novembro de 2007: Aprova a Política Farmacêutica do Estado do Espírito Santo e dá outras providências* (Vitória: Gabinete do governador).
- Guimarães, R. C. M., and Palheiro, P. H. D. (2015). "Medidas adotadas para enfrentar a judicialização na secretaria de saúde do Estado do Rio De Janeiro e a experiência da Câmara de Resolução de Litígios de Saúde," in *Conselho Nacional dos Secretários de Saúde. Direito à saúde. Para Entender a Gestão do SUS, 1ª ed.* (Brasília/BR: CONASS).
- Haby, M. M., Chapman, E., Clark, R., Barreto, J., Reveiz, L., and Lavis, J. N. (2016). Designing a rapid response program to support evidence-informed decisionmaking in the Americas region: using the best available evidence and case studies. *Implement. Sci.* 11 (117), 12. doi: 10.1186/s13012-016-0472-9
- Handtke, O., Schilgen, B., and Mösko, M. (2019). Culturally competent healthcare: A scoping review of strategies implemented in healthcare organizations and a model of culturally competent healthcare provision. *PloS One* 14 (7), e0219971. doi: 10.1371/journal.pone.0219971
- Health Metrics Network & World Health Organization (2008). *Framework and Standards for Country Health Information Systems. 2 ed.* (Geneva: World Health Organization).
- Henrique, M. C., Brito, J. O. B., and Mel, M. D. S. M. (2013). Eficiência na solução das demandas de judicialização da saúde na Comarca de Araguaína/TO. *Cad. IberAmer Direito Sanit* 2 (2), 19. doi: 10.17566/ciads.v2i2.86
- Henrique, M. C., Mendonça, M. R. L., and Braga, E. A. (2018). "NatJus e desjudicialização da saúde," in *Boas Práticas e Diálogos Institucionais. Coletânea Direito à Saúde. 3, 1ª ed.* Eds. A. O. Santos and L. T. Lopes (Brasília/BR: CONASS).
- Holloway, K., and Green, T. (2003). *Drug and therapeutics committees: A practical guide. WHO/EDM/PAR/2004. 1 ed.* (Geneva: World Health Organization & Management Sciences for Health).
- Imprensa da DPE/RN (2019). *SUS Mediado registra 26% de resolatividade em 2018 e celebra retorno da Secretaria Municipal de Saúde*. Available at: <https://www.defensoria.rn.def.br/noticia/sus-mediado-registra-26-de-resolutividade-em-2018-e-celebra-retorno-da-secretaria-municipal> (Accessed April 6, 2019).
- Instituto de Ensino e Pesquisa (2019). *Judicialização da saúde no Brasil: perfil das demandas, causas e propostas de solução* (Brasília: Conselho Nacional de Justiça).
- Junior, P. B. R. (2008). *A judicialização do acesso a medicamentos: a perspectiva da secretaria municipal de saúde do Rio de Janeiro (dissertation/master's thesis)* (Rio de Janeiro/BR: Fundação Getúlio Vargas - Escola Brasileira de Administração Pública e de Empresas).
- Júnior, L. M. R. R. (2017). *A mediação como instrumento de efetivação do direito à saúde: análise dos relatórios de atendimentos realizados pelo programa "SUS*

- Mediado”, no ano de 2014 (dissertation/master’s thesis) (Recife: Universidade Católica de Pernambuco).
- Leite, S. N., Manzini, F., Álvares, J., Guerra Junior, A. A., Costa, E. A., Acúrcio, F. D. A., et al. (2017). Infrastructure of pharmacies of the primary health care in the Brazilian Unified Health System: Analysis of PNAUM – Services data. *Rev. Saúde Pública* 51 (Suppl 2), 13s. doi: 10.11606/s1518-8787.2017051007120
- Levac, D., Colquhoun, H., and O’Brien, K. K. (2010). Scoping studies: advancing the methodology. *Implement. Sci.* 5 (1):69. doi: 10.1186/1748-5908-5-69
- Macêdo, D. F., Ataide, J. A. R., Costa, A. C. S., Souza, W. A. R., and Rita, L. P. S. (2015). Análise da judicialização do direito à saúde, subfinanciamento do setor e políticas públicas: estudo de caso no Estado de Alagoas. *Rev. Administração Roraima-UFRR* 5 (2), 25. doi: 10.18227/2237-8057rarr.v5i2.2949
- Macedo, M. B. (2016). *A judicialização da saúde pública e o diálogo institucional: os espaços interinstitucionais como garantia fundamental de acesso à saúde* (dissertation/master’s thesis) (Uberlândia: Universidade Federal de Uberlândia).
- Mariano, C. M., Furtado, E. T., Albuquerque, F. B., and Pereira, FHLCS. (2018). Interinstitutional health dialogues and the NAT-JUS deployment experience. *Rev. Investigações Constitucionais* 5 (1), 169–188. doi: 10.5380/rinc.v5i1.56027
- Mauad, M. L. M. E., Tanaka, N. Y. Y., and Fazan, W. C. (2009). “Protocolo inicial da comissão de análise de solicitações especiais para dieta enteral,” in *Coordenação-Geral da Política de Alimentação e Nutrição. II Mostra de Alimentação e Nutrição do SUS I Seminário Internacional de Nutrição na Atenção Primária: trabalhos selecionados para apresentação oral. Comunicação e Educação em Saúde* (Brasília/BR: Ministério da Saúde).
- Messeder, A. M., Osorio-de-Castro, C. G. S., and Luiza, V. L. (2005). Can court injunctions guarantee access to medicines in the public sector? The experience in the State of Rio de Janeiro, Brazil. [Mandados judiciais como ferramenta para garantia do acesso a medicamentos no setor público: a experiência do Estado do Rio de Janeiro, Brasil, in Portuguese]. *Cadernos Saude Publica* 21, 525–534. doi: 10.1590/S0102-311X2005000200019
- Ministério da Saúde, Assistência Farmacêutica (2013). *Sistema Hórus*. Available at: <http://portalmms.saude.gov.br/assistencia-farmacautica/sistema-horus/sobre-o-sistema> (Accessed April 2, 2019).
- Ministério da Saúde (2009). *Diretrizes para estruturação de farmácias no âmbito do Sistema Único de Saúde* (Brasília: Ministério da Saúde).
- Ministério da Saúde (2016a). *Manual de planejamento no SUS / Ministério da Saúde, Fundação Oswaldo Cruz. 1ª rev ed* (Brasília: Ministério da Saúde).
- Ministério da Saúde (2016b). *QUALIFARSUS: Programa nacional de qualificação da assistência farmacêutica no âmbito do Sistema Único de Saúde. 1ª ed.* (Brasília: Ministério da Saúde).
- Ministério da Saúde (2019a). *Síntese de evidências para políticas de saúde: Judicialização da Saúde* (Brasília: Ministério da Saúde).
- Ministério da Saúde (2019b). *Sistema Único de Saúde (SUS): estrutura, princípios e como funciona* (Brasília: Ministério da Saúde). Available at: <http://www.saude.gov.br/gestao-do-sus> (Accessed June 10, 2019).
- Ministério do Planejamento Orçamento e Gestão, Secretaria de Gestão Pública (2007). *Programa Nacional de Gestão Pública e Desburocratização (GESPÚBLICA); Cadernos GESPÚBLICA – Documento de Referência* (Brasília: MP, GESPÚBLICA, SEGES).
- Ministério do Planejamento Orçamento e Gestão, Secretaria de Gestão Pública (2014). *Programa GESPÚBLICA: modelo de excelência em gestão pública. Versão 1/2014 ed* (Brasília/BR: MP, SEGEP).
- Ministério Público do Estado de São Paulo (2019). *Saúde Pública*. Available at: http://www.mpsp.mp.br/portal/page/portal/Saude_Publica (Accessed April 6, 2019).
- Naffah-Filho, M., Chieffi, A. L., and Correa, MCMMA. (2010). S-Codes: um novo sistema de informações sobre ações judiciais da Secretaria de Estado da Saúde de São Paulo. *BEPA* 7 (84), 12.
- Nantes, L. F. L., and Dobashi, B. F. (2015). “A experiência da secretaria estadual de saúde de Mato Grosso do Sul no enfrentamento das ações judiciais em saúde,” in *Direito à saúde. Para Entender a Gestão do SUS - 2015*. Ed. Conselho Nacional dos Secretários de Saúde, 1ª ed. (Brasileiro: CONASS), p. 113.
- Núcleo de Comunicação Social (2017). *Notícia: lançado o programa “Acessa SUS”, que facilita acesso da população a medicamentos* (São Paulo: Ministério Público do Estado de São Paulo). Available at: http://www.mpsp.mp.br/portal/page/portal/noticias/noticia?id_noticia=16584466&id_grupo=118 (Accessed April 6, 2019).
- Nunes, H. E. N. (2016). *A prática da mediação e a (des)judicialização da saúde no Maranhão* (dissertation/master’s thesis) (São Luís/BR: Universidade CEUMA).
- Oliveira, R. (2018). *Relatório de gestão 2015-2018: avanços e perspectivas* (Vitória: Secretaria de Estado da Saúde do Estado do Espírito Santo).
- Organisation for Economic Co-operation and Development (2018). *OECD Legal Instruments* (Paris: OECD). Available at: <http://www.oecd.org/legal/legal-instruments.htm> (Accessed March 14, 2020).
- Orsatto, S. D. (2014). “Núcleo de conciliação de demandas em saúde,” in *XI edição do Prêmio Inovare; 2014 Dec 16, Supremo Tribunal Federal, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Paim, P., Marqueto, A., and Lopes, I. O. (2015). “Câmara permanente distrital de mediação em saúde: experiência do Distrito Federal,” in *Conselho Nacional de Secretários de Saúde, editor. Direito à saúde. Para Entender a Gestão do SUS - 2015, 1ª ed.* (Brasília: CONASS).
- Pan American Health Organization (2017). *Health in the Americas+* (Washington, D.C.: Pan American Health Organization). Available at: <https://www.paho.org/salud-en-las-americas-2017/> (Accessed June 5, 2019).
- Panerai, R. B., and Peña-Mohr, J. (1989). *Health technology assessment methodologies for developing countries* (Washington: Pan-American Health Organization), p. 119.
- Pereira, L. R., and Carneiro, R. (2012). “Judicialização da saúde e mudanças organizacionais: o impacto das decisões judiciais na estrutura da secretaria de Estado de saúde de Minas Gerais (SES-MG),” in *V Encontro da Divisão de Administração Pública/APB da ANPAD; 2012 Nov 18 - 20, Salvador, Brazil* (Maringá: Associação Nacional de Pós-Graduação e Pesquisa em Administração).
- Pereira, L. R. (2012). *Judicialização da saúde e mudanças organizacionais: o impacto das decisões judiciais na estrutura da Secretaria Estadual de Saúde de Minas Gerais (SES-MG)* (dissertation/master’s thesis) (Belo Horizonte/BR: Escola de Governo Professor Paulo Neves de Carvalho).
- Perin, I. G., Tassinari, M. T. R., Santos, M. G., Santos, I. E. S., Larogian, A. P. A., Teixeira, V. M., et al. (2008). “Desafios e avanços da comissão de análise de solicitações especiais visando a equidade e o aprimoramento da gestão do SUS,” in *Unidade de Desenvolvimento e Melhoria das Organizações. Prêmio Mario Covas, 5ª edição, ciclo 2008; Theatro Municipal de São Paulo* (São Paulo/BR: Secretaria Estadual de Planejamento e Gestão).
- Perlingeiro, R. (2014). Recognizing the public right to healthcare: the approach of Brazilian courts [Reconhecendo o direito público à saúde: a abordagem dos tribunais brasileiros]. *Rev. Investigações Constitucionais* 1 (1), 19–37. doi: 10.5380/rinc.v1i1.40246
- Peters, M. D. J., Godfrey, C. M., Khalil, H., McInerney, P., Parker, D., and Soares, C. B. (2015). Guidance for conducting systematic scoping reviews. *Int. J. Evidence-Based Healthcare* 13 (3), 141–146. doi: 10.1097/xe.0000000000000050
- Pinheiro, T. P. (2010). “Comitê Interinstitucional de Resolução Administrativa de Demandas da Saúde (CIRADS),” in *VII edição do Prêmio Inovare: Justiça sem burocracia e acesso do preso à Justiça; 2010 Dec 3, Tribunal Federal de Justiça, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Pinzón-Flórez, C. E., Chapman, E., Cubillos, L., and Reveiz, L. (2016). Prioritization of strategies to approach the judicialization of health in Latin America and the Caribbean. *Rev. Saúde Pública* 50, 10–14. doi: 10.1590/S1518-8787.2016050005728
- Pontarolli, D. R. S., Silva, G. R. P. P., and Strapasson, G. C. (2015). “O enfrentamento das demandas judiciais por medicamentos na secretaria de Estado da saúde do Paraná,” in *Conselho Nacional dos Secretários de Saúde. Direito à saúde. Para Entender a Gestão do SUS, 1ª ed.* (Brasília/BR: CONASS).
- Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., et al. (2006). *Guidance on the conduct of narrative synthesis in systematic reviews* (Swindon: ESRC Methods Programme).
- Prefeitura Municipal de Lages (2015). *Núcleo de Medicamentos. Município e Tribunal de Justiça firmarão convênio*. Available at: <http://www.lages.sc.gov.br/noticia/5800/municipio-e-tribunal-de-justica-firmarao-convenio/> (Accessed April 3, 2019).
- Queiroz, C. C. (2013). *A mediação como instrumento concretizador do direito fundamental à saúde: uma alternativa à judicialização de conflitos* (dissertation/master’s thesis) (Natal/BR: Universidade Federal do Rio Grande do Norte).

- Reis, B. B. (2011). "Defensoria especializada da saúde," in *Concurso de práticas exitosas 2011, X Congresso Nacional de Defensores Públicos (ANADEP)*; 2011 Nov 15 - 18, Centro de Convenções de Natal/RN. Ed. Associação Nacional de Defensores Públicos (Brasília/BR: ANADEP), p. 16.
- Reis, V. (2018). *Mario Scheffer fala sobre a queda da judicialização do SUS paulista*. Available at: <https://www.abrasco.org.br/site/outras-noticias/sistemas-de-saude/mario-scheffer-fala-sobre-queda-da-judicializacao-do-sus-paulista/33433/> (Accessed April 6, 2019).
- Ribeiro, E. M., Chomatas, E. R. V., and Neto, M. C. (2004). "Integralidade e redes de atenção básica e saúde familiar: A experiência do município de Curitiba-PR," in *Experiências e desafios da atenção básica e saúde familiar: Caso Brasil. Série Técnica*. Eds. J. Seclen and A. S. Fernandes (Brasília: Organização Pan-Americana da Saúde).
- Ringeisen, A. T. S. (2016). *Mediação de conflitos no Sistema Único de Saúde: visões e práticas de uma experiência no município de Natal/RN (dissertation/master's thesis)* (Natal/BR: Universidade Federal do Rio Grande do Norte).
- Sanchez, L. A., Santos, L. N., Gomes, R. A. C., Chieffi, A. L., Souza, C. Z. B., Camargo, C. R., et al. (2008). "Uma parceria inovadora para fazer frente ao fenômeno da "judicialização das políticas públicas de saúde": a otimização da gestão pública," in *Unidade de Desenvolvimento e Melhoria das Organizações. Prêmio Mario Covas, 5ª edição, ciclo 2008; Teatro Municipal de São Paulo* (São Paulo/BR: Secretaria Estadual de Planejamento e Gestão).
- Santos-Pinto, C. D. B. (2013). *Demandas judiciais por medicamentos e estratégias de gestão da assistência farmacêutica em municípios do Estado de Mato Grosso do Sul* (Rio de Janeiro: Fundação Oswaldo Cruz (FIOCRUZ)).
- Sant'Ana, R. N. (2017). *A judicialização como instrumento de acesso à saúde: propostas de enfrentamento da injustiça na saúde pública (thesis/ doctorate thesis)* (Brasília: Centro Universitário de Brasília).
- Schulze, C. J. (2017). *Números atualizados da Judicialização da Saúde no Brasil Florianópolis: Empório do Direito*. Available at: <http://emporiiodireito.com.br/leitura/numeros-atualizados-da-judicializacao-da-saude-no-brasil-por-clenio-jair-schulze> (Accessed February 21, 2018).
- Schulze, M. (2018). "A desjudicialização da saúde no Rio Grande do Sul: cabal redução do número das ações ativas e estratégia de interiorização," in *Boas Práticas e Diálogos Institucionais. Coletânea Direito à Saúde. 3, 1ª ed.* Eds. A. O. Santos and L. T. Lopes (Brasília/BR: CONASS).
- Secretaria da Saúde do Estado de São Paulo (2012). *Resolução SS-54, de 11 de maio de 2012. Aprova, no âmbito da Pasta, estrutura e funcionamento da Comissão de Farmacologia da Secretaria de Estado da Saúde de São Paulo, e dá outras providências* (São Paulo: Diário Oficial Estado de São Paulo).
- Secretaria da Saúde do Estado do Amapá (2017). *Núcleo de Ouvidoria e Apoio Técnico*. Available at: <https://saude.portal.ap.gov.br/conteudo/cidadao/nucleo-de-ouvidoria-e-apoio-tecnico> (Accessed April 2, 2019).
- Secretaria da Saúde do Município de Ribeirão Preto (2017). *Serviço de Atenção Domiciliar (SAD)*. Available at: <https://www.ribeiraopreto.sp.gov.br/ssaudef/programas/sad/i16indice.php> (Accessed April 6, 2019).
- Secretaria de Estado da Saúde de Alagoas (2013). *Portaria n. 110, de 2 de maio de 2013. Institui o Núcleo Interinstitucional de Judicialização da Saúde (NIJUS)* (Maceió: Diário Oficial do Estado de Alagoas).
- Secretaria de Estado da Saúde do Espírito Santo (2018). *Sesa lança Mandado Judicial On-line em parceria com o TJES*. Available at: <https://saude.es.gov.br/Noticia/sesa-lanca-mandado-judicial-on-line-em-parceria-com-o-tjes> (Accessed April 3, 2019).
- Secretaria de Estado da Saúde do Estado de Alagoas (2015). *Núcleo de Saúde da PGE facilita respostas para o Judiciário sobre as demandas dos alagoanos*. Available at: <http://www.saude.al.gov.br/2015/11/16/nucleo-de-saude-da-pge-facilita-respostas-para-o-judiciario-sobre-as-demandas-dos-alagoanos/> (Accessed April 6, 2019).
- Secretaria de Estado da Saúde do Estado de São Paulo (2019). *Comissão de Farmacologia*. Available at: <http://saude.sp.gov.br/ses/perfil/gestor/comissao-de-farmacologia/> (Accessed April 6, 2019).
- Secretaria de Estado da Saúde do Estado do Maranhão (2015). *Governo, Prefeitura e defensorias unem esforços para agilizar acesso à Saúde*. Available at: <http://www.saude.ma.gov.br/governo-prefeitura-e-defensorias-unem-esforcos-para-agilizar-acesso-a-saude/> (Accessed April 3, 2019).
- Secretaria de Estado da Saúde do Paraná (2008). *Superintendência de Gestão de Sistemas de Saúde. Assistência Farmacêutica* (Curitiba: Secretaria de Estado da Saúde do Paraná).
- Secretaria de Estado de Saúde do Mato Grosso do Sul (2018). *Resolução nº 009/SES/MS. Campo Grande, 22 de fevereiro de 2018. Regulamenta o cumprimento de determinações judiciais em saúde de pequeno valor nos termos que especifica* (Campo Grande/BR: Diário Oficial do Estado).
- Secretaria Estadual de Saúde (2016). *SES-MG e Defensoria Pública estabelecem parceria pioneira para agilizar assistência farmacêutica no Norte de Minas*. Available at: <http://www.crfmg.org.br/site/Noticias/SES-MG-e-Defensoria-Publica-estabelecem-parceria-pioneira-para-agilizar-assistencia-farmacautica-no-Norte-de-Minas> (Accessed April 6, 2019).
- Secretaria-Geral e Departamento de Gestão Estratégica (2017). *Relatório Anual 2017* (Brasília: Conselho Nacional de Justiça).
- Silva, M. V. (2012). *O processo decisório judicial e a assessoria técnica: a argumentação jurídica e médico-sanitária na garantia do direito à assistência terapêutica no Sistema Único de Saúde (thesis/ doctorate thesis)* (Rio de Janeiro: Fundação Oswaldo Cruz).
- Simabuku, E. M. G., Catanheide, I. D., Biella, C. A., Rabelo, R. B., Santos, V. C. C., and Petramale, C. A. (2015). Comissão nacional de incorporação de tecnologias no SUS e a judicialização do acesso à saúde. *Rev. Eletrônica Gestão Saúde* 6 (Supl. 4), 18.
- Simões, F. H. S. (2015). *Judicialização do acesso ao tratamento do diabetes no Estado de Minas Gerais (dissertation/master's thesis)* (Belo Horizonte: Universidade Federal de Minas Gerais).
- Siqueira, P. S. F., Martins, M. A., and Domingues, R. (2018). "S-CODES: sistema informatizado para o trato da judicialização," in *Boas Práticas e Diálogos Institucionais. Coletânea Direito à Saúde. 3, 1ª ed.* Eds. A. O. Santos and L. T. Lopes (Brasília/BR: CONASS).
- Siqueira, P. S. F. (2015). "Judicialização em saúde no Estado de São Paulo," in *Conselho Nacional dos Secretários de Saúde. Direito à saúde. Para Entender a Gestão do SUS, 1ª ed.* (Brasília/BR: CONASS).
- Souza, A. M. (2016). *A atuação em rede de instituições governamentais na resolução de conflitos sobre demandas sanitárias no Rio de Janeiro (dissertation/master's thesis)* (Rio de Janeiro: Fundação Getúlio Vargas).
- Tavares, G. R. P., Silva, D. M., and Bernardos, A. (2009). "Sistema de regulação da dispensação de medicamentos excepcionais," in *Conselho Nacional de Secretários de Estado da Administração. II Congresso Consad de Gestão Pública; 2009 May 6 - 8, Centro de Convenções Ulysses Guimarães, Brasília-DF* (Brasília: CONSAD).
- Tavares, G. R. P., Silva, D. M., Barcelos, P. C., Ribeiro, C., and Moreira, G. L. (2010). "Diagnóstico das ações judiciais direcionadas à secretaria de Estado da saúde do Espírito Santo," in *Conselho Nacional de Secretários de Estado da Administração. III Congresso Consad de Gestão Pública; 2010 March 15 - 17, Centro de Convenções Ulysses Guimarães, Brasília/DF* (Brasília/BR: CONSAD).
- Tavares, L. L. G., Grynberg, C., Mascarenhas, R., Palheiro, P. H. D. M., Filho, H. G. G., and Saraiva, M. L. L. B. (2014). "Câmara de Resolução de Litígios de Saúde (CRLS)," in *XI edição do Prêmio Inovare; 2014 Dec 16, Supremo Tribunal Federal, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Teixeira, M. F. (2011). *Criando alternativas ao processo de judicialização da saúde: o sistema de pedido administrativo, uma iniciativa pioneira do estado e município do Rio de Janeiro". (dissertation/master's thesis)* (Rio de Janeiro: Fundação Oswaldo Cruz).
- Toma, T. S., Soares, A. C., Bortoli, M. C., Pirota, K. C. M., Venâncio, S. I., Derbli, M., et al. (2015). *Avaliação de tecnologias e inovação em saúde no SUS: desafios e propostas para a gestão* (São Paulo: Instituto de Saúde).
- Toma, T. S., Soares, A. C., Siqueira, P. S. F., and Domingues, R. (2017). Estratégias para lidar com as ações judiciais de medicamentos no estado de São Paulo. *Cad Ibero-Amer Dir Sanit* 6 (1), 19. doi: 10.17566/ciads.v6i1.323
- Triagem farmacêutica no juizado especial da fazenda pública de São Paulo (2013). *10ª edição do Prêmio Inovare; 2013 Nov 28, Supremo Tribunal Federal, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Tribunal de Contas da União (2017). *Acórdão nº 1787/2017 - TCU - Plenário* (Brasília: Diário Oficial da União).
- Tribunal de Justiça de Mato Grosso do Sul (2013). *Comitê Estadual do Judiciário para a Saúde. Núcleo de Apoio Técnico - NAT Jus*. Available at: <http://www.tjms.jus.br/nat/> (Accessed April 6, 2019).
- Tribunal de Justiça do Estado de Alagoas (2016). *Resolução nº 18, de 15 de março de 2016. Institui a Câmara Técnica de Saúde no âmbito do Poder Judiciário do Estado de Alagoas e adota providências correlatas* (Maceió/BR: Tribunal de Justiça do Estado de Alagoas).

- Tribunal de Justiça do Estado da Bahia (2017a). *Decreto judiciário nº 795, de 30 de agosto de 2017. Dispõe sobre a estrutura e funcionamento do NAT-JUS do Tribunal de Justiça* (Salvador: Diário da justiça eletrônico).
- Tribunal de Justiça do Estado da Bahia (2017b). *NAT JUS: Núcleo de Apoio Técnico do Poder Judiciário*. Available at: <https://www.tjba.jus.br/natjus/> (Accessed April 2, 2019).
- Tribunal de Justiça do Estado do Ceará (2017c). *Direito à Saúde*. Available at: <https://www.tjce.jus.br/saude/> (Accessed April 2, 2019).
- Tribunal de Justiça do Estado do Espírito Santo (2018). *Ato normativo conjunto Nº 44/2018. Dispõe, no âmbito do Poder Judiciário do Estado do Espírito Santo, sobre a utilização do sistema de intimações eletrônicas da Secretaria Estadual de Saúde – SESA/ES, denominado MJ Online (Mandado Judicial Online)* (Vitória/BR: Tribunal de Justiça do Estado do Espírito Santo).
- Tribunal de Justiça do Estado do Pará (2013). *Comitê Executivo de Saúde*. Available at: <http://www.tjpa.jus.br/PortalExterno/institucional/Comite-Executivo-de-Saude/330244-Normativos-NAT-Jus.xhtml> (Accessed April 6, 2019).
- Tribunal de Justiça do Maranhão (2018). *Portaria-GP nº 6832018. Dispõe sobre a composição da Comissão do Comitê Estadual de Saúde do Estado do Maranhão* (São Luís: Tribunal de Justiça do Maranhão).
- Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., et al. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Internal Med.* 169 (7), 467. doi: 10.7326/m18-0850
- Ungaro, G. (2011). "O combate às fraudes judiciais em ações para fornecimento de medicamentos no Estado de São Paulo," in *VIII edição do Prêmio Inovare; 2011 Dec 15, Tribunal Federal de Justiça, Brasília, Brazil* (Rio de Janeiro: Instituto Inovare).
- Vargas-Pelaez, C. M., Rover, M. R. M., Soares, L., Blatt, C. R., Mantel-Teeuwisse, A. K., Rossi, F. A., et al. (2019). Judicialization of access to medicines in four Latin American countries: a comparative qualitative analysis. *Int. J. Equity Health* 18 (68), 1–14. doi: 10.1186/s12939-019-0960-z
- Vasconcellos, J. (2015). *Núcleo de conciliação de Lages/SC soluciona 90% dos conflitos na saúde*. Available at: <http://cnj.jus.br/noticias/cnj/79305-nucleo-de-conciliacao-de-lages-sc-soluciona-90-dos-conflitos-na-saude> (Accessed April 3, 2019).
- Vieira, F. S., and Zucchi, P. (2007). Distortions to national drug policy caused by lawsuits in Brazil. [Distorções causadas pelas ações judiciais à política de medicamentos no Brasil, in Portuguese]. *Rev. Saúde Pública* 41, 214–222. doi: 10.1590/S0034-89102007000200007
- Vieira, F. S., Marques, D. C., and Jeremias, S. A. (2014). "Assistência Farmacêutica no Sistema Único de Saúde," in *Assistência Farmacêutica: gestão e prática para profissionais de saúde*. Eds. C. G. S. Osório-de-Castro, V. L. Luizia, S. Castilho, M. A. Oliveira and N. M. Jaramillo (Rio de Janeiro: Fiocruz).
- Vieira, F. S. (2016). "Garantia do direito à saúde, judicialização e o mito de que os recursos não são escassos: Desafios atuais e futuros do estado brasileiro," in *IX Congresso CONSAD de Gestão Pública; Centro de Convenções Ulysses Guimarães, Brasília, Brazil* (Brasília: CONSAD).
- WHO Regional Office for the Western Pacific (2004). *Developing health management information systems: A practical guide for developing countries* (Geneva: World Health Organization).
- World Bank (2004). *World Development Report 2005: A Better Investment Climate for Everyone*. World Bank. Available at: <https://openknowledge.worldbank.org/handle/10986/5987> (Accessed March 14, 2020).
- World Bank (2007). *Brazil - Governance in Brazil's Unified Health System: Raising the Quality of Public Spending and Resource Management* (Washington, DC: World Bank), 180. Contract Nº.: 36601-BR.
- World Health Organization (2010a). *Continuity and change: implementing the third WHO Medicines Strategy 2008-2013. WHO Policy Perspectives on Medicines* (Geneva: World Health Organization).
- World Health Organization (2010b). *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies. Health statistics and information systems* (Geneva: World Health Organization).
- World Health Organization (2019). *Health Systems Strengthening Glossary. Genebra: WHO*. Available at: https://www.who.int/healthsystems/hss_glossary/en/ (Accessed April 26, 2019).
- Yoshinaga, J. Y. (2011). *Judicialização do direito à saúde: a experiência do Estado de São Paulo na adoção de estratégias judiciais e extrajudiciais para lidar com esta realidade. Revista Eletrônica sobre a Reforma do Estado*. Available at: <http://www.direitodoestado.com.br/rere/edicao/24> (Accessed April 6, 2019).

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Serious Adverse Drug Reactions and Safety Signals in Children: A Nationwide Database Study

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Children are more exposed to inappropriate medicine use and its consequent harms. Spontaneous reporting of suspected Serious Adverse Drug Reactions (SADR) increases knowledge and prevention of pharmacotherapy risk. Disproportionality measures are useful to quantify unexpected safety issues associated with a given drug-event pair (signals of disproportionality). This cross-sectional study aimed to assess SADR reporting and safety signals for Brazilian children from 0-12 years old, notified between January 2008 and December 2013 from the Brazilian Surveillance Agency (Notivisa). Information from serious reports (gender and age of the patient, event description, suspected drug) was included. Disproportionality analysis based on Reporting Odds Ratios with a confidence interval of 95% was conducted to identify possible signals of disproportionate reporting (SDR). Almost 30% of 1,977 suspected SADR was related to babies (0-1-year-old). 69% of reports happened with intravenous dosage forms, and 35% of suspected SADR involved off label use according to age. Laronidase, miglustat, imipenem/cilastatin, and clofarabine were involved in six or more suspected deaths among 75 deaths reported. There were 107 SDRs, of which 16 events (15%) were not described in the product labels. There was a relatively higher number of SADR in Brazilian children compared with studies from other countries. SDRs found, (especially drug-event pairs 'imipenem/cilastatin-pneumonia' and 'laronidase-respiratory insufficiency') should be investigated more. The reports of SADR with IV dosage forms and OL drug use suggest the need for drug research and the use of better dosage forms for children in Brazil.

Keywords: serious adverse drug reactions, children, spontaneous reports, off label drug use, safety signals

INTRODUCTION

Ensuring safety, efficacy, and quality of medicines for the pediatric population is a challenge because data on many medicines are scarce due to the lack of clinical trials involving children (Joseph et al., 2015). As a result, children may be exposed to age-inappropriate medicines that can lead to increased incidence of Adverse Drug Reactions (ADRs) (Bellis et al., 2014). Risk factors associated with ADRs in

children include polypharmacy, age, off-label (OL) use, and unlicensed (UL) use (Bellis et al., 2014; Lombardi et al., 2018).

Reports of ADRs screening from surveillance systems may offer information about a different drug-event combination (or pairs) by the mining of a large volume of data (Harpaz et al., 2012). Such safety signals—a potentially causal association or a new aspect of a known association between an intervention and a set of related events—may be critical for drug regulation and improvements in child health (CIOMS, 2010; Osokogu et al., 2016).

Electronic data use for children's safety is increasing, especially in North America and Europe (Black et al., 2015). ADR prevalence may vary due to differences in pharmacovigilance and polypharmacy management among low and middle-income countries (Olsson et al., 2015; Angamo et al., 2016). In Brazil, the first exclusive investigation about children from the Brazilian database (*Notivisa*) assessed 3,330 spontaneous reports of suspected ADRs and showed approximately 60% were classified as serious events (Lima et al., 2019). This new study aimed to analyze deaths and other serious ADR reports and to identify safety signals in children.

MATERIALS AND METHODS

We carried out a cross-sectional study of children with suspected SADR notified on the *Notivisa*, created in 2008. *Notivisa* is a computerized system developed by the National Health Surveillance Agency (*Anvisa*) to receive notifications of incidents, adverse events, and technical complaints related to the use of health products and medicines by manufacturers, users, health professionals, and health services—mainly those within the Sentinel Network observatory.

The Sentinel Network is an observatory constituting around 200 (general and specialized) accredited hospitals and other health services for monitoring and reporting adverse drug events. Sentinel functions include strategies for surveillance of ADRs and precise mechanisms for identification and investigation, dissemination of results, mandatory risk minimization plans and integration of other institutions for network hospitals. Training for this network was carried out by *Anvisa*, and it considers the elements described above, including the seriousness and causality assessment of ADRs. SADRs are investigated in health services by patient safety teams before being reported to *Notivisa* (Brazil, 2011; Brazil, 2015; Teixeira et al., 2017; Mota et al., 2018; Brazil, 2019a).

Anvisa supplied data on *Notivisa* website reports as a Microsoft Excel® file for the first years of reporting system consolidation, and only complete data between 2008 to 2013 were available for analysis.

Data on suspected ADRs in children (0–12 years old) were identified and selected by age information on the date of the adverse event or the calculation of the difference between the date of onset event and the patient's birth date. There were no linkage processes with other databases.

The events were described according to the WHO Adverse Reaction Terminology (WHO-ART) and classified following the

International Conference on Harmonisation guidance (CIOMS, 1987; ICH Expert Working Group, 2003; WHO, 2018) on the *Notivisa* database as serious outcomes (i) death; life-threatening; hospitalization; disability (significant or persistent); congenital anomaly, medically important events, and (ii) not serious. All reports classified as 'not serious' were excluded.

Information about all suspected drugs reported, including pharmaceutical form and administration route, were collected and encoded using the Anatomic Therapeutic Chemical (ATC) classification system (1st and 5th level). OL use in children was verified from the Brazilian labels (summary of product characteristics) of each drug (approved by *Anvisa*). Drugs not approved for use by the children's age group were classified as OL use, and drugs not licensed in Brazil were classified as UL (Gonçalves and Heineck, 2016; Aronson and Ferner, 2017). Age group classification was based on the pediatric stage of development (AAP, 2019).

Disproportionality analysis of ADR reporting was used to identify signals of disproportionate reporting (SDR). SDR refers to statistical associations between drugs and adverse events. The disproportionality analysis method recommended by the European Medicines Agency, namely Reporting Odds Ratio (ROR) and thresholds, is based on its 95% confidence interval and the number of individual cases (European Medicines Agency, 2016). ROR measure is defined by the formula $[(a.d)/(c.b)]$, based on a two-dimensional contingency table where value "a" indicates the number of individual cases that list the target drug P and the target ADR R; value "b" indicates the number of individual cases that list the target drug P but not the target ADR R; value "c" indicates the number of individual cases that list the target ADR R but not the target drug P, and value "d" indicates the number of individual cases that do not list the target ADR R or the target drug P. They should be distinguished from signals that can originate from individual case analysis and epidemiological studies. This method assumes that when a signal (involving a particular adverse event) is identified for a drug, this adverse event is reported relatively more frequently in association with this drug than with other drugs (European Medicines Agency, 2006).

We adopted the following criteria to define a SDR (European Medicines Agency, 2016): number of individual cases is greater than or equal to 3 for active substances contained in medicinal products included in an additional monitoring list defined by the EMA; number of individual cases is greater than or equal to 5 for the other active substances and event belongs to the important medical event terms list. ROR calculations were performed for all drugs with a ≥ 3 . Nevertheless, we differentiate between the cases where $3 \leq a < 5$ and $a \geq 5$. A situation occurs when $c=0$, or when all database reports containing a target ADR are associated with only one drug. In this case, ROR cannot be computed. ROR value is arbitrarily set at 99.9 to reflect the presence of a possible SDR.

Other analyses were conducted using SPSS version 22.0 for Windows (IBM Corporation, USA). The chi-square test with a significance level of 5% was used to assess the association between the seriousness of ADR, age group, and the number of drugs prescribed as OL.

The use of *Notivisa* data was formally authorized by *Anvisa*. This study was approved by the Hospital Universitário Clementino Fraga Filho Ethics Committee (registration number 931.400).

RESULTS

General Findings

One-thousand-nine-hundred-and-seventy-seven SADR were assessed, and almost 30% involved 0-1-year-olds. The frequency of serious events was significantly different between pediatric age groups ($p < 0.05$) (**Table 1**). SADRs were more common in boys (54%) than in girls. However, 1% of the total reports of suspected SADRs did not include a specification of gender. More than 70% of reports were done from hospitals, mainly from the Sentinel Network, by patient safety teams. Approximately 28% of suspected SADRs were associated with death, were life-threatening, and caused prolonged hospitalization (**Table 1**).

Two-thousand-two-hundred-and-twenty-nine drugs were identified as being associated with reports of SADRs (mean: 1.1 drugs by report; range from 1 to 6). Anti-infectives for systemic use ($n = 1048$; 47%), drugs for the nervous system, including non-steroidal anti-inflammatory drugs, ($n=384$; 17.2%) and antineoplastic, and immunomodulating agents ($n=221$; 10%) were most commonly involved in suspected SADRs (**Table 2**).

Intravenous powder or solutions were the main pharmaceutical forms reported (69%), followed by tablets (9.3%), oral solutions (4.5%), and oral suspensions (3.7%). Administration route and pharmaceutical form was indeterminate in 9.6% of reports.

Twenty-five percent ($n=564$) of drugs present in suspected SADRs reports involved OL use by age, according to the Brazilian label, and less than 1% ($n=11$) of cases were classified as UL use. The frequency of OL prescriptions was significantly higher in events reported, such as persistent disability, prolonged hospitalization, and death ($p<0.05$) (**Table 3**).

Deaths

There were 75 deaths involving 89 suspected drugs. The majority of deaths were related to either cardiovascular events (22%), respiratory disorders (19%), or general disorders (23%). Sixty-seven percent of these fatal events were not described on Brazilian labels.

Three ATC groups concentrated the major part of suspected drugs: alimentary tract and metabolism ($n=26$; 29%), antineoplastic ($n=19$; 22%), and anti-infectives ($n=18$; 20%). Miglustat and imipenem/cilastatin showed 88% and 25% of OL age use, respectively. Drug indication, as represented by ICD (International Classification of Diseases) classification, showed the predominance of metabolic disorders and infections. These findings are presented in **Table 4**.

Drugs classified in other groups: heparin, bosentan, furosemide, gentamicin, hydrocortisone, methylprednisolone, ibuprofen, metamizole sodium, methadone, alpha poractant, fenoterol, fluticasone and salmeterol, technetium (^{99m}Tc) ethylenedicysteine, coagulation factor viii, coagulation factor IX, II, VII, and X in combination, were also reported. There were four cases, all involving newborns, related to contamination of solutions (parenteral nutrition and sodium chloride).

Safety Signals

Using the disproportionality analysis, applying a signal threshold of (N) ≥ 3 , results pointed to 65 SDRs involving mostly anti-infectives for systemic use (34%), antineoplastic agents (15%), nervous system drugs (12%), and alimentary tract and metabolism drugs (11%). For (N) ≥ 5 , 42 signals were involved mostly with anti-infectives for systemic use (55%), nervous system (17%), antineoplastic agents (12%), and sensory organs drugs (12%). From 107 signals of disproportionate reporting, 16 events (15%) were not described on the Brazilian label, (**Table 5**). Two pairs were suspected with deaths: imipenem/cilastatin–pneumonia, and laronidase–respiratory insufficiency.

DISCUSSION

Our study found a higher frequency of SADRs in children (60%) than is generally reported compared to other pediatric studies, in which rates of SADRs reported in national databases ranged from 0% to 66.7% (Aagaard et al., 2010; Smyth et al., 2012). The relatively high reported frequency of SADRs in children in this study may be due to the high proportion of *Notivisa* data attributed to inpatients. Another hypothesis is that this database does not discriminate the adverse drug reactions caused by medication errors. The Adverse Drug Reactions in Children (ADRIC) program in the UK reported the incidence of

TABLE 1 | Distribution of SADR reports ($n=1977$) by patient age in Brazil between 2008-2013.

Seriousness	Baby (aged 0 – 1 y)	Toddler (aged 1 – 3 y)	Preschool (aged 3 – 5 y)	Primary school (aged 5 – 8 y)	Secondary school (aged 8 – 12 y)	Total (%)
1 – Death	24	14	10	13	14	75 (4,0)
2 - Life threatening	102	36	26	19	33	216 (11,0)
3 - Prolonged hospitalization	65	61	44	28	65	263 (13,0)
4 - Congenital abnormalities	2	1	0	0	0	3 (0,2)
5 - Persistent or significant disability	4	3	9	4	7	27 (1,3)
6 - Medically important events	345	230	192	203	423	1393 (70,5)
Total	542	345	281	267	542	1977

SADR, Serious Adverse Drug Reaction; y = year(s). Congenital abnormalities: SADR in children related to medicine use during the mother's pregnancy. Source: *Notivisa/Anvisa*. P value $< 0,001$ (Chi Square test).

TABLE 2 | Distribution of suspected drugs by ATC classification involved in 1977 reports of SADR in Brazil between 2008-2013.

Description	Frequency	
	[n]	%
Drug class (ATC)	2229	100
Alimentary tract and metabolism (A)	153	6,9
Blood and blood forming organs (B)	100	4,5
Cardiovascular system (C)	54	2,4
Dermatological (D)	9	0,4
Genito urinary system and sex hormones (G)	2	0,1
Systemic hormonal preparations (H)	56	2,5
Anti-infectives for systemic use (J)	1048	47,0
Antineoplastic and immunomodulating agents (L)	221	10,0
Musculo-skeletal system (M)	51	2,3
Nervous system (N)	384	17,2
Antiparasitic products, insecticides and repellents (P)	24	1,0
Respiratory system (R)	47	2,1
Sensory organs (S)	43	1,9
Various (V)	37	1,7

ATC, Anatomical Therapeutic Chemical Code; SADR, Serious Adverse Drug Reactions. Source: Notivisa/Anvisa.

TABLE 3 | Distribution of suspected drugs (total and OL prescription by age) by seriousness of SADR in children in Brazil between 2008-2013.

Seriousness classification	Number of drugs		P value
	Total	Prescribed as OL (%)	
Death	89	26 (29%)	0.043*
Life threatening	239	50 (21%)	
Prolonged hospitalization	306	89 (29%)	
Congenital abnormalities	3	2 (67%)	
Persistent or significant disability	31	12 (39%)	
Medically important events	1561	385 (25%)	
Total	2229	564 (25%)	

OL, Off-label; SADR, Serious Adverse Drug Reaction. Values in parenthesis are percentages. *Statistically significant at level of $P < 0.05$ (Chi Square test).

ADRs for hospitalized children as 15.9% (Smyth et al., 2014). A retrospective analysis based on 5 years of pharmacovigilance studies (2012-2016) in an Italian hospital observed 834 ADRs, of which 239 (29%) were serious (Lombardi et al., 2018).

One study reported age as a risk factor for an ADR (Lombardi et al., 2018). Our results suggest evidence of an association ($p < 0.05$) between age and the seriousness of an ADR (Table 1).

Vancomycin ($n=9,2\%$), Ceftriaxone (5,9%), and Oxacillin ($n=5,7\%$) were the specific drugs most commonly reported as being associated with a suspected SADR in the current study. Anti-infectives and antiepileptics represent the most frequently reported therapeutic classes associated with ADRs in children admitted to hospital, and non-steroidal anti-inflammatory drugs were often reported as associated with ADRs in outpatient children (Smyth et al., 2012). Our findings agree with this review, although the proportion of ADRs associated with antiepileptic drugs was small (1%).

The intravenous route represented the most common dosage form (69%) associated with a suspected SADR, which also may be attributable to the Sentinel Network notifications being dominated by inpatients. However, this route represents a higher risk for the incidence of medical errors than with other formulations (Grissinger, 2010), which reinforces the necessity of discussions about the selection and development of better

formulations for children in Brazil. Furthermore, cases of contamination of sterile solutions have been reported, which may be related to problems in preparing and administering these products for newborns.

The Food and Drug Administration (FDA) and EMA implemented regulatory initiatives for pediatric medicines in the early 2000s. Both agencies created legislation to perform studies in children for products seeking marketing authorization in adults that meet certain criteria based on the relevance to public health (Turner et al., 2014). These initiatives have had a positive impact on pediatric drug development, and pediatric considerations have become an integral part of pharmaceutical development across the US and Europe (European Commission, 2016; Food and Drug Administration, 2016).

In Brazil, even with the participation of Anvisa in the Pediatric medicines Regulators' Network (PmRN) (WHO, 2010), no similar initiative was taken by any Brazilian regulatory authority regarding pediatric drug development. Nevertheless, prioritization of license analysis of a new drug, further pharmaceutical form, new therapeutic indication, and new concentrations for children (fast track) can be requested (Brazil, 2017).

Regarding other policies to ensure safer pharmacotherapy, Brazilian regulatory standards for manufacturers currently do

TABLE 4 | Description of suspected drugs (from main ATC groups reported) involved in child deaths on Notivisa between 2008-2013.

Suspected Drug	ICD Classification (drug indication)	Total reports by drugs (n)/OL or UL* use (n)	Main events ¹ classified by System Organ Class
A - Alimentary tract and metabolism		26 (12)	
Alfaglicosidase	Glycogen storage disease	3 (0)	Cardiovascular/Respiratory
Calcium gluconate	Not reported	1 (0)	General disorders
Imiglucerase	Lipid deposit disorders	3 (0)	General disorders/Respiratory
Laronidase	Mucopolysaccharidosis type I	6 (0)	General disorders/Cardiovascular/Respiratory
Metoclopramide	Nausea and vomiting	3 (3)	Blood/Cardiovascular
Miglustat	Not reported	9 (8)	General disorders/Gastro-intestinal system/Neurologic/Respiratory
Ondansetron	Nausea and vomiting	1 (1)	Cardiovascular
J - Anti-infectives for systemic use		18 (4)	
Ampiciline	Not reported	3 (0)	Neurologic
Benzylpenicillin	Not reported	1 (0)	Neurologic
Caspofungin	Localized infections of the skin and subcutaneous tissue	1 (1)	General disorders
Ceftriaxone	Acute upper airway infection	1 (1)	Respiratory
Imipenem/Cilastatin	Complications of heart defects; Bacterial pneumonia; Infections due to other mycobacteria; Other bacterial diseases; Unspecified microorganism pneumonia	8 (2)	Blood/General disorders/Cardiovascular/Endocrine/Gastro-intestinal/Musculo-skeletal system/Neurologic/Respiratory system/Urinary
Imunoglobuline (human)	Not reported	1 (0)	Cardiovascular
Meropenem	Not reported	1 (0)	Neurologic
Metronidazole	Other venous embolism and thrombosis	1 (0)	Blood
Oxacillin	Not reported	1 (0)	Skin
L - Antineoplastic and immunomodulating agents		19 (14)	
Carboplatin	Not reported	1 (1)	General disorders
Carmustine +	Not reported	4 (4)	Cardiovascular
Cytarabine + Etoposide + Melphalan			
Clofarabine	Lymphoid leukemia	8 (8)*	Blood/General disorders/Cardiovascular/Respiratory
Ifosfamide	Not reported	2 (0)	Gastro-intestinal
Methotrexate	Not reported	2 (0)	Blood/General disorders/Cardiovascular/Gastro-intestinal system/Neurologic/Respiratory/Skin
Rituximab	Adverse effects of primarily systemic action substances	1 (1)	Endocrine
Vincristine	Lymphoid leukemia	1 (0)	General disorders

ATC, Anatomical Therapeutic Chemical Code; ICD, International Classification of Diseases; OL, Off-label; UL*, Unlicensed use; Not reported, no information about drug indication on database.

not provide differentiated strategies for monitoring drugs used in children. *Anvisa* became a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2016. There was a public consultation for update rules (in 2018) in which the Periodic Benefit-Risk Evaluation Report (PBRER) and the pharmacovigilance planning would meet the criteria adopted by ICH, concerning the information on the benefit-risk profile of drugs in special populations, such as children. Unfortunately, the new regulation is not yet published due to challenges in the resources required to complete the guidance *Anvisa* (Brazil, 2019b). Such challenges in the development and dissemination of territory-specific safety guidance can increase the risk associated with the use of children's medicines in middle-income countries like Brazil.

The percentage of drugs associated with any serious SADR level, which used OL, was 25% (range 21-67%) (Table 3). Children are especially vulnerable to SADRs due to the lack of

data for this age group and the extensive use of OL and UL drugs (Elzagallaai et al., 2017). Reducing OL use in children could decrease the impact of SADRs, such as prolonged hospitalization, persistent disability, and death, as shown in Table 3 ($p < 0.05$). In 2013, a prospective cohort study conducted in a pediatric hospital in the United Kingdom evaluating the impact of OL and UL prescribing on ADRs causing admissions to a pediatric hospital showed a 23% increase in ADR risk due to OL use (Bellis et al., 2014).

Of the SADR reports which were associated with deaths, babies (0-1-year-old) ($n=24$; 32%) were the age group most implicated (Table 1). Neoplasms, respiratory, infectious and parasitic, related nervous or cardiovascular system diseases, and chromosomal abnormalities or congenital malformation stand out as causes of mortality and or morbidity in Brazilian children (Vieira et al., 2017). Considering that most records were from hospitalized children, it was expected that serious ADRs in Brazil would involve babies and drugs with related indications, as shown in

TABLE 5 | Drug-event pairs associated with Signals of Disproportionate Reporting (SDR) not described in drug label (Brazilian label).

Suspected Drug	Event description	ROR	Lower bound 95%	Seriousness of suspected ADRs found	Thresholds of number of cases (n)
Alphaglucosidase	Asthenia	66.77	27.10	Medically important	≥5
Amphotericin B	Hypokalemia	54.24	24.95	Life threatening	≥5
				Prolonged hospitalization	
				Medically important	
Ciclosporin	Nystagmus	47.11	13.70	Medically important events	≥3
	Psychosis	15.30	4.30	Medically important events	≥3
	Blurred vision	212.5	37.38	Life threatening	≥3
				Prolonged hospitalization	
				Persistent or significant disability	
				Medically important	
Imipenem and Cilastatin	Pneumonia	42.80	11.68	Death	≥3
Laronidase	Respiratory insufficiency	29.05	7.53	Death	≥3
				Prolonged hospitalization	
	Papules	15.02	3.70	Medically important	≥3
Metoclopramide	Psychosis	15.30	54.27	Medically important	≥3
Oxacillin	Cough	2.94	1.00	Life threatening	≥3
				Prolonged hospitalization	
				Medically important	
Tropicamide	Apnea	75.95	18.33	Life threatening	≥3
	Asthenia	33.67	13.89	Medically important events	≥5
	Bradycardia	33.67	13.89		≥5
	Persistent crying	677.71	82.54		≥5
	Dyspnea	11.11	4.72		≥5
Vancomycin	Petechiae	3.38	1.23	Medically important events	≥5

ROR, Reporting Odds Ratio; ADR, Adverse Drug Reaction.

Table 4. Furthermore, drugs indicated for metabolism disorders (ICD class E) and infection diseases (ICD class J), as observed in **Table 4**, are well described in literature such as patterns of off-label prescribing in children (Luedtke and Buck, 2014; Gonçalves et al., 2017). In severe clinical conditions, there is a complex assessment of the balance between risks and benefits, and, even if there is a higher chance of a fatal adverse event, the use of the drug might be the best medical decision. However, labels are a primary source of safety information from manufacturers for healthcare professionals and must be up to date with the frequency of ADRs in order to take precautionary and management measures in case of serious events (Brazil, 2010).

There were only three reports classified as congenital anomalies. Although these are not drugs directly administered to children, damage to the fetus was suspected, making this information relevant for the pharmacotherapy monitoring and evaluation in special populations, including pregnant women. The pediatric disease burden in low-and middle-income countries is particularly affected by congenital anomalies, and the spontaneous notification of these events, as expected, was meager, which reinforces the demand for studies with better power to recognize these cases (WHO, 2020).

The present analysis described a high number of fatal events (67%) and were also associated with signals of disproportionate reporting (15%) (**Table 5**) not expressed in the product label.

Three drugs were suspected of eight or more fatal events: Miglustat, imipenem/cilastatin, and clofarabine. Of the suspected drugs associated with death, there was a high proportion of OL/UL use and specifically OK use, and, specifically the OL use (e.g., miglustat and imipenem/cilastatin) and UL use (e.g., clofarabine) associated with them (**Table 4**).

Disturbances such as diarrhea and flatulence are the most common adverse effects associated with miglustat therapy (Belmatoug et al., 2011; Remenova et al., 2015). In one fatal case, this event was present (**Table 4**). For imipenem/cilastatin, nausea and vomiting were also reported in the literature (Oliva et al., 2005) and was present in cases of deaths. Most of the events reported in the literature for clofarabine, such as blood disorders (e.g., neutropenia) and respiratory disorders (e.g., respiratory distress), have been described (Jeha et al., 2006; O'Connor et al., 2011) (**Table 4**).

Star et al. analyzed (2019) pediatric individual case safety reports from Vigibase and founded 27 potential signals. After an in-depth assessment, they pointed out eight signals involving dextromethorphan (OL use), olanzapine (accidental overdose), atomoxetine (two signals), temozolomide, deferiasirox, levetiracetam, and desloratadine. They used a data-driven predictive model that prioritized reporting a series of emergent signals by weighing disproportionate reporting patterns, completeness, recency, and geographic spread of individual case reporting and availability of case narratives.

Although it is one of Anvisa's goals, the Notivisa data analyzed in this study could not be sent to the Uppsala Monitoring Center, due to the incompatibility of notification systems, this study suggests the identification of new signals. However, we acknowledge that local practices, specific characteristics of the pediatric population, and pharmaceutical characteristics used in Brazil may have influenced our results.

We found 16 pairs involving serious events that need more assessment and follow-up. Imipenem/cilastatin and laronidase must be monitored for the risk of pneumonia and respiratory insufficiency, respectively. These pairs were reported as fatal events. A case report of imipenem/cilastatin-induced acute

eosinophilic pneumonia in a 60-year-old woman (Foong et al., 2016) reinforces a suspected link of this ADR.

Disproportionality analysis in pharmacovigilance databases is an exploratory and reliable method to generate signals. Once a new disproportionality ratio for a drug has been observed, further studies can be conducted to confirm the signal (Montastruc et al., 2011).

Spontaneous reporting is considered an accessible and low-cost pharmacovigilance method that provides drug use assessment in real-life situations for large sample sizes (Pal et al., 2013). However, underreporting of adverse reactions makes it impossible to estimate the actual frequency of events. Another limitation of secondary database use is missing data, which is particularly important for causality assessment. Although notifiers were trained for a prior analysis of the suspected ADR, some of the necessary data had not been captured by *Anvisa* and cannot be undertaken retrospectively.

CONCLUSION

We found substantial SADR reporting from the Brazilian database involving IV dosage forms and OL drug use in children. Imipenem and cilastatin, laronidase, clofarabine (unlicensed use), and miglustat (off label use) were suspected drugs related to deaths which were more frequently reported in the study period.

Moreover, the high number of signals of disproportionate reporting observed, mainly for anti-infectives, suggests that the safety profile of these medicines in children should be further investigated.

Finally, we recommend the dissemination and use of information from the periodic safety update reports for children, the development of pediatric formulations, and specific policy approval in Brazil following the examples of pediatric drug regulations in the US and Europe.

REFERENCES

- Aagaard, L., Christensen, A., and Hansen, E. H. (2010). Information about adverse drug reactions reported in children: a qualitative review of empirical studies. *Br. J. Clin. Pharmacol.* 70 (4), 481–491. doi: 10.1111/j.1365-2125.2010.03682.x
- AAP American Academy of Pediatrics (2019). *Ages and stages*. Available at: <https://www.healthychildren.org/English/ages-stages/Pages/default.aspx> (Accessed 11/01/2019).
- Angamo, M. T., Chalmers, L., Curtain, C. M., and Bereznick, L. R. E. (2016). Adverse-drug-reaction-WHO adverse drug reaction terminology related hospitalisations in developed and developing countries: a review of prevalence and contributing factors. *Drug Saf.* 39, 847–857. doi: 10.1007/s40264-016-0444-7
- Aronson, J. K., and Ferner, R. E. (2017). Unlicensed and off-label uses of medicines: definitions and clarification of terminology. *Br. J. Clin. Pharmacol.* 83 (12), 2615–2625. doi: 10.1111/bcp.13394
- Bellis, J. R., Kirkham, J. J., Nunn, A. J., and Pirmohamed, M. (2014). Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. *Br. J. Clin. Pharmacol.* 77 (3), 545–553. doi: 10.1111/bcp.12222
- Belmatoug, N., Burlina, A., Giraldo, P., Hendriks, C. J., Kuter, D. J., Menqel, E., et al. (2011). Gastrointestinal disturbances and their management in miglustat-

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital Universitário Clementino Fraga Filho Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EL conceptualized the study. JV and EL led data collection, carried out the analysis, and drafted the initial manuscript. GM, FS, LB, and MP assisted with interpretation of the data and preparation of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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- treated patients. *J. Inherit. Metab. Dis.* 34 (5), 991–1001. doi: 10.1007/s10545-011-9368-7
- Black, C., Tagiyeva-Milne, N., Helms, P., and Moir, D. (2015). Pharmacovigilance in children: adverse drug reactions in routine electronic healthcare records. A systematic review. *Br. J. Clin. Pharmacol.* 80 (4), 844–854. doi: 10.1111/bcp.12645
- Brazil (2010). *Guias de Farmacovigilância para Detentores de Registro de Medicamentos*. Agência Nacional de Vigilância Sanitária. Gerência de Farmacovigilância (Brasília: Editora MS), 156.
- Brazil (2011). *Agência Nacional de Vigilância Sanitária. Critérios para credenciamento de instituições na Rede Sentinela*. Available at: <http://portal.anvisa.gov.br/documents/33868/1853050/Crit%C3%A9rios+para+participa%C3%A7%C3%A3o+na+Rede+Sentinela/1e9915f2-180b-4581-9828-617c7629b2a0> (Accessed 05/14/2020).
- Brazil (2015). *Agência Nacional de Vigilância Sanitária. Nota Técnica GVIMS/GGTES/ANVISA no 01/2015. Orientações gerais para a notificação de eventos adversos relacionados à assistência à saúde*. Available at: <http://portal.anvisa.gov.br/documents/33852/271858/Nota+tecnica+GVIMS+GGTES+ANVISA+01+de+2015+-GVIMS-GGTES-ANVISA/b98ec033-1676-4443-9603-24a4edae1505> (Accessed 05/30/2020).
- Brazil (2017). *Agência Nacional de Vigilância Sanitária. Resolução de Diretoria Colegiada no 204, de 27 de dezembro de 2017*. Available at: <http://portal.anvisa.gov.br/documents/33852/271858/Resolucao+de+Diretoria+Colegiada+no+204,+de+27+de+dezembro+de+2017>

- gov.br/documents/10181/2718376/RDC_204_2017_.pdf/b2d4ae64-2d91-44e9-ad67-b883c752c094 (Accessed 05/14/2020).
- Brazil (2019a). Agência Nacional de Vigilância Sanitária. Sistema de Notificação em Vigilância Sanitária (Notivisa). Available at: <http://portal.anvisa.gov.br/notivisa> (Accessed 12/17/2019).
- Brazil (2019b). Agência Nacional de Vigilância Sanitária. Boletim de Farmacovigilância no. 6 [Online]. Available at: <http://portal.anvisa.gov.br/documents/33868/2894786/Boletim+de+Farmacovigil%C3%A2ncia+n%C2%BA+06/33f0afc5-f188-4bef-9378-14c6a9c6f624> (Accessed 05/14/2020).
- CIOMS (1987). International reporting of adverse drug reactions. International reporting of adverse drug reactions. Work Group Report. Available at: <https://cioms.ch/wp-content/uploads/2017/07/Int-Reporting-Adv-Drug-Reactions-1987.pdf> (Accessed 05/07/2019).
- CIOMS (2010). Practical Aspects of Signal Detection in Pharmacovigilance (Geneva: Council for International Organizations of medical Sciences). Available at: <https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf> (Accessed 02/02/2019).
- Elzagallaai, A. A., Greff, M., and Rieder, M. J. (2017). Adverse drug reactions in children: the double-edged sword of therapeutics. *Clin. Pharmacol. Ther.* 101 (6), 725–735. doi: 10.1002/cpt.677
- European Commission (2016). 10-year Report to the European Commission: general report on the experience acquired as result of the application of the Paediatric Regulation. Available at: https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf (Accessed 06/20/2018).
- European Medicines Agency (2006). Guideline on the use of statistical signal detection methods in the Eudravigilance Data Analysis System. Available at: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-guideline-use-statistical-signal-detection-methods-eudravigilance-data-analysis-system_en.pdf (Accessed 05/14/2019).
- European Medicines Agency (2016). Screening for Adverse Reactions in EudraVigilance. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf (Accessed 02/06/2019).
- Food and Drug Administration (2016). Best pharmaceuticals for children act and pediatric research equity act. Available at: <https://www.fda.gov/downloads/scienceresearch/specialtopics/pediatrictherapeuticsresearch/ucm509815.pdf> (Accessed 04/02/2019).
- Foong, K. S., Lee, A., Pekez, M., and Bin, W. (2016). Imipenem/cilastatin-induced acute eosinophilic pneumonia. *BMJ Case Rep.* 4. doi: 10.1136/bcr-2016-214804
- Gonçalves, M. G., and Heineck, I. (2016). Frequency of prescriptions of off-label drugs and drugs not approved for pediatric use in primary health care in a southern municipality of Brazil. *Rev. Paul Pediatr.* 34 (1), 11–17. doi: 10.1016/j.rppede.2015.06.023
- Gonçalves, A. C. S., Reis, A. M. M., Marçal, A. C. G., and Bouzada, M. C. F. (2017). Use of unlicensed and off-label drugs in neonates in a Brazilian university hospital. *Braz. J. Pharm. Sci.* 53 (3), e00252.
- Grissinger, M. (2010). Reducing errors with injectable medications: unlabeled syringes are surprisingly common. *Pharm. Ther.* 35 (8), 428–451.
- Harpaz, R., DuMouchel, W., Shah, N. H., Madigan, D., Ryan, P., and Friedman, C. (2012). Novel data-mining methodologies for adverse drug event discovery and analysis. *Clin. Pharmacol. Ther.* 91 (6), 1010–1021. doi: 10.1038/clpt.2012.50
- ICH Expert Working Group (2003). International Conference on Harmonisation. Post-approval safety data management: definitions and standards for expedited reporting. Published in the Federal Register. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf (Accessed 09/22/2019).
- Jeha, S., Gaynon, P. S., Razzouk, B. I., Franklin, J., Kadota, R., Shen, V., et al. (2006). Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J. Clin. Oncol.* 24 (12), 1917–1923. doi: 10.1200/JCO.2005.03.8554
- Joseph, P. D., Craig, J. C., and Caldwell, P. H. (2015). Clinical trials in children. *Br. J. Clin. Pharmacol.* 79 (3), 357–369. doi: 10.1111/bcp.12305
- Lima, E. C., Matos, G. C., Vieira, J. M. L., Gonçalves, I. C. C. R., Cabral, L. M., and Turner, M. (2019). Suspected adverse drug reactions reported for Brazilian children: cross-sectional study. *J. Pediatr. (Rio J)* 95 (6), 682–688. doi: 10.1016/j.jped.2018.05.019
- Lombardi, N., Crescioli, G., Bettiol, A., Marconi, E., Vitiello, A., Bonaiuti, R., et al. (2018). Characterization of serious adverse drug reactions as cause of emergency department visit in children: a 5-years active pharmacovigilance study. *BMC Pharmacol. Toxicol.* 19 (1), 1–8. doi: 10.1186/s40360-018-0207-4
- Luedtke, K. E., and Buck, M. L. (2014). Evaluation of off-label prescribing at a children's rehabilitation center. *J. Pediatr. Pharmacol. Ther.* 19 (4), 296–301. doi: 10.5863/1551-6776-19.4.296
- Montastruc, J. L., Sommet, A., Bagheri, H., and Lapevre-Mestre, M. (2011). Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br. J. Clin. Pharmacol.* 72, 905–908. doi: 10.1111/j.1365-2125.2011.04037.x
- Mota, D. M., Vigo, A., and Kuchenbecker, R. S. (2018). Evolution and key elements of the Brazilian pharmacovigilance system: a scoping review beginning with the creation of the Brazilian Health Regulatory Agency. *Cad Saúde Pública* 34 (10), e00000218. doi: 10.1590/0102-311x00000218
- Oliva, M. E., Rekha, A., Yellin, A., Pasternak, J., Campos, M., Rose, G. M., et al. (2005). A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [Study ID Numbers: 3074A1-301-WW; ClinicalTrials.gov Identifier: NCT00081744]. *BMC Infect. Dis.* 19;5, 88. doi: 10.1186/1471-2334-5-88
- Olsson, S., Pal, S. N., and Dodoo, A. (2015). Pharmacovigilance in resource-limited countries. *Expert Rev. Clin. Pharmacol.* 8 (4). doi: 10.1586/17512433.2015.1053391
- O'Connor, D., Sibson, K., Caswell, M., Connor, P., Cummins, M., Mitchel, C., et al. (2011). Early UK experience in the use of clofarabine in the treatment of relapsed and refractory paediatric acute lymphoblastic leukaemia. *Br. J. Haematol.* 154 (4), 482–485. doi: 10.1111/j.1365-2141.2011.08752.x
- Osokogu, O. U., Dodd, C., Pacurariu, A., Kagueldou, F., Weibel, D., and Sturkenboom, M. C. J. M. (2016). Drug safety monitoring in children: performance of signal detection algorithms and impact of age stratification. *Drug Saf.* 39 (9), 873–881. doi: 10.1007/s40264-016-0433-x
- Pal, S. N., Duncombe, C., Falzon, D., and Olsson, S. (2013). WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug Saf.* 36, 75–81. doi: 10.1007/s40264-012-0014-6
- Remenova, T., Morand, O., Amato, D., Chadha-Boreham, H., Tsurutani, S., and Marquardt, T. (2015). A double-blind, randomized, placebo-controlled trial studying the effects of *Saccharomyces boulardii* on the gastrointestinal tolerability, safety, and pharmacokinetics of miglustat. *Orphanet J. Rare Dis.* 10, 81. doi: 10.1186/s13023-015-0297-7
- Smyth, R. M. D., Gargon, E., Kirkham, J., Cresswell, L., Golder, S., Smyth, R., et al. (2012). Adverse drug reactions in children—a systematic review. *PLoS One* 7 (3), e24061. doi: 10.1371/journal.pone.0024061
- Smyth, R. L., Peak, M., Turner, M. A., Nunn, A. J., Williamson, P. R., Young, B., et al. (2014). ADRIC: Adverse Drug Reactions In Children—a programme of research using mixed methods (Southampton (UK: NIHR Journals Library), 214.
- Star, K., Sandberg, L., Bergvall, T., Choonara, I., Caduff-Janosa, P., and Edwards, I. R. (2019). Paediatric safety signals identified in VigiBase: Methods and results from Uppsala Monitoring Centre. *Pharmacoepidemiol. Drug Saf.* 28 (5), 680–689. doi: 10.1002/pds.4734
- Teixeira, A. P. C. P., Leitão, L. O., Barbosa, P. F. T., Cammarota, D. M. O. T., and Rocha, V. L. C. (2017). Perfil de estabelecimentos de saúde brasileiros participantes da Rede Sentinela. *Vigil. Sanit. Debate* 5 (4), 88–93. doi: 10.22239/2317-269x.01006
- Turner, M. A., Catapano, M., Hirschfeld, S., Giaquinto, C. GRIP (Global Research in Paediatrics) (2014). Paediatric drug development: the impact of evolving regulations. *Adv. Drug Delivery Rev.* 73: 30, 2–13. doi: 10.1016/j.addr.2014.02.003
- Vieira, J. M. L., Lima, E. C., Land, M. G. P., Ventura, M., and Coelho, H. L. L. (2017). Profile of clinical trials enrolling Brazilian Children. *Cad Saúde Pública* 33 (5), e00169515. doi: 10.1590/0102-311x00169515
- WHO. World Health Organization (2010). Paediatric Medicines Regulators' Network. Available at: http://www.who.int/childmedicines/paediatric_regulators/objectives/en/ (Accessed 08/11/2019).
- WHO. World Health Organization (2018). Adverse Reaction Terminology WHO-ART Uppsala (Sweden: The Uppsala Monitoring Center). Available at: <http://www.ums-products.com/DynPage.aspx> (Accessed 06/11/2019).

WHO. World Health Organization (2020). *Congenital anomalies*. Available at: https://www.who.int/health-topics/congenital-anomalies#tab=tab_1 (Accessed 05/30/2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Medication Review by Community Pharmacists for Type 2 Diabetes Patients in Routine Care: Results of the DIATHEM-Study

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Most elderly patients with type 2 diabetes take multiple drugs. Earlier studies in other countries suggested that interdisciplinary medication reviews are beneficial for these patients regarding medication safety and therapy optimization. In Germany, medication reviews by community pharmacies are rarely performed, although it is a service stipulated in the "Apothekenbetriebsordnung" (rules governing the operation of pharmacies in Germany) since 2012. Therefore, the aim of the DIATHEM study (type 2 DIabetes: optimizing THerapy by Medication review in community pharmacies) was to evaluate the impact of medication reviews from German community pharmacies under real-life conditions. Primary outcomes were: identification of drug related problems (DRPs) and to evaluate to what extent they could be solved by the medication review. Secondary outcomes were: evaluation of changes in the number of drugs and the interdisciplinary cooperation between pharmacists and physicians. In a single arm interventional study, 121 patients aged 65 or older with type 2 diabetes, taking at least five drugs for long-term treatment were provided with one medication review between February 2016 and April 2017. Physicians were not pre-informed about the review and neither patients nor physicians nor the 13 participating community pharmacies were reimbursed for their contributions to the study. For 121 patients, 586 DRPs were identified (4.84 DRPs per patient) of which 31.6% were related to the antidiabetics. Due to the medication review, 46.9% of these DRPs could be completely resolved, indicating a statistically significant decline from 4.84 DRPs to 2.57 DRPs per patient ($p < 0.001$). The average number of drugs was significantly reduced from 9.5 drugs (standard deviation, SD = 2.9) to 9.3 drugs (SD = 2.8) per patient ($p < 0.001$). The pharmacists received feedback for 76.7% of the intervention proposals sent to the physicians. In total 59.5% of the intervention proposals were accepted, of which 643 (85.3%) were accepted and fully implemented. In conclusion, the study shows that medication reviews performed by community pharmacists under routine care conditions reduced the frequency and number of DRPs, even though the pharmacies had to face obstacles such as lack of cooperation by the prescriber or lack of reimbursement.

Keywords: type 2 diabetes, pharmaceutical care, medication review, medication management, drug safety, community pharmacy, interprofessional collaboration, Germany

INTRODUCTION

Type 2 diabetes (T2DM) is a widespread disease with severe complications. In 2017, approximately 425 million adults worldwide and 58 million Europeans were diagnosed with diabetes and 4 million deaths were caused by this disease. The percentage of T2DM in all diabetes patients is around 90%, but currently increasing in most countries (International DiabetesFederation, 2017). In the US, 30.3 million people (9.4% of the population) suffered from diabetes in 2015 (Centers for Disease Control and Prevention, 2017). In 2017, around 7.5 million adults aged 20–79 in Germany were diagnosed with diabetes, plus an estimated 2.6 million with undiagnosed diabetes (International DiabetesFederation, 2017). T2DM has a prevalence of 7%–8% in German adults, with the highest prevalence for people aged 80 or older (currently around 1 million) (DDG Deutsche Diabetes Gesellschaft, 2018). There are many chronic complications of diabetes such as coronary artery disease and peripheral artery diseases leading to myocardial infarction, stroke, and diabetic foot. Cardiovascular and renal complications are the main causes of death in diabetes patients (International DiabetesFederation, 2017). Mortality rates for people with diabetes (15.6 per 1,000 person-years) are similar to those with a history of stroke or myocardial infarction at the age of 60 years. Without any of these conditions the mortality risk is 6.8 per 1,000 person-years, while any combination of these three conditions further multiplies the risk (The Emerging Risk Factors Collaboration, 2015). Appropriate treatment can avoid these complications and risks. Pharmaceutical care interventions such as a medication review (MR) for patients with T2DM (Wermeille et al., 2004; Machado et al., 2007) and multimorbidity (Koberlein-Neu et al., 2016) may largely contribute to reach that aim. It was shown before that the effect of a MR correlates with the number of drugs in use (Rose et al., 2016).

A MR is “a structured evaluation of a patient’s medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting DRPs and recommending interventions” (Griese-Mammen et al., 2018). The positive impact of pharmacist-led interventions such as MR on medical treatment and quality of life was repeatedly shown in international studies (Isetts et al., 2003; Isetts et al., 2008; Laaksonen et al., 2010; Pringle et al., 2014; Chau et al., 2016). Also in the field of diabetes, international investigations demonstrated the positive impact of pharmacist-led interventions on diabetes patients by reduction of HbA1c (Wermeille et al., 2004; Machado et al., 2007; Anaya et al., 2008; Wubben and Vivian, 2008), blood pressure (Wermeille et al., 2004), blood glucose (Anaya et al., 2008), lipid profile (Wermeille et al., 2004; Anaya et al., 2008) as well as the impact on cost reduction (Anaya et al., 2008). In Germany, MRs are at present not comprehensively implemented in community pharmacies, even though it is officially defined as a pharmaceutical service according to the “Apothekenbetriebsordnung” (Vierte Verordnung zur Änderung der Apothekenbetriebsordnung, 2012) (the rules governing the operation of pharmacies) since 2012. Apart from some pilot studies or regional projects (Koberlein-Neu et al., 2016; Seidling et al., 2017; Aktas, 2019; ARMIN, 2019), no

remuneration is provided for the community pharmacies by the German healthcare system as an incentive for them to perform MRs.

The aim of the DIATHEM study (type 2 DIabetes: optimizing THErapy by Medication review in community pharmacies) was to examine the effect of MRs in community pharmacies under routine care conditions in Germany. The influence of MRs performed in a real-life setting on elderly multimorbid patients with TD2M on the frequency of DRPs and on the number of drugs as well as the extent of interprofessional collaboration between pharmacist and physicians were analyzed.

MATERIALS AND METHODS

This study was designed as a single arm interventional trial (Dickson et al., 2020).

Primary Outcomes

Primary outcomes were the identification of type and frequency of DRPs. In particular, the primary outcomes were assessed as type and frequency of DRPs that could be totally, partially, or not at all solved by the MR.

Secondary Outcomes

Secondary outcomes were the identification of type and frequency of antidiabetic drugs and co-medication, evaluation of changes in the number of drugs by the MR and evaluation of the interprofessional cooperation between pharmacists and physicians in the context of the MR, for example willingness to cooperate in general and acceptance or refusal of intervention proposals.

Sample Size Calculation

The sample for the primary outcome (reduction in the number of DRPs) was calculated assuming a similar reduction of DRPs as in a comparable study, where a reduction of 0.45 DRPs was shown (Koberlein-Neu et al., 2016). Thus, when comparing the number of DRPs per patient before and after the intervention MR, the aim was an average reduction of 0.5 DRP per patient with an estimated standard deviation of differences of 2.2. Considering 80% power and 5% significance level (alpha) in a paired means power analysis, a minimum of 117 participants were needed (Zar, 1984; Machin et al., 1997).

Setting

For this one arm interventional trial, type 2 diabetes patients matching the inclusion criteria were recruited in 13 community pharmacies in the area of Munich.

Prior to recruiting, employees (including at least one pharmacist per community pharmacy) of all participating community pharmacies were trained in the study procedure by the study coordinator. The study coordinator (consultant pharmacist) is a pharmacist herself and has acquired additional qualifications and professional experience in the field of medication safety and MR.

The trial patient recruitment started in February 2016 until March 2017. Patients were contacted for recruiting purposes either *via* telephone, post or in person while visiting the community pharmacy. Only patients who were known to the pharmacist to suffer from T2DM or patients who had a prescription for an antidiabetic (excluding insulin) were contacted for recruitment. The MR was carried out during or after a patient's pharmacy visit.

All patients meeting the inclusion criteria were provided with a MR, type 2a or 2b according to the definition of the PCNE (Griese-Mammen et al., 2018). For a MR type 2a, information is evaluated from medication history and patient interviews, for type MR 2b medication history and clinical data were assessed (Griese-Mammen et al., 2018). DRPs can be potential (in future possibly leading to real problems for the patient) or manifest (the problem already has an impact on the patient and his or her therapy) (Pharmaceutical Care Network Europe, 2019a). One MR per patient was performed.

Inclusion Criteria

Inclusion criteria were a patient's age of 65 years or older, diagnosis of T2DM, treatment with at least five different drugs regarding the total medication (prescription-only or over-the-counter drugs) as long-term treatment (drug use for more than 14 days) including at least one antidiabetic drug and that they could speak German. Either a drug that was taken as long-term medication or a drug that was given on-demand was counted as one drug, but a patient with four drugs as long-term treatment and one drug on-demand for example did not meet the inclusion criteria. The limit value five or more drugs was chosen because polypharmacy, in the majority of cases, is defined as the routine use of five or more medications (World Health Organization, 2019).

Data Collection

Patients that met the inclusion criteria were invited to participate in the study by the participating community pharmacies. They had to sign a written declaration of consent for the MR. A documentation sheet with the patient's data and medication was completed by the patient and discussed with a pharmacist during an appointment in the community pharmacy and forwarded to the consultant pharmacist.

If a patient met the inclusion criteria but was being cared for by an outpatient nursing service and, therefore, unable to visit the community pharmacy by themselves, communication took place between the community pharmacy and the outpatient nursing service. In this case, a detailed medication plan was presented to the community pharmacy, which was then forwarded to the consultant pharmacist.

Patient-related data was collected including name, sex, age, main health complaints, allergies, and medication plan, if available. For each drug the following aspects were recorded: drug name (brand), active ingredient, dosage form, strength, dosage regimen, dosage recommendation, indication for drug if known by the patient, prescribing physician (if the drug was prescribed).

Any additionally available treatment-related information as prescribed by the patient was documented, e.g. laboratory values,

vital parameters and diagnosis. If a patient had been prescribed an antidiabetic (oral or injectable, except insulin) and in conversation with the pharmacist stated that he or she was suffering from T2DM, we assumed that this was indeed the truth. In most cases, a medication review was sent to the patient's physician and we presume that the physician would have informed us if the diagnosis was incorrect.

Drugs were coded with the Anatomical Therapeutic Chemical (ATC) Classification System (WHO Collaborating Centre for Drug Statistics and Methodology, 2019).

Intervention

After data collection, the consultant pharmacist performed a PCNE type 2a MR for patients who had an appointment at the community pharmacy, respectively type 2b for those patients supported by an outpatient nursing service. The pharmaceutical personnel of the community pharmacy were informed about any detected DRPs and intervention proposals in order to solve the DRPs by the consultant pharmacist.

The DRPs were intended to be solved in cooperation with the responsible physician except where the nature of the DRP could be resolved by direct interaction between pharmacist and patient. Otherwise, the physicians were contacted in writing (via fax or post) by the community pharmacy and provided with a detailed description of the detected DRPs as well as intervention proposals and feedback requests. No clinical investigators were recruited to the study. The physicians in our study were not informed in advance about this pharmaceutical service, in order to avoid prescription bias or bias by being on the alert for DRPs in advance of the intervention. Another reason why the physicians were not specifically asked to participate in advance was to avoid bias in terms of cooperation or refusal to cooperate with the pharmacists.

If the physician responded, the community pharmacy generated an updated medication plan including any accepted intervention proposals or other changes made by the physician. If there was no response, the physician was contacted a second time, after 2 weeks at the latest, and once again asked for feedback. By non-response after the second inquiry, a medication list was generated on the basis of information exclusively given by the patient or outpatient nursing service.

In a concluding appointment with a pharmacist in the community pharmacy, the patient was provided with the updated medication plan and respective medication list, changes in the medication—made by the physician—were explained, interventions were proposed to the patient and the patient's questions were answered. According to German law, some interventions, such as altering prescription medication, is not allowed to be done by pharmacists. Therefore, interventions that were proposed to the patient by the pharmacist involved only those interventions that are possible in a German community pharmacy, for example interventions concerning the dose timing of a drug or changes regarding over-the-counter drugs, which have not been prescribed or recommended by a physician. If the patient was supported by an outpatient nursing service, the service personnel were provided with the updated medication plan or medication list. The patient or nursing service was asked to present

the medication plan or medication list at the following medical appointment.

As a follow-up and for evaluating the status of the DRPs after the MR, patients were asked about the implementation of proposed interventions and any further medication changes by their physician relating to the MR. The follow-up took place at one of the patient's next visits after the MR in the community pharmacy or by telephone within 4 weeks after the MR. The involved outpatient nursing services were asked regularly about updated medication plans for patients that were provided with a MR. The final follow-up data was collected in April 2017. Depending on the patient, the time between the concluding appointment, when the medication plan or medication list was handed over to the patient, and the follow-up varied considerably and was not evaluated. The last patient was enrolled in the study at the beginning of April 2017. It is a coincidence that the follow-up for this patient also took place in April 2017 and not later.

Financial Compensation

Patients did not have to pay for this pharmaceutical service and were not paid for participating in the study. Neither the community pharmacies nor the physicians were reimbursed for participating in the study or performing the MR.

Detection and Classification of DRPs

Prescription-only drugs or drugs only available *via* pharmacies were considered for analysis. Homeopathic drugs were not taken into consideration.

DRPs were categorized using the PCNE (Pharmaceutical Care Network Europe) classification for Drug-Related Problems V9.0 (Pharmaceutical Care Network Europe, 2019b). Drug-drug interactions were identified using the drug interaction module of the German ABDA database in all medications. Regarding ADRs (adverse drug reactions) and drug interactions, only ADRs and drug interactions that were considered clinically relevant were categorized as a DRP.

Data Analysis and Statistics

De-identified data was used for evaluation. Sample size calculation was determined with PASS 14 Software (PASS, 2015). Statistical analysis was performed using SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA). Test of normal distribution was performed using the Kolmogorov-Smirnov goodness of fit test. The non-parametric two-sided Wilcoxon signed-rank test was used to examine the differences in frequency of DRPs and number of drugs before and after the MR.

Differences with a P value less than 0.05 were considered significant in all tests. Descriptive analysis was performed to examine:

- Demographic data
- Drugs used: antidiabetic drugs and co-medication (examination of the active ingredients, no distinction between originator and generics)
- Type and frequency of identified DRPs
- Drug interactions
- Changes in the number of drugs by the MR

- Type and frequency of identified DRPs that were totally, partially or not at all solved by the MR
- Measures that were taken to solve the DRPs
- Interprofessional collaboration: Proportion of physicians cooperating with the pharmacists in the context of the MR and extent of cooperation.

Ethics Approval

Before the beginning of the study, the responsible ethics committee was provided with a detailed project description. As the research project was classified as quality assurance, the ethical committee of the Bavarian State Chamber of Medicine (Bayerische Landesärztekammer) stated, that no ethic vote was required for this study.

Only patients that had signed a written declaration of consent for data-retention in the associated community pharmacies were recruited for the study. To participate in the study, the patients had to sign an additional written declaration of consent for the MR. This declaration of consent included the release from the confidentiality obligations for the community pharmacy and the patient's treating physician(s).

RESULTS

Patient Population

Overall, 121 patients were included in the DIATHEM study. More information on baseline characteristics are presented in **Table 1**.

Analysis of Drugs Used

Taken together the 121 patients received 1.149 drugs, of which 221 drugs were diabetic-related (oral or injectable antidiabetics including insulins).

Antidiabetics

Of the 221 antidiabetic drugs, biguanides with 43.0% (95 times; only Metformin) were most common, followed by Dipeptidyl-peptidase-4 inhibitors with 21.7% (48 times: Sitagliptin or Saxagliptin), insulins with 15.8% (33 times: most frequent: insulin glargine and insulin detemir) and sulfonylureas with 10.0% (22 times; Glimepirid, Glibenclamid, Gliquidon). Only one insulin or insulin analogue and no other antidiabetic drug was received by two patients (1.7%).

TABLE 1 | Demographic and baseline characteristics of patients.

Type 2 Diabetes Patients	
N	121
Gender (male/female; percentage)	58 (47.9)/63 (52.1)
Age at examination (years mean $\pm$ SD)	76.7 $\pm$ 7.6
Age 65-79 (years)	66.9
Age $\geq$ 80 (years)	33.1
Patients supported by an outpatient nursing service (percentage)	24.8
Involved community pharmacies (number)	13

SD, standard deviation.

Overall, almost half of all patients (47.1%) took only one antidiabetic drug, while 28.1% of the patients took two antidiabetics, 20.7% three antidiabetics, 3.3% four antidiabetics, and 0.8% five antidiabetics.

Co-Medication

In total, 928 drugs (80.8% of all drugs) were assigned to co-medication. The five most frequent drug classes classified by ATC-level 2 (WHO Collaborating Centre for Drug Statistics and Methodology, 2019) were agents acting on the renin-angiotensin system (C09), diuretics (C03), lipid modifying agents (C10), antithrombotic agents (B01), and beta blocking agents (C07), see **Table 2**.

Type and Frequency of Identified DRPs

A total of 586 DRPs were discovered in 121 patients, corresponding to 4.84 DRPs per patient. No DRP was identified in only three

patients (2.5%). Of all 586 DRPs, 401 DRPs involved the co-medication (68.4%) and 185 DRPs were diabetes-related. A DRP was assigned to the category diabetes-related if an antidiabetic drug (oral and injectable antidiabetics including insulin) was involved, for example a drug-drug interaction between an antidiabetic drug and an antihypertensive drug was categorized as diabetes-related. Categorized as manifest were 74.6% of all DRPs, the others were potential DRPs (**Figure 1**).

Classified by the PCNE classification for DRPs V9.0, the majority of DRPs were assigned to the problem domain *P1—Treatment effectiveness* (53.6%) and related mainly to the subdomain *P1.2 Effect of drug treatment not optimal* (45.9%). Second most prevalent problem domain was *P2—Treatment safety* (42.0%), related to the subdomain *P2.1—Adverse drug event (possibly) occurring* (42.0%) (**Table 3**). Most often, a DRP was assigned to the sub-section *P1.2 Effect of drug treatment not*

TABLE 2 | Shows the number and frequency of the ten most frequent drug classes (classified by ATC-Code level 2 (WHO Collaborating Centre for Drug Statistics and Methodology, 2019)) and the number and frequency of the most frequent drugs from each drug class out of all drugs (1.149).

Drug class (ATC-Code level 2)	Number of drugs in this drug class	Frequency of drugs in this drug class [%]	Drug name	Number of this drug	Frequency of this drug [%]
Antidiabetics (A10)	221	19.2	Metformin	95	8.3
			Sitagliptin	46	4.0
			Insulin	35	2.9
			Glimepiride	19	1.7
			Other	26	2.4
Agents acting on the renin-angiotensin system (C09)	100	8.7	Ramipril	51	4.4
			Valsartan	14	1.2
			Candesartan	13	1.1
			Other	22	1.9
			Hydrochlorothiazide	50	4.4
Diuretics (C03)	95	8.3	Torsemide	30	2.6
			Spironolactone	9	0.8
			Other	6	0.5
			Other	6	0.5
Lipid modifying agents (C10)	86	7.5	Simvastatin	53	4.6
			Atorvastatin	22	1.9
			Pravastatin	4	0.3
			Other	7	0.6
Antithrombotic agents (B01)	85	7.4	Acetylsalicylic acid	58	5.0
			Phenprocoumon	13	1.1
			Rivaroxaban	6	0.5
			Other	8	0.7
Beta blocking agents (C07)	63	5.5	Bisoprolol	43	3.7
			Metoprolol	17	1.5
			Nebivolol	2	0.2
			Other	1	0.1
Drugs for acid related disorders (A02)	51	4.4	Pantoprazole	41	3.6
			Omeprazole	8	0.7
			Hydrotalcite	1	0.1
			Other	1	0.1
Calcium channel blockers (C08)	45	3.9	Amlodipine	37	3.2
			Lercanidipine	4	0.3
			Nitrendipine	3	0.3
			Other	1	0.1
Thyroid therapy (H03)	39	3.4	Levothyroxine Sodium	38	3.3
Analgesics (N02)	38	3.3	Carbimazole	1	0.1
			Metamizole Sodium	12	1.0
			Tilidine	10	0.9
			Acetylsalicylic acid	4	0.3
Other drug classes	326	28.4	Other	12	1.0

optimal (45.9%). Although information on blood glucose level and HbA1c value were in most cases not available, an assignment to this category was possible for diabetes-related DRPs based on information provided by the patient and/or—if available—the medication plan. For example, if a patient was treated with Metformin 2.0 g once a day the code *P1.2 Effect of drug treatment not optimal* was chosen and a change to Metformin 1.0 g twice a day instead of 2.0 g once a day was recommended to the physician.

For all 586 DPRs, 617 causes have been identified, mostly categorized into C1—Drug selection (45.2%) and C3—Dose selection (49.3%). **Table 4** shows the detailed distribution of the causes.

In total, 1,267 interventions were made or proposed by the pharmacist, on average 2.2 interventions per DPR, referring to categories I1—At prescriber level (40.9%), I2—At patient level (22.6%) and I3—At drug level (36.5%). No intervention was made or proposed for 32 DRPs. For example, an intervention proposal was made to the prescriber (code I1.3) if a patient seemed to suffer from T2DM and hypertension, but received no angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor blockers (ARB). The suggestion was to prescribe an ACE-inhibitor or ARB if there was no contraindication or intolerance as these drugs are recommended by guidelines for patients with T2DM and hypertension due to

TABLE 3 | Classification of the DRPs—Problem domain.

Classification of the DPRs (n = 586)	Number of problems	Frequency of problems [%]
P1—Treatment effectiveness	314	53.6%
P1.1—No effect of drug treatment	27	4.6%
P1.2—Effect of drug treatment not optimal	269	45.9%
P1.3—Untreated symptoms or indication	18	3.1%
P2—Treatment safety	246	42.0%
P2.1—Adverse drug event (possibly) occurring	246	42.0%
P3—Other	26	4.4%
P3.1—Problem with cost-effectiveness of the treatment	6	1.0%
P3.2—Unnecessary drug-treatment	20	3.4%

their nephroprotective potential. **Table 5** shows the detailed distribution of the interventions.

Drug Interactions

A total of 694 interactions (5.7 per patient) with a minimum of 0 and a maximum of 19 interactions per patient (SD = 4.2), classified by the ABDA database, were identified among the 121 participants. Only 1 of all 694 interactions was within grades 1-3 of the ABDA Database. 11.8% of the interactions were considered clinically relevant and regarded as a DPR in the course of the MR. From the clinically relevant interactions, 80 were drug-drug interactions and two drug-food interactions.

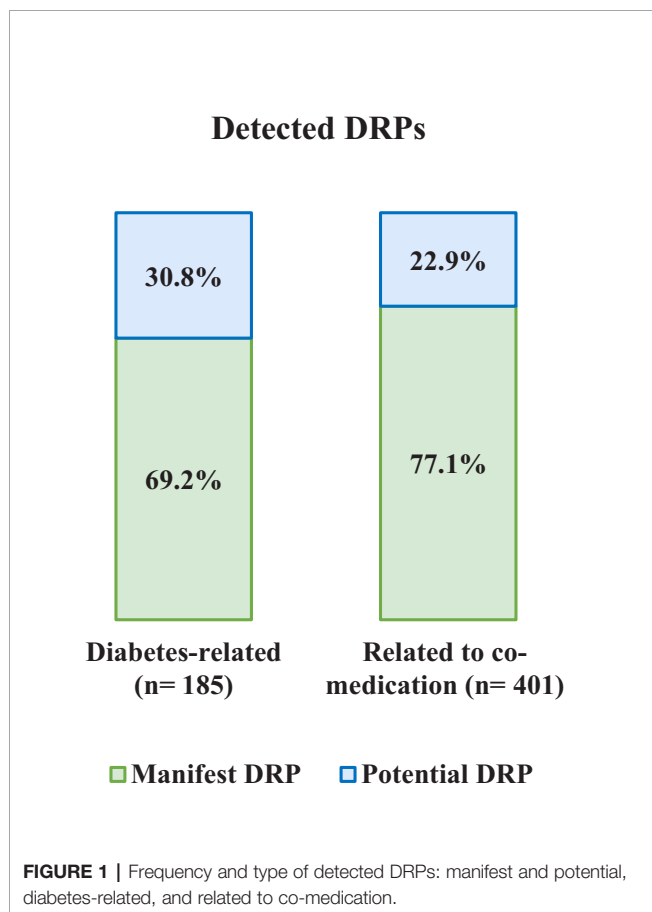
Reduction of the Detected DRPs

In total, 275 out of 586 DRPs (46.9%) could be totally solved. This indicates a statistically significant average decline from 4.84 DRPs to 2.57 DRPs per patient (reduction of 2.27 DRPs per patient, $p < 0.001$) achieved by the MR. Examining DRPs related to the antidiabetics, 37.3% of the DRPs were completely resolved, which corresponds to an average reduction of 0.96 DRPs per patient. More detailed information on solving the DRPs is provided in **Figure 2**.

Changes in Number of Drugs

Patients received a total number of 9.5 drugs on average (SD = 2.9). The median number was 9 with a minimum of 5 and a maximum of 19 drugs per patient. Of these drugs, 95.0% (9.0 per patient) were taken as long-term medication, the rest were on-demand medication. Another 19.2% (1.8 drugs per patient) were antidiabetics with a minimum of 1 and a maximum of 5 drugs per patient.

After the MR, patients received a total number of 9.3 drugs on average (SD = 2.8), which indicates a small, but statistically significant lower average number of drugs per patient than before the outset of the MR ($p < 0.001$). Changes in the number of drugs only affected long-term medication, not on-demand medication. The average number of antidiabetics was reduced by 2.3% (0.04 drugs per patient). The average number of co-medications was reduced by 2.2% (0.17 drugs per patient). It was not evaluated if changes were within the same drug class or between different drug classes.



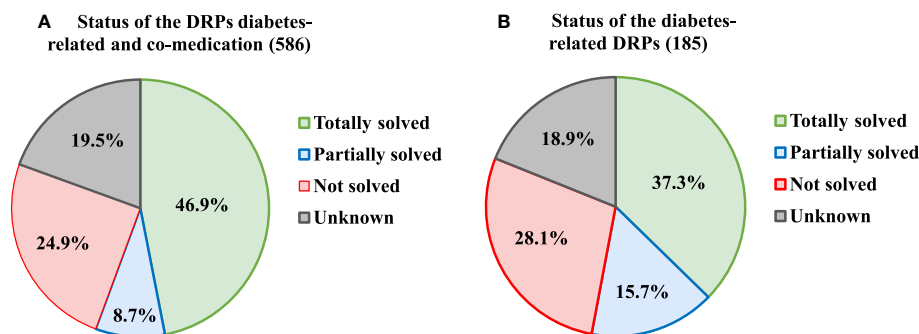


FIGURE 2 | Status of the DRPs after the MR, (A) diabetes-related and related to the co-medication, (B) diabetes-related only.

Interprofessional Collaboration Physicians' Feedback on MR

The proportion of physicians cooperating with the pharmacists in the context of the MR and the extent of the cooperation were examined. In this context, the term cooperation was chosen if the physician answered the pharmacist's question, regardless of whether the intervention proposals were accepted or not. Acceptance of intervention proposals was analyzed separately.

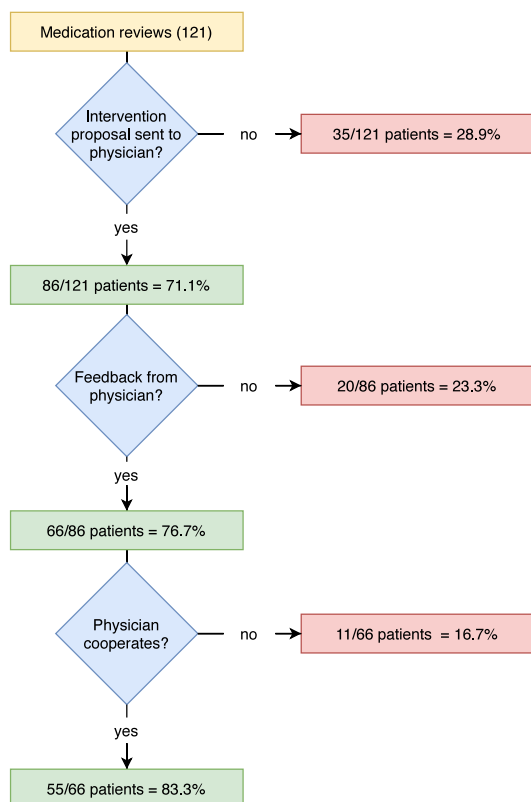


FIGURE 3 | Overview of physicians' feedback on MR.

For 86 patients (71.1%), intervention proposals for the reduction of detected DRPs were submitted to the responsible physician by the community pharmacy and feedback was requested, see **Figure 3**. In 76.7% of the cases the pharmacy received feedback from the physician, although in almost half of all cases, the pharmacies only received a delayed response after a second feedback request was initiated. No feedback was received for 20 patient cases (23.3%), meaning that the outcome and the status of the DRP after the MR could not be assessed for all DPRs (see **Figure 2**, status of the DRP unknown for 19.5%). In most cases (78.8%), the feedback was given exclusively in writing, sometimes (21.2%) there was also a telephone call between pharmacist and physician. The pharmacy received feedback after an average of 18 days. The overall willingness to cooperate by the physicians involved was 64.0% (55 out of 86 cases where intervention proposals were sent to the physician).

Acceptance of Intervention Proposals

More than half of the (59.5%; 754 out of 1267) intervention proposals were accepted, of which 643 (85.3%) were accepted and fully implemented. 220 (17.4%) of the intervention proposals were not accepted, of which 37.3% due to there being no agreement by either the prescriber or the patient and 61.4% for unknown reasons. For 293 (23.1%) of the intervention proposals, the level of acceptance was unknown.

DISCUSSION

The DIATHEM study aimed to examine the influence of MRs provided by community pharmacies in Germany for elderly type 2 diabetes patients under routine care conditions on type and frequency of DRPs, number of drugs and interprofessional collaboration. Overall, almost half of all DRPs could be totally resolved in the DIATHEM study, indicating a significant reduction of the number of DRPs from 4.84 DRPs to 2.57 DRPs per patient (reduction of 2.27 DRPs per patient).

The benefit of MRs in diabetes patients by community pharmacists in regard to quality of life and drug treatment has already been proven in other countries (Wermeille et al., 2004; Machado et al., 2007; Anaya et al., 2008; Wubben and Vivian, 2008). In the last years, increasing numbers of studies have investigated the positive effects of MRs in Germany, for example in patients with polymedication or with Parkinson's disease (Henrichsmann and Hempel, 2016; Koberlein-Neu et al., 2016; Müller-Rebstein et al., 2017; Seidling et al., 2017; Aktas, 2019; Bitter et al., 2019). For diabetes patients, a study investigated the impact of pharmaceutical care in adolescents with T1DM (Obarcanin et al., 2015) and another, the GLICEMA study (Schmiedel et al., 2015), showed the significant benefit of a prevention program carried out in German community pharmacies for patients with T2DM. However, to our knowledge, no comparable interventional MR study during the routine care of type 2 diabetes patients in community pharmacies in Germany, has been described to date.

The results from our study demonstrate that elderly type 2 diabetics are multimorbid patients with polymedication leading to a high number of DRPs. This is in concordance with the findings of similar studies, where the number of DRPs was found to be associated with age of the patients and number of drugs (Lenssen et al., 2016). The number of drugs could be marginally reduced in the DIATHEM study, which would have been desirable in terms of patient adherence. However, a relevant reduction in the number of drugs per patient is often impossible to achieve in geriatric patients due to increasing number of different diseases in the elderly. Furthermore, diabetes is often accompanied with severe cardiovascular disease and metabolic syndrome, and patients receive a broad range of drugs for prevention and treatment of this disease. Thus, in the DIATHEM study, the most frequently used drugs belonged to the ATC code group C (cardiovascular system) ahead of the group A (alimentary tract and metabolism, which contains antidiabetics) and N (nervous system). The pattern of the most frequently used drugs is consistent with that of the study by Seidling et al., a post-hoc analysis of MRs provided by community pharmacies in the German ATHINA-project (Seidling et al., 2017). More than 80% of the patients in our study received a drug acting on the renin-angiotensin system, i.e. ACE inhibitors or ARBs. ACE inhibitors respectively ARBs are the preferred drugs for treating hypertension in patients with T2DM because of their nephroprotective potential. Diuretics, lipid modifying agents and beta blockers - drug groups belonging to the group cardiovascular system such as ACE inhibitors and ARBs—were also taken by at least half of the patients. About two-thirds of all patients received one or two antithrombotics, i.e. platelet aggregation inhibitors or anticoagulants. As antithrombotics are high risk drugs, this patient collective from our study is supposed to benefit from a MR as an instrument to improve patient safety. Regarding the antidiabetic medication Metformin was by far the most used drug, received by 78.5% of patients, followed by Sitagliptin (38.0%) and Glimepiride (15.7%). This distribution is consistent with current national guidelines on the treatment of type 2 diabetes. In the German National Care Guideline

(Nationale Versorgungs Leitlinie) for therapy of type 2 diabetes, Metformin is still the preferred drug (Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2014). This guideline from 2014 is currently under revision, an update is expected soon (Programm für Nationale VersorgungsLeitlinien, 2019). Changes in the first line recommendations for atherosclerotic and cardiovascular high-risk patients—as already implemented in the 2019 ESC/EASD Guidelines on diabetes, pre-diabetes, and cardiovascular diseases (Cosentino et al., 2019)—are considered possible. The basis for these recommendations is that in recent years there has been new and convincing evidence from cardiovascular safety studies [i.e. LEADER-, SUSTAIN-6-, EMPA-REG OUTCOME-, and CANVAS-study (Zinman et al., 2015; Marso et al., 2016a; Marso et al., 2016b; Neal et al., 2017)] demonstrating mortality benefits for type 2 diabetics with cardiovascular disease or at high cardiovascular risk and treatment with sodium-glucose co-transporter 2 inhibitors or glucagon-like peptide-1 analogues. However, at the time of data collection for the DIATHEM study, these studies had not yet or only recently been published and these findings were not yet integrated in treatment regimens.

DRPs in patients with type 2 diabetes are not only associated with the antidiabetic drugs, but even more with the co-medication. Nearly 70% of all DRPs in our study were related to the co-medication, which corresponds to 3.31 DRPs per patient compared to 1.53 diabetes-related DRPs per patient on average. Only in 2.5% of the patients no DRP could be identified, indicating a high need for MRs in elderly patients with T2DM. Regarding the distribution of DRPs, the most frequently found DRPs concerned drug dosage and drug selection, both in antidiabetics and in co-medication. These findings are in concordance with those of comparable studies, where dosage and drug selection were also among the most frequent detected DRPs (Koberlein-Neu et al., 2016; Bitter et al., 2019). In our study inappropriate dosage affected underdosing, e.g. underdosing of an antidiabetic drug resulting in insufficient blood sugar control, and also overdosing, e.g. no dose adjustment even though it was necessary due to renal failure. Problems in the drug selection process involved combinations of antidiabetics with high risk for hypoglycaemia in patients with a history of hypoglycaemia. Often, no adjustments of drug dosage and drug selection is made during long-term treatment. In such cases, MRs help to discover and resolve those DRPs. Patients should be encouraged to regularly visit their physicians for check-ups and to inform them of side effects. Another frequent DRP in the total medication was an unsuitable or inappropriate dosage regimen. A correct dosage regimen is not only important for the effect of drugs, but also has an influence on possible side effects and on patient adherence. In order to maintain patient adherence at the highest possible level, the number of doses of drugs to be taken daily should be as low as possible, as it is known that adherence decreases with increasing number of doses to be taken (Claxton et al., 2001; Saini et al., 2009). In this respect, the pharmacokinetic knowledge of pharmacists is particularly valuable. Drug-drug interactions

TABLE 4 | Classification of the DRPs—Causes domain.

Causes of DRPs (n= 617 causes for 586 DRPs)	Number of causes	Frequency of causes [%]
C1—Drug selection	279	45.2%
C1.1—Inappropriate drug according to guidelines/formulary	74	12.0%
C1.2—Inappropriate drug (within guidelines but otherwise contra-indicated)	93	15.1%
C1.4—Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	78	12.6%
C1.5—Inappropriate duplication of therapeutic group or active ingredient	8	1.3%
C1.6—No or incomplete drug treatment in spite of existing indication	22	3.6%
C1.7—Too many drugs prescribed for indication	4	0.6%
C3—Dose selection	304	49.3%
C3.1—Drug dose too low	22	3.6%
C3.2—Drug dose too high	88	14.3%
C3.3—Dosage regimen not frequent enough	35	5.7%
C3.4—Dosage regimen too frequent	86	13.9%
C3.5—Dose timing instructions wrong, unclear or missing	73	11.8%
C4—Treatment duration	26	4.2%
C4.1—Duration of treatment too short	1	0.2%
C4.2—Duration of treatment too long	25	4.1%
C7—Patient related	2	0.3%
C7.5—Patient takes food that interacts	2	0.3%
C9—Other	6	1.0%
C9.1—No or inappropriate outcome monitoring (incl. TDM)	6	1.0%

were common but not predominant DRPs in the DIATHEM study and in many cases related to risk of bleeding, potassium level and possible QTc-prolongation. Also here, the patient-specific drug selection and regular check-ups play an important role. Pharmacists are trained to recognize and evaluate drug-drug interactions and to develop intervention proposals for treatment optimization and therefore well suited to use these skills in the course of a MR.

This study shows that the intervention MR is a highly effective instrument to reduce DRPs in elderly patients with T2DM. A comparison with studies in similar settings that have investigated the influence of MR provided by community pharmacies in Germany shows that the number of detected and resolved DRPs varies relatively strongly. A recent study from Bitter et al. (mean age 84 years, long-term care residents, MRs provided for 94 patients) found on average 1.6 DRPs per patient, of which one third of the pharmacist's interventions to resolve the DRPs were successfully implemented (Bitter et al., 2019). The WestGem study (mean age 76.8 years, mean number of drugs 10.5 per patient, MRs provided for 142 patients) showed a mean number of 7.3 DRPs per patient on baseline of which 0.45 DRPs per patient were resolved (Koberlein-Neu et al., 2016). This variety shows that there are currently no standard criteria in Germany for the assessment and classification of DRPs.

TABLE 5 | Classification of the DRPs—Intervention domain.

(Planned) Interventions (n = 1267 interventions for 586 DRPs)	Number of (planned) interventions	Frequency of (planned) interventions [%]
I0.1—No Intervention	32	—
I1—At prescriber level	518	40.9%
I1.1—Prescriber informed only	74	5.8%
I1.3—Intervention proposed to prescriber	384	30.3%
I1.4—Intervention discussed with prescriber	60	4.7%
I2—At patient level	286	22.6%
I2.1—Patient (drug) counselling	236	18.6%
I2.3—Patient referred to prescriber	50	3.9%
I3—At drug level	463	36.5%
I3.1—Drug changed to...	78	6.2%
I3.2—Dosage changed to...	77	6.1%
I3.4—Instructions for use changed to...	180	14.2%
I3.5—Drug paused or stopped	94	7.4%
I3.6—Drug started	34	2.7%

Regarding interdisciplinary cooperation, the study shows the immense importance of the interprofessional collaboration between pharmacists and physicians. An enormous amount of DRPs could be resolved by pharmacists and physicians working together in the context of the MRs. The extent of interprofessional collaboration in the DIATHEM study was positive with an overall 64.0% of the physicians willing to cooperate. Furthermore, the overall acceptance of the pharmacist's intervention proposals by the patients and physicians was 59.5%. The DIATHEM study demonstrates that these results can actually be achieved under routine care conditions. In contrast to our study, existing studies on MR in Germany do not fully reflect the real-life situation in community pharmacies. In most studies, clinical investigators were involved or the physicians were informed in advance about the MR, had agreed to participate in the study and/or were reimbursed for participating. Patients could also be chosen with a bias, i.e. based on the knowledge that the responsible physician was willing to cooperate with the community pharmacy. In our study, patients who met the inclusion criteria could receive a MR and participate in the study, regardless of their physician. Due to the fact that few physicians were aware that the MR is also a service provided by the community pharmacies, it is assumed that involving clinical investigators or having personal contact between pharmacist and physician beforehand would have increased the proportion of physicians agreeing to a collaboration. The fact that there was no reimbursement for any of the interest groups is also believed to have had a negative influence on cooperation. A few physicians even refused to communicate with the community pharmacy during the course of the MR with the explanation that they were not paid for their time investment. These factors, which were challenging in execution of the study, are consistent with findings in international studies evaluating facilitators and barriers within pharmaceutical services in community pharmacies and primary care teams (Roberts et al., 2008; Jorgenson et al., 2014).

Thus, although MR can already be successfully carried out in German community pharmacies within their day-to-day routine, the prerequisites are poor, even though the ABDA has developed

a manual for the performance of a MR (ABDA, 2018) and there are some training programs offered for pharmacists such as the ATHINA project (Information on the ATHINA project, 2020) or the Apo-AMTS project (Information on the Apo-AMTS project, 2020). Interprofessional cooperation should be expanded and promoted throughout the whole of the healthcare system, e.g. joint courses during medical and pharmaceutical education as a starting-point. Furthermore, by giving physicians the possibility to prescribe a pharmacist-led MR for patients at risk, working together to solve the prevailing DRPs and appropriate reimbursement for all involved partners. An appropriate reimbursement of costs is also necessary because performing a MR is time consuming. For this service to be widely implemented in community pharmacies, a suitable amount of time must be appointed to staff members in order to perform all duties in context of a MR. Moreover, pharmaceutical education should be extended to enable all pharmacists to conduct MRs without the necessity of additional qualifications. In this study, a consultant pharmacist with broad professional experience and additional education regarding drug safety was responsible for the MRs.

The limitations of this study are mainly attributed to the real-life setting. In daily care conditions in German community pharmacies, the pharmacies do not routinely obtain data on either laboratory values or diagnosis of the patient, including the severity and duration of the diseases. Therefore, we cannot provide detailed information on these particular issues. If patients received an antidiabetic and in conversation with the pharmacist stated that they were suffering from T2DM, we assumed that this was indeed the truth. In most cases, a medication review was sent to a physician and we presume that the physician would have informed us if the listed diagnosis was incorrect. It is also not feasible in routine care conditions to measure HbA1c value and blood glucose for every single patient in addition to the standard care of all patients or to acquire data on patient adherence i.e. pill count. Therefore, information on clinical data that are in general valuable for a study on T2DM patients is missing. The study shows that DRPs were reduced by the MR, but the impact of reduced DRPs on safety and tolerability as well as on morbidity and mortality remains unclear, because it was not evaluated. It was likewise not evaluated if the demonstrated reduction in the number of drugs results in improved clinical outcomes. Another limitation of the study is, when examining the reduction of DRPs and the number of drugs by the MRs, it was only distinguished between diabetes-related drugs and drugs related

to the co-medication, but no further differentiation between antidiabetic drugs (injectable versus oral) was made. Further limitations of this study were shown partly by a lack of willingness to cooperate by some of the physicians involved. This led to unsolved DRPs and other DRPs left with an unknown status after the MR. In the study, patients received the service MR at no personal costs. We did not test patient satisfaction with the MR or examine changes in quality of life, and did not evaluate if they would be willing to pay for the service themselves. Furthermore, no adjustments were made for multiplicity of exploratory outcomes.

On a whole, the DIATHEM study demonstrates that structured MRs in elderly patients with type 2 diabetes under routine care conditions in German community pharmacies are successful and shows the high benefit of this service. Enhancement of interprofessional collaboration and pharmaceutical education as well as reasonable remuneration are necessary factors in reducing existing barriers. Data from real-life studies are precious and of great importance in order to improve patient care.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

Study concept and design: ES, CC, and CH. Data collection and analysis: ES. Wrote the paper: ES, CC, and CH.

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REFERENCES

- ABDA. (2018). *Leitlinie Medikationsanalyse*. Available at: https://www.abda.de/fileadmin/user_upload/assets/Praktische_Hilfen/Leitlinien/Medikationsanalyse/LL_MedAnalyse.pdf (Accessed 05/18/2020).
- Aktas, B. (2019). Umfassende Medikationsanalyse und abgestimmte Zusammenarbeit Apotheker/Arzt. Ergebnisse eines Pilotprojekts. *Med. Monatsschr. Pharm.* 42 (2), 60–66.
- Anaya, J. P., Rivera, J. O., Lawson, K., Garcia, J., Luna, J., and Ortiz, M. (2008). Evaluation of pharmacist-managed diabetes mellitus under a collaborative drug therapy agreement. *Am. J. Heal Pharm.* 65 (19), 1841–1845. doi: 10.2146/ajhp070568
- ARMIN. (2019). *Die Arzneimitteliniziativa Sachsen-Thüringen*. Available at: <https://www.arzneimitteliniziativa.de> (Accessed 11/03/2019).
- Bitter, K., Pehe, C., Krüger, M., Heuer, G., Quinke, R., and Jaehde, U. (2019). Pharmacist-led medication reviews for geriatric residents in German long-term care facilities. *BMC Geriatr.* 19 (1), 1–8. doi: 10.1186/s12877-019-1052-z

- Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) (2014). *Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Langfassung 1. Auflage. Version 4* (2013) zuletzt geändert: November 2014. *Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes*. ÄZQ (Ärztliches Zentrum für Qualität in der Medizin).
- Centers for Disease Control and Prevention (2017). *National Diabetes Statistics Report* (Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services), 2017.
- Chau, S. H., Jansen, A. P., van de Ven, P. M., Hoogland, P., Elders, P. J., and Hugtenburg, J. G. (2016). Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands. *Int. J. Clin. Pharm.* 38 (1), 46–53. doi: 10.1007/s11096-015-0199-8
- Claxton, A. J., Cramer, J., and Pierce, C. J. A. B. (2001). A Systematic Review of the Associations Between Dose Regimens and Medication Compliance. *Clin. Ther.* 23 (8), 1296–1310. doi: 10.1016/S0149-2918(01)80109-0
- Cosentino, F., Grant, P. J., Aboyans, V., Bailey, C. J., Ceriello, A., Delgado, V., et al. (2019). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* 2019, 1–69. doi: 10.1093/eurheartj/ehz486
- DDG Deutsche Diabetes Gesellschaft (2018). *diabetes DE Deutsche Diabetes-Hilfe. Deutscher Gesundheitsbericht - Diabetes 2018 - Die Bestandsaufnahme*. Available from: https://www.diabetesde.org/system/files/documents/gesundheitsbericht_2018.pdf.
- Dickson, D., Johnson, J., Bergan, R., Owens, R., Subbiah, V., and Kurzrock, R. (2020). Snapshot: Trial Types in Precision Medicine. *Cell* 181 (1), 208–208.e1. doi: 10.1016/j.cell.2020.02.032
- Griese-Mammen, N., Hersberger, K. E., Messerli, M., Leikola, S., Horvat, N., Foppe Van Mil, J. W., et al. (2018). PCNE definition of medication review: reaching agreement. *Int. J. Clin. Pharm.* 40 (3), 1199–1208. doi: 10.1007/s11096-018-0696-7
- Henrichsmann, M., and Hempel, G. (2016). Impact of medication therapy management in patients with Parkinson's disease. *Int. J. Clin. Pharm.* 38 (1), 54–60. doi: 10.1007/s11096-015-0206-0
- Information on the Apo-AMTS project (2020). Available at: <https://www.akwl.de/inhalt.php?id=703> (Accessed 05/18/2020).
- Information on the ATHINA project (2020). Available at: <https://www.aknr.de/apotheker/inhalt.php?id=153> (Accessed 05/18/2020).
- International DiabetesFederation (2017). *IDF Diabetes Atlas 8th Edition*. Available from: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf
- Isetts, B. J., Brown, L. M., Schondelmeyer, S. W., and Lenarz, L. A. (2003). Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. *Arch. Intern Med.* 163 (15), 1813–1820. doi: 10.1001/archinte.163.15.1813
- Isetts, B. J., Schondelmeyer, S. W., Artz, M. B., Lenarz, L. A., Heaton, A. H., Wadd, W. B., et al. (2008). Clinical and economic outcomes of medication therapy management services: the Minnesota experience. *J. Am. Pharm. Assoc.* 48 (2), 203–211, 3 p following 211. doi: 10.1331/JAPhA.2008.07108
- Jorgenson, D., Laubscher, T., Lyons, B., and Palmer, R. (2014). Integrating pharmacists into primary care teams: Barriers and facilitators. *Int. J. Pharm. Pract.* 22 (4), 292–299. doi: 10.1111/ijpp.12080
- Koberlein-Neu, J., Mennemann, H., Hamacher, S., Waltering, I., Jaehde, U., Schaffert, C., et al. (2016). Interprofessional Medication Management in Patients With Multiple Morbidities. *Dtsch Arztebl Int.* 113 (44), 741–748. doi: 10.3238/arztebl.2016.0741
- Laaksonen, R., Duggan, C., and Bates, I. (2010). Performance of community pharmacists in providing clinical medication reviews. *Ann. Pharmacother.* 44 (7–8), 1181–1190. doi: 10.1345/aph.1M719
- Lenßen, R., Heidenreich, A., Schulz, J. B., Trautwein, C., Fitzner, C., Jaehde, U., et al. (2016). Analysis of drug-related problems in three departments of a German University hospital. *Int. J. Clin. Pharm.* 38 (1), 119–126. doi: 10.1007/s11096-015-0213-1
- Machado, M., Bajcar, J., Guzzo, G. C., and Einarson, T. R. (2007). Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. *Ann. Pharmacother.* 41 (10), 1569–1582. doi: 10.1345/aph.1K151
- Machin, D., Campbell, M., Fayers, P., and Pinol, A. (1997). *Sample Size Tables for Clinical Studies, 2nd Edition* (Malden, MA: Blackwell Science).
- Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F. E., Nauck, M. A., et al. (2016a). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl. J. Med.* 375 (4), 311–322. doi: 10.1056/NEJMoa1603827
- Marso, S. P., Bain, S. C., Consoli, A., Eliaschewitz, F. G., Jódar, E., Leiter, L. A., et al. (2016b). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl. J. Med.* 375 (19), 1834–1844. doi: 10.1056/NEJMoa1607141
- Müller-Rebstein, S., Trenkwalder, C., Ebentheuer, J., Oertel, W. H., Culmsee, C., and Höglinger, G. U. (2017). Drug Safety Analysis in a Real-Life Cohort of Parkinson's Disease Patients with Polypharmacy. *CNS Drugs* 31 (12), 1093–1102. doi: 10.1007/s40263-017-0478-0
- Neal, B., Perkovic, V., Mahaffey, K. W., de Zeeuw, D., Fulcher, G., Erond, N., et al. (2017). Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl. J. Med.* 377 (7), 644–657. doi: 10.1056/NEJMoa1611925
- Obarcanin, E., Kruger, M., Müller, P., Nemitz, V., Schwender, H., Hasanbegovic, S., et al. (2015). Pharmaceutical care of adolescents with diabetes mellitus type 1: the DIADEMA study, a randomized controlled trial. *Int. J. Clin. Pharm.* 37 (5), 790–798. doi: 10.1007/s11096-015-0122-3
- PASS (2015). *14 Power Analysis and Sample Size Software* (Kaysville, Utah, USA: NCSS, LLC). ncss.com/software/pass.
- Pharmaceutical Care Network Europe (2019a). *PCNE-wiki. Wiki_Medication Review*. Available at: <https://www.pcne.org/working-groups/1/medication-review> (Accessed 11/03/2019).
- Pharmaceutical Care Network Europe (2019b). *PCNE Classification for Drug-Related Problems V 9.0*. Available at: https://www.pcne.org/upload/files/334_PCNE_classification_V9-0.pdf (Accessed 08/12/2019).
- Pringle, J. L., Boyer, A., Conklin, M. H., McCullough, J. W., and Aldridge, A. (2014). The Pennsylvania Project: pharmacist intervention improved medication adherence and reduced health care costs. *Heal Aff.* 33 (8), 1444–1452. doi: 10.1377/hlthaff.2013.1398
- Programm für Nationale VersorgungsLeitlinien (2019). *DIABETES*. Available at: <https://www.leitlinien.de/nvl/diabetes> (Accessed 12/07/2019).
- Roberts, A. S., Benrimoj, S. I., Chen, T. F., Williams, K. A., and Aslani, P. (2008). Practice change in community pharmacy: Quantification of facilitators. *Ann. Pharmacother.* 42 (6), 861–868. doi: 10.1345/aph.1K617
- Rose, O., Mennemann, H., John, C., Lautenschläger, M., Mertens-Keller, D., Richling, K., et al. (2016). Priority Setting and Influential Factors on Acceptance of Pharmaceutical Recommendations in Collaborative Medication Reviews in an Ambulatory Care Setting – Analysis of a Cluster Randomized Controlled Trial (WestGem-Study). *PLoS One* 11 (6), e0156304. doi: 10.1371/journal.pone.0156304
- Saini, S. D., Schoenfeld, P., Kaulback, K., and Dubinsky, M. C. (2009). Effect of medication dosing frequency on adherence in chronic diseases. *Am. J. Manag. Care* 15 (6), e22–e33.
- Schmiel, K., Mayr, A., Fiessler, C., Schlager, H., and Friedland, K. (2015). Effects of the lifestyle intervention program GLICEMIA in people at risk for type 2 diabetes: a cluster-randomized controlled trial. *Diabetes Care* 38 (5), 937–939. doi: 10.2337/dc14-2206
- Seidling, H. M., Send, A. F., Bittmann, J., Renner, K., Dewald, B., Lange, D., et al. (2017). Medication review in German community pharmacies - Post-hoc analysis of documented drug-related problems and subsequent interventions in the ATHINA-project. *Res. Soc. Adm. Pharm.* 13 (6), 1127–1134. doi: 10.1016/j.sapharm.2016.10.016
- The Emerging Risk Factors Collaboration (2015). Association of Cardiometabolic Multimorbidity With Mortality. *JAMA* 314 (1), 52–60. doi: 10.1001/jama.2015.7008
- Vierte Verordnung zur Änderung der Apothekenbetriebsordnung (2012). *Bundesgesetzblatt Jahrgang 2012 Teil I Nr. 25*. Available at: http://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&jumpTo=bgbl112s1254.pdf (Accessed 09/06/2019).
- Wermeille, J., Bennie, M., Brown, I., and McKnight, J. (2004). Pharmaceutical care model for patients with type 2 diabetes: integration of the community pharmacist into the diabetes team - a pilot study. *Pharm. World Sci.* 26 (1), 18–25. doi: 10.1023/B:PHAR.0000013465.24857.a8
- WHO Collaborating Centre for Drug Statistics and Methodology (2019). *ATC Index*. Available at: <https://www.whocc.no> (Accessed 05/13/2019).

- World Health Organization (2019). *Medication Safety in Polypharmacy* (Geneva: WHO/UHC/SDS/2019.11).
- Wubben, D. P., and Vivian, E. M. (2008). Effects of pharmacist outpatient interventions on adults with diabetes mellitus: A systematic review. *Pharmacotherapy* 28, 421–436. doi: 10.1592/phco.28.4.421
- Zar, J. H. (1984). *Biostatistical Analysis (Second Edition)* (New Jersey: Prentice-Hall, Englewood Cliffs).
- Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., et al. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl. J. Med.* 373 (22), 2117–2128. doi: 10.1056/NEJMoa1504720

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Use of Proton Pump Inhibitors in Hungary: Mixed-Method Study to Reveal Scale and Characteristics

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Background: Due to their efficacy and tolerability, utilization of proton pump inhibitors (PPI) has significantly increased worldwide. Parallel to the clinical benefits, potential long-term side effects have been observed, which, along with increasing medical expenses and potential drug interactions, justifies the analysis of the trends of utilization.

Objective: The aim of the present study was to show the level, pattern, and characteristics of PPI use.

Methods: We assessed the nationwide use of proton pump inhibitors in ambulatory care based on aggregated utilization data from the National Health Insurance database. The annual PPI utilization was expressed as the number of packages and as number of DDDs per 1,000 inhabitants and per year. For 2018, we estimated PPI exposure as the number of packages and as the number of DDDs per user per year. The annual reimbursement costs of proton pump inhibitors were also calculated. Moreover, three patient-level surveys were carried out in non-gastroenterological inpatient hospital departments to reveal characteristics of proton pump inhibitor use, namely dose, duration, and indication.

Results: The PPI utilisation increased from 5867.8 thousand to 7124.9 thousand packages and from 41.9 to 50.4 DDD per 1,000 inhabitants and per day between 2014 and 2018. Nationwide data showed that 14% of the adult population was exposed to proton pump inhibitors in 2018, while among hospitalized patients, the prevalence of proton pump inhibitor use was between 44.5% and 54.1%. Pantoprazole was the most frequently used active ingredient, both in the nationwide data and in the patient-level surveys. In the patient-level survey in majority of patients (71.5%–80.0%) proton pump inhibitors were prescribed for prophylaxis. Many inpatients (29.4%–36.9%) used 80 mg pantoprazole per day. The average number of PPI packages per user was 6.5 in 2018 in the nationwide data. The duration of PPI therapy was typically between 1 and 5 years in the patient-level surveys and nearly 20% of the inpatients had been taking proton pump inhibitors for more than 5 years.

Conclusions: Our data suggests that Hungarian patients receive proton pump inhibitors in high doses and for a long time. Use of proton pump inhibitors beyond their recommended indications was also found.

Keywords: proton pump inhibitors, proton pump inhibitors exposure, proton pump inhibitors dose, proton pump inhibitors therapy duration, nationwide data, patient-level survey

INTRODUCTION

In the 1990s, widespread use of proton pump inhibitors (PPIs) radically changed the treatment of acute and chronic gastroenterological diseases caused by hyperacidity (Garner et al., 1996; Savarino et al., 2018a). Different PPI products have an equivalent mechanism of action and a similar clinical efficacy (Strand et al., 2017). Due to their excellent efficacy, tolerability and positive adverse event profile, PPI utilization has significantly increased all over the world (Hollingworth et al., 2010; Tett et al., 2013; Lanas, 2016; Ying et al., 2019). Besides official, evidence-based use of PPIs, less understandable and justifiable prescriptions have also occurred (Savarino et al., 2017; Savarino et al., 2018a). More than 10 years ago, additional costs resulting from PPI overuse were estimated to be 2 billion pounds worldwide (Forgacs and Loganayagam, 2008).

Parallel to the clinical benefits of long-term PPI therapy in some clinical conditions (e.g. severe erosive esophagitis, Barrett's esophagus), potential side effects have also been observed, especially among the elderly (Maleth and Hegyi, 2013; Freedberg et al., 2017; Maes et al., 2017; Yu et al., 2017; Haastrup et al., 2018; Igaz et al., 2018; Devitt et al., 2019; Lanas-Gimeno et al., 2019). Some of these are controversial and based on extremely loose associations (e.g. dementia, chronic nephropathy), while others (e.g. enteric infections, micronutrient deficiency) have been confirmed by sound evidence (Bajor, 2017; Strand et al., 2017; Ayele et al., 2018; Schubert, 2018; Schubert, 2019).

Potential long-term side effects, increasing medical expenses, and potential drug interactions (Hu et al., 2018) justify the recognition and analysis of the trends and characteristics of PPI utilization. Utilization of PPIs has been analyzed in many countries (Pillans et al., 2000; Chia et al., 2014; Larsen et al., 2014; Kelly et al., 2015; Meli et al., 2015; Lodato et al., 2016; Pottegard et al., 2016; Pujal Herranz, 2016; Juntunen et al., 2017; Del Giorno et al., 2018; Halfdanarson et al., 2018; Luo et al., 2018; Ying et al., 2019), but no data from Hungary has been published yet, as emphasized in the study of Igaz et al. (2018). The aim of the present study was to show the level, pattern, and characteristics of PPI use, using mixed methods.

METHODS

National Data

The source of annual national drug utilization data was the public, aggregated report of the National Health Insurance Fund of Hungary (Hungarian acronym: NEAK) (2014–2018). This report contains information on all dispensed and reimbursed prescription

drugs in Hungary. As NEAK is the sole and mandatory health insurance agency in Hungary, it covers 100% of the population. Over the counter dispensations (including some PPI products), and non-reimbursed drugs are not included in the dataset.

The reimbursement rate is 55% for all PPI substances, regardless of the indication and the prescriber. Only the products with the highest price (usually the originator) are excluded from the reimbursement status. Currently, there are eleven PPI products that are available without prescription (nine products containing 20 mg pantoprazole and two products containing 20 mg esomeprazole), all the other PPI products (N=74) are prescription-only. General practitioners can initiate and prescribe PPI therapy with a similar reimbursement rate as gastroenterologists.

PPIs were classified using the WHO ATC [World Health Organisation (WHO), 2020] methodology (version 2020). PPI use was expressed as the number of annual packages and as WHO defined daily doses (DDD, version 2020) standardized for the population (i.e. DDD per 1,000 inhabitants and per day). Furthermore, regarding certain PPI active ingredients (ATC subgroup A02BC), for the year 2018, we determined the average number of packages per user per year and the average number of DDDs per user per year. The public drug utilization report of NEAK includes reimbursement costs. Summarizing these numbers, we calculated the annual reimbursement cost of PPIs.

Patient-Level Surveys

Three patient-level cross-sectional surveys were carried out in inpatient hospital departments. For Surveys 1 and 2, all hospital pharmacists were invited from hospitals (N=12) where daily dose drug dispensation was supervised by a pharmacist and medical reconciliation practice was in place in 2016. This is approximately 10% of all Hungarian hospitals. Out of the 12 hospitals, 10 agreed to take part in the survey. To enable generalizability the surveys were conducted in adult departments (N=29) of these hospitals with a non-gastroenterological profile, to exclude units where acid-related diseases are specifically treated. Intensive care units and psychiatry units were not included as communication with the patient is difficult/not possible that may introduce response bias. The most important characteristics of the surveys are shown in **Table 1**. The different surveys consecutively followed each other, and revealed progressively more characteristics of PPI use (e.g. Survey 1 did not assess duration of PPI use, but Surveys 2 and 3 did). The precise overall medication regimen was recorded in Survey 3. All adult (age 18 years or above), cooperative inpatients on the specific study days were included in the surveys to avoid selection bias. On the specific study days, the responsible ward pharmacist recorded medication use from medical records (that

TABLE 1 | Methodological characteristics of patient-level Surveys 1, 2, and 3.

	Survey 1	Survey 2	Survey 3
Survey Date(s)	27 July 2016	25 January 2017	April 2017–March 2018 On 12 appointed days (1 day per 3–4 weeks)
Survey Design	point prevalence		point prevalence (on multiple days)
Survey Site	29 wards from 10 hospitals surgical, trauma, neurological, or dermatological wards (10 outside the capital; 19 in the capital)		vascular surgery ward
Dosing of PPI therapy	recorded	recorded	recorded
Indication of PPI therapy	recorded	recorded	recorded
Duration of PPI therapy	not recorded	recorded	recorded
Initiation of PPI use	not recorded	only hospital initiation	recorded
De-prescribing attempt	not recorded	not recorded	recorded
Total number of the patient's chronic medications	not recorded	recorded	recorded

were filled in by the pharmacist during the admission) and consulted the patients about PPI indication, therapy duration, etc. In Survey 3, the initiation of PPI therapy was also asked from the patient (GP or specialist).

According to sample size calculations, at least 300–400 responses were required to estimate the occurrence of non-rare events, such as PPI use. Due to further stratification of data we sought for a higher sample size in the multicenter surveys (Surveys 1 and 2).

The data sheet for anonymous data collection contained demographic data and characteristics (active ingredient, daily dose, etc.) of PPI treatment. In all surveys, data were obtained during the medication reconciliation process. Polypharmacy was defined as taking five or more concomitant medications chronically (Duerden et al., 2013). Descriptive statistics were used with measures of central tendency (mean) and spread of the distribution (standard deviations minimum-maximum range). Data processing and evaluation were carried out using MS Office and R.3.5.1. software.

RESULTS

National Data

In 2018, a total of 7.12 million PPI packages were prescribed and dispensed, which corresponds to 730 packages per 1000 inhabitants, while in 2014, these numbers were under 5.87 million packages and 600 packages per 1000 inhabitants. Expressing the utilisation in DDD per 1,000 inhabitants and per day, it increased from 41.9 to 50.4 (see **Table 2B**). Over the last 5 years, PPI utilization has shown an upward trend, which is mostly due to an increase in pantoprazole use (**Table 2A**). Assuming that no active agent switch occurred, nearly 1.1 million Hungarian inhabitants were exposed to PPIs. This represents 14% of the adult population aged 18 years or above.

Every year (2014–2018), more than half of the used PPIs contained pantoprazole as the active ingredient. In 2018, more than 663,000 inhabitants redeemed at least one package of a pantoprazole product (**Table 3**), which means that 7% of the Hungarian population (including children) was exposed to pantoprazole. Considering the annual number of packages, the average number of packages per user in case of pantoprazole products was almost 7 (6.9) in 2018. Since in most cases, one

package equals 1 month of PPI use, this suggests average long-term PPI therapy of up to 6 to 8 months.

Due to generic competition, the previous decade brought a significant price reduction of PPIs, but still the National Health Insurance Fund of Hungary reimbursed 1622 million forints (5.1 million Euros) for these products in 2018 (**Table 4**).

Patient-Level Surveys

The results are summarized in **Table 5** and **Table 6**. Among the hospitalized patients, the prevalence of PPI utilization was around 50% (ranged between 44.5% and 54.1% in different surveys), and all patients were on oral PPI therapy. Up to 21.5% of the patients had been put on PPI therapy during hospitalization (**Table 5**). However, in all surveys, most of the patients only continued their previously prescribed PPI treatment. PPI therapy was initiated by a general practitioner in 81.5% of cases, and in only a few cases was PPI treatment started by a gastroenterologist (Survey 3).

The average age of patients in all surveys was >65 years. The prevalence of polypharmacy among PPI users was >70%. In all surveys, the most commonly used active ingredient was pantoprazole. The prescribed daily dose of pantoprazole varied from 20 mg to 160 mg. According to our survey data, most patients received 40 mg (43.1%–48.4%) or 80 mg pantoprazole (29.4%–36.9%) per day (**Table 6**). Duration of PPI therapy was typically between 1 and 5 years. Nearly 20% of the patients had been taking PPIs for more than 5 years. None of the patients reported an attempt to de-prescribe (Survey 3).

In 20% of the cases, the indication for PPI utilization was therapy in all three surveys, mostly for gastro-esophageal reflux or peptic ulcer. However, most patients received PPI as prevention. Most patients had other diseases besides the main reason for their hospitalization, which is not surprising considering their average age. This means that most patients were on polypharmacy and PPIs were prescribed as prevention against potential gastric mucosal irritation caused by other medications (see indications in **Table 5**).

Applying a conservative estimate, in Survey 2, of the 399 PPI users, 66 patients (16.5%) did not have any therapeutic indication for PPI use, and also had not used any potentially ulcerogenic or anticoagulant/antiplatelet drug. Similarly, most patients in Survey 3 received clopidogrel therapy, but only a few of them had also

TABLE 2A | Utilization of certain proton pump inhibitors (PPIs) over the last 5 years in Hungary (organized in descending order based on the data from 2018)—number of packages.

ATC	Active Ingredient	1,000 packages (share in %)					trend
		2014	2015	2016	2017	2018	
A02BC02	pantoprazole	3171.74 (54.05)	3842.92 (58.22)	4144.39 (60.68)	4444.86 (62.21)	4603 (64.60)	
A02BC05	esomeprazole	1101.76 (18.78)	1210.43 (18.34)	1241.44 (18.18)	1307.98 (18.31)	1282.82 (18.00)	
A02BC04	rabeprazole	768.73 (13.10)	742.15 (11.24)	696.3 (10.19)	673.08 (9.42)	596.48 (8.37)	
A02BC03	lansoprazole	630.61 (10.75)	586.23 (8.88)	538.59 (7.89)	495.21 (6.93)	417.06 (5.85)	
A02BC01	omeprazole	194.97 (3.32)	218.66 (3.31)	209.74 (3.07)	223.58 (3.13)	225.52 (3.17)	
All PPIs (A02AB)		5867.8 (100.00)	6600.4 (100.00)	6830.47 (100.00)	7144.72 (100.00)	7124.88 (100.00)	

TABLE 2B | Utilization of certain proton pump inhibitors (PPIs) over the last 5 years in Hungary (organized in descending order based on the data from 2018)—defined daily dose (DDD) per 1,000 inhabitants and per day.

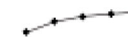
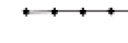
ATC	Active Ingredient	DDD per 1,000 inhabitants and per day (share in %)					trend
		2014	2015	2016	2017	2018	
A02BC02	pantoprazole	21.06 (50.27)	25.78 (54.41)	28.03 (56.87)	29.36 (57.62)	30.04 (59.64)	
A02BC05	esomeprazole	9.33 (22.28)	10.33 (21.80)	10.60 (21.5)	11.21 (21.99)	11.04 (21.91)	
A02BC04	rabeprazole	5.54 (13.22)	5.38 (11.36)	5.12 (10.40)	5.00 (9.82)	4.42 (8.77)	
A02BC03	lansoprazole	4.36 (10.41)	4.08 (8.61)	3.78 (7.67)	3.51 (6.88)	2.97 (5.89)	
A02BC01	omeprazole	1.60 (3.82)	1.81 (3.82)	1.75 (3.55)	1.88 (3.69)	1.91 (3.79)	
All PPIs (A02AB)		41.88 (100.00)	47.37 (100.00)	49.29 (100.00)	50.96 (100.00)	50.37 (100.00)	

TABLE 3 | Annual proton pump inhibitor (PPI) use in packages and in DDDs in 2018, number of proton pump inhibitor users of certain active ingredients, and sales standardized by number of users (based on the public database of the National Health Insurance Fund of Hungary).

ATC	Active Ingredient	Package number	Number of DDDs	Number of PPI users*	Average package number per user per year	Average number of DDDs per user per year
A02BC01	omeprazole	225 518	6 817 868	54 739	4.12	124.55
A02BC02	pantoprazole	4 603 004	107 216 453	663 339	6.94	161.63
A02BC03	lansoprazole	417 055	10 595 214	57 440	7.26	184.46
A02BC04	rabeprazole	596 482	15 763 302	94 218	6.33	167.31
A02BC05	esomeprazole	1 282 824	39 386 331	226 502	5.66	173.89
All PPI (A02AB)		7 124 883	179 779 168	**1 096 238	6.50	164.00

*user: person who purchased a prescribed proton pump inhibitor product (of the given active ingredient) at least once a year.

** estimation as sum of individual active agents users.

received NSAID treatment, or had had a history of peptic ulcer or bleeding prior to hospitalization. Dual antiplatelet therapy administration occurred in up to 27.7% of the patients taking PPIs (Table 5).

DISCUSSION

Due to the superiority of PPIs over H₂ receptor blockers in both effectiveness and pharmacokinetics, their use soon replaced H₂

receptor blockers in the treatment of gastroenterological diseases caused by increased hydrochloric acid secretion [van Pinxteren et al., 2006; Kahrilas et al., 2008; National Institute for Health and Care Excellence (NICE), 2014; Iwakiri et al., 2016; Brunton, 2017; Savarino et al., 2017]. In addition, increased awareness of ulcer prophylaxis requirements has resulted in endless expansion of the PPI market (Savarino et al., 2017).

Besides official, evidence-based indications for PPI treatment and prophylaxis, unjustifiable prescriptions occurred in clinical

TABLE 4 | Reimbursement cost of proton pump inhibitors and reimbursement share of individual PPIs.

ATC	Active Ingredient	Reimbursement—million Hungarian forint—(%)				
		2014	2015	2016	2017	2018
A02BC01	omeprazole	401.45 (15.50)	349.41 (15.27)	44.00 (4.07)	40.93 (3.63)	98.29 (6.06)
A02BC02	pantoprazole	475.77 (18.37)	578.39 (25.28)	617.04 (57.06)	659.19 (58.42)	738.16 (45.51)
A02BC03	lansoprazole	241.72 (9.33)	190.65 (8.33)	81.47 (7.53)	76.07 (6.74)	97.11 (5.99)
A02BC04	rabeprazole	475.04 (18.34)	376.68 (16.46)	110.36 (10.21)	108.57 (9.62)	177.23 (10.93)
A02BC05	esomeprazole	996.07 (38.46)	793.06 (34.66)	228.55 (21.13)	243.58 (21.59)	511.16 (31.52)
All PPI (A02AB)		2590.04 (100.00)	2288.18 (100.00)	1081.43 (100.00)	1128.34 (100.00)	1621.95 (100.00)

practice (Savarino et al., 2017; Savarino et al., 2018a). A review found the mean rate of PPI overuse was 57% in hospitals, and 50% in primary care settings (Savarino et al., 2017).

Prevalence of PPI Utilization

Based on national data, it was estimated that 14% of the Hungarian adult population was exposed to PPIs in outpatient care per year, while in adult hospital inpatients, this number was considerably higher, nearly 50%. Lower exposure was found in a Danish nationwide study, where gradual increase of PPI use was detected, and 7.4% of the adult population was exposed to PPIs in 2014. The high exposure of Hungarian patients to PPIs can be explained by the fact that PPI therapy can also be initiated by General practitioners (GPs) who can prescribe PPIs as gastroenterologists (i.e. with the same reimbursement rate). The high prevalence of PPI use (nearly 50% or above) among hospitalized patients has previously been reported in other countries as well (Chia et al., 2014; Kelly et al., 2015; Meli et al., 2015; Lodato et al., 2016; Pujal Herranz, 2016; Del Giorno et al., 2018).

Active Ingredient/Pharmaceutical Form/Dosing of PPIs/Expenses

In Hungary (as in Denmark), pantoprazole was the most frequently prescribed and dispensed PPI, while in Iceland, omeprazole and esomeprazole were the most frequently used PPIs (Pottegard et al., 2016; Halfdanarson et al., 2018). The dominance of pantoprazole in Hungary can be explained by the high number of generic products and their consequent lower price compared to other PPI agents.

Every third patient in our study was on a high dose pantoprazole regimen, despite the fact that only those with extra-esophageal gastro-esophageal reflux symptoms (Zollinger–Elisson syndrome) require higher than standard dose PPI treatment (Savarino et al., 2018a). The high rate of high-dose pantoprazole treatment can be explained by the general suboptimal practice that despite the longer duration of action due to the irreversible inhibition of the proton pump, similarly to H₂ receptor antagonists, doctors often prescribe PPI to be taken twice daily regardless of indication.

Moreover, in the most common indications for PPIs (symptomatic gastro-esophageal reflux, maintenance therapy of reflux esophagitis, or gastro protection with concomitant NSAID

use), 20 mg pantoprazole (low dose) is recommended in the summary of product characteristics. In the Icelandic study, 95% of patients started high dose PPI (they defined this “high dose” category as standard dose or high dose), and 21% remained on that treatment after 1 year (Halfdanarson et al., 2018). Similar overdosing of PPIs has been reported from China (Ying et al., 2019).

Despite the continuous increase in PPI utilization in the study period, the reimbursement costs have decreased. The Hungarian reimbursement system is very complex and under continuous change (e.g. new prices are published monthly). During the five study years, the continuous growth in the number of available products (mainly pantoprazole) in the market generated a considerable price competition and lower reimbursement costs.

Duration of PPI Use

Based on nationwide ambulatory drug use data, we estimated that each PPI user took PPIs for more than half a year on average. In the patient-level surveys, we observed that most patients were on PPI therapy for more than a year, and every fifth patient received PPI for more than 5 years. One possible explanation for the long duration of PPI treatment can be the lack of national guidelines on PPI use and PPI de-prescribing, and lack of medication review service provided by pharmacists. As the average age of PPI users admitted to the hospital was >65 years in all patient-level surveys, our data is similar to the findings of Halfdanarson et al., who reported remarkably higher PPI therapy duration in the elderly (Halfdanarson et al., 2018). Prolonged treatment was observed in other studies. In a Danish study, 44% of PPI users received PPI therapy for at least 3 years (Pottegard et al., 2016), while in Iceland 22% of PPI users remained on PPI treatment after 1 year (Halfdanarson et al., 2018). Appropriate duration of PPI use varies for different indications, but in general, it rarely exceeds 3 months in clinical guidelines (Halfdanarson et al., 2018). According to the newest National Institute for Health and Care Excellence guideline (National Institute for Health and Care Excellence (NICE), 2014), for the vast majority of patients with gastro-esophageal reflux [those without severe erosive esophagitis, Barrett’s Esophagus, or dilation of esophageal stricture] short-term PPI treatment is recommended for a maximum of 8 weeks (National Institute for Health and Care Excellence (NICE), 2014).

TABLE 5 | Patient-level survey results.

	Survey 1	Survey 2	Survey 3
PPI users/all patients	382/706	399/864	65/146
prevalence (%)	54.11	46.18	44.52
95% confidence interval	50.42–57.75	42.88–49.51	36.70–52.62
Sex ratio (males per females)	183:199	192: 207	32:33
Males %	47.91	48.12	49.23
Age: mean $\pm$ SD	68.62 $\pm$ 15.11	69.59 $\pm$ 14.21	65.69 $\pm$ 11.56
min-max	18–96	23–98	31–86
Polypharmacy in the PPI user group (number of patients)	unknown	343	59
%		85.96	73.29
Administered active ingredient: number of patients (%)			
Pantoprazole	366 (95.81)	384 (96.24)	51 (78.46)
Lansoprazole	2 (0.52)	2 (0.5)	8 (12.31)
Rabeprazole	2 (0.52)	3 (0.75)	5 (7.69)
Omeprazole	3 (0.79)	2 (0.5)	0 (0.00)
esomeprazole	9 (2.36)	8 (2.01)	1 (1.54)
Duration of PPI treatment: number of patients (%)	unknown		
started during		84 (21.05)	0 (0.00)
hospitalization/after admission			
less than 1 year		99 (24.81)	3 (4.62)
1 to 5 years		125 (31.33)	48 (73.85)
more than 5 years		82 (20.55)	14 (21.54)
		missing	
		answer: nine people	
Indication of PPI utilization: number of patients (%)			
Therapy			
GORD	48 (12.57)	41 (10.28)	8 (12.31)
Helicobacter eradication	6 (1.57)	1 (0.25)	4 (6.15)
Peptic ulcer long-term treatment	40 (10.47)	43 (10.78)	1 (1.54)
Prevention			
Stress ulcer prophylaxis	15 (3.93)	8 (2.01)	0 (0.00)
Other—"gastro protection" (e.g. ASA, NSAID, polypharmacy)	273 (71.47)	296 (74.19)	52 (80.00)
ASA	47 (12.3)	118 (29.57)	27 (41.54)
Clopidogrel	no info	48 (12.03)	42 (64.62)
ASA and Clopidogrel	no info	40 (10.03)	18 (27.69)
NSAID	64 (16.75)	52 (13.03)	3 (4.62)
Anticoagulants*	no info	no info	4 (6.15)
Missing answer	–	10 (2.51)	–

*Low molecular weight heparins, vitamin K antagonist, novel anticoagulants.

PPI, proton pump inhibitor; SD, standard deviation; GORD, Gastro-oesophageal reflux disease; ASA, acetyl salicylic acid; NSAID, non steroid anti-inflammatory drugs.

The estimated overall prevalence of gastro-esophageal reflux, the most common indication for PPI use, is around 9%–26% in the European population (El-Serag et al., 2014). The prevalence of diseases requiring long-term PPI use is low (Savarino et al., 2018a; Savarino et al., 2018b): e.g. severe erosive esophagitis (Los Angeles grade C/D) 0.5%, Barrett's esophagus with confirmed intestinal metaplasia 1.6%, while Zollinger Ellison syndrome is a rare disease (Ronkainen et al., 2005a; Ronkainen et al., 2005b).

Considering continuous, long-term use of PPIs without the supervision of a gastroenterologist, duration of therapy is particularly alarming, since adverse events (e.g. *Clostridioies difficile* infection) may develop due to persistent PPI utilization,

TABLE 6 | Prescribed pantoprazole daily doses in patient-level surveys.

	Survey 1	Survey 2	Survey 3
Number of patients (%)	N=366 (100)	N=384 (100)	N=51 (100)
Pantoprazole daily dose			
20 mg (low dose/on demand dose)	51 (13.93)	72 (18.75)	12 (23.53)
40 mg (standard dose-WHO DDD)	177 (48.36)	174 (45.31)	22 (43.14)
60 mg	2 (0.55)		
80 mg (high dose)	135 (36.80)	136 (35.42)	15 (29.41)
120 mg			1 (1.96)
160 mg		1 (0.26)	
missing data	1 (0.27)	1 (0.26)	1 (1.96)

and the economic burden is also substantial (Bajor, 2017; Savarino et al., 2017; Ayele et al., 2018; Devitt et al., 2019).

Initiation/De-Prescribing PPIs

Despite the fact that PPIs are available as Over the Counter products in Hungary, in none of the surveyed patients was the PPI therapy initiated by the patients themselves. According to Survey 3, which also assessed who initiated PPI use, most PPI regimens were started by GPs. In Iceland, GPs were also responsible for 60% of the PPI use (Halfdanarson et al., 2018). In Survey 2, which gathered data from 29 units, PPIs were initiated during the hospital stay in 20% of cases. Another US study evaluating PPI use at hospital admission and discharge found a higher rate of PPI continuation upon discharge (Gupta et al., 2010). As the prescribed drug regimen during the hospital stay is indicated on the discharge letter, this guides GPs to automatically continue prescribing PPIs. Pharmacist intervention could significantly promote rational PPI use in the hospital setting (Luo et al., 2018) by decreasing inappropriate indications, dosages and durations, so their medical reconciliation before discharge should be promoted to avoid irrational long-term PPI use.

According to the newest National Institute for Health and Care Excellence guideline [National Institute for Health and Care Excellence (NICE), 2014], periodic medication reviews are needed if PPI treatment is prolonged. The American guidelines also emphasize the need for de-prescribing, including using the lowest effective dose (Freedberg et al., 2017). De-prescribing guidelines are available for patients with uncomplicated, mild-moderate gastro-esophageal reflux disease who completed a minimum of 4 weeks of PPI therapy, and responded to it (Farrell et al., 2017; Freedberg et al., 2017). In our survey, none of the patients reported an attempt at de-prescribing. Automatic renewal of prescriptions without re-evaluation of patient symptoms is of great concern, as, without upper gastrointestinal endoscopy to confirm the presence of erosive esophagitis, long-term use of PPIs is debatable (Lassen et al., 2004). Also, ambulatory pH/impedance monitoring may help to distinguish gastro-esophageal reflux disease from a functional syndrome, and consequently avoid lifelong PPI therapy (Freedberg et al., 2017).

Indications for PPI Use

Most patients in this study received PPI as a prophylactic agent. According to the literature, the most common drivers of PPI misuse are related to unjustified, long-term prophylactic use: prevention of gastro-duodenal ulcers in patients without risk factors for gastric injury (NSAID users, antiplatelet/anticoagulant therapy); stress ulcer prophylaxis in non-intensive care units; steroid therapy alone; selective serotonin reuptake inhibitor therapy alone (Pottegard et al., 2016; Savarino et al., 2018a). In the Icelandic study, nearly half of the patients used PPI concurrently with acetyl salicylic acid, NSAID, platelet inhibitors, or oral anticoagulant (Halfdanarson et al., 2018). The concurrent use of ulcerogenic agents and/or anticoagulant/antiplatelet drugs was also considerable in the PPI users in our study (see **Table 5**). On the other hand, in Survey 2, out of the 399 PPI users, 66 patients (16,5%) did not have any therapeutic indication for PPI use, and also had not used any potentially ulcerogenic or anticoagulant/antiplatelet drug, which is a clear evidence of PPI overuse. Similarly, in Survey 3 only a minority of patients taking clopidogrel received NSAID treatment, or had had a history of peptic ulcer/bleeding, or were on dual antiplatelet therapy, which may question the need for PPI use.

Other studies from inpatients reported a high discordance from evidence-based indications of PPI use (Pillans et al., 2000; Chia et al., 2014; Meli et al., 2015; Lodato et al., 2016; Pujal Herranz, 2016; van den Bemt et al., 2016; Ying et al., 2019). In the expert review of Savarino et al. PPIs are considered as “harmless, cheap remedy for any digestive problems by doctors” (Savarino et al., 2018a). Moreover, as a Chinese article revealed, procurement incentives for doctors may also play a role (Zeng et al., 2015) in the non-prudent prescribing of PPIs.

The present study has some limitations inherent in the database and the study design. The National Health Insurance Fund database contains drug dispensing data for only prescribed and reimbursed drugs. As over the counter PPI products and prescribed but non-reimbursed PPI products are not included in the database, the scale of nationwide use of PPIs has been underestimated. In the patient-level point prevalence survey the prevalence of PPI use was assessed on the given study days and from hospitals where daily drug dispensation is supervised by a pharmacist. This study design did not allow for the precise determination of hospital initiation of PPI use, which could occur during the hospitalisation but after the specific study day. As hospital PPI initiation could differ in hospitals without ward pharmacists, our results cannot be extrapolated to all Hungarian hospitals. On the other hand, this study focused on chronic PPI use, initiated before hospital admission. As we excluded specific gastroenterological units and did not apply any specific inclusion criteria for the inpatients, we believe that results of the multicenter surveys are generalizable for the hospitalized patients in Hungary. Also, much of the information (indication, duration, initiation, de-prescribing) were gained from the patients, so recall bias should be considered. In Survey 3, due to the low number of patients, the data on de-prescribing should be regarded as a signal, not as a valid, generalizable assessment. In the absence of national and local guidelines on PPI use, we did

not aim to precisely determine the appropriateness of PPI therapy.

CONCLUSION

Our data suggests that Hungarian patients may receive PPIs in high doses and for a long time. PPI use beyond the recommended indications were found, so PPI treatment should be initiated more cautiously for specific indications, and PPI dosing and duration of therapy should be reconsidered regularly.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hungarian Medical Research Council. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, RB, and GS had the original idea for the manuscript. MM, RB, MS, RV, and GS organized data collection. MM, RB, ZE, and GS contributed to the analysis. MM, RB, PD, KS, and RV drafted the manuscript, which was reviewed and approved by ZE, MS, and GS.

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REFERENCES

- Ayele, H. T., Dormuth, C. R., and Filion, K. B. (2018). Long-term use of proton pump inhibitors and community-acquired pneumonia: adverse effect or bias? *J. Am. Geriatr. Soc.* 66, 2427–2428. doi: 10.1111/jgs.15575
- Bajor, J. (2017). A tartós protonpumpa-gátló kezelés hatásainak kritikus elemzése. *Cent. Eur. J. Gastroenterol. Hepatol.* 3, 129–133.
- Brunton, L. (2017). *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (New York, USA: MCGraw-Hill Education).
- Chia, C. T. W., Lim, W. P., and Vu, C. K. F. (2014). Inappropriate use of proton pump inhibitors in a local setting. *Singapore Med. J.* 55, 363–366. doi: 10.11622/smedj.2014087
- Del Giorno, R., Ceschi, A., Pironi, M., Zasa, A., Greco, A., and Gabutti, L. (2018). Multifaceted intervention to curb in-hospital over-prescription of proton pump inhibitors: a longitudinal multicenter quasi-experimental before-and-after study. *Eur. J. Intern. Med.* 50, 52–59. doi: 10.1016/j.ejim.2017.11.002
- Devitt, J., Lyon, C., Swanson, S. B., and DeSanto, K. (2019). What are the risks of long-term PPI use for GERD symptoms in patients > 65 years? *J. Fam. Pract.* 68, E18–E19.
- Duerden, M., Avery, T., and Payne, R. (2013). *Polypharmacy and Medicines Optimization* (London: King's Fund).
- El-Serag, H. B., Sweet, S., Winchester, C. C., and Dent, J. (2014). Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 63, 871–880. doi: 10.1136/gutjnl-2012-304269
- Farrell, B., Pottie, K., Thompson, W., Boghossian, T., Pizzola, L., Rashid, F. J., et al. (2017). Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. *Can. Fam. Phys.* 63, 354–364.
- Forgacs, I., and Loganayagam, A. (2008). Overprescribing proton pump inhibitors. *BMJ* 336, 2–3. doi: 10.1136/bmj.39406.449456.BE
- Freedberg, D. E., Kim, L. S., and Yang, Y.-X. (2017). The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American gastroenterological association. *Gastroenterology* 152, 706–715. doi: 10.1053/j.gastro.2017.01.031
- Garner, A., Fadlallah, H., and Parsons, M. (1996). 1976 an all that! - 20 years of antisecretory therapy. *Gut* 39, 784–786. doi: 10.1136/gut.39.6.784
- Gupta, R., Garg, P., Kottoor, R., Munoz, J. C., Jamal, M. M., Lambiase, L. R., et al. (2010). Overuse of acid suppression therapy in hospitalized patients. *South Med. J.* 103, 207–211. doi: 10.1097/SMJ.0b013e3181ce0e7a
- Haastруп, P. F., Thompson, W., Søndergaard, J., and Jørbøl, D. E. (2018). Side effects of long-term proton pump inhibitor use: a review. *Basic Clin. Pharmacol. Toxicol.* 123, 114–121. doi: 10.1111/bcpt.13023
- Hálfadánarson, O. O., Pottgärd, A., Björnsson, E. S., Lund, S. H., Ogmundsdóttir, M. H., Steingrímsson, E., et al. (2018). Proton-pump inhibitors among adults: a nationwide drug-utilization study. *Therap. Adv. Gastroenterol.* 11:1756284818777943. doi: 10.1177/1756284818777943
- Hollingworth, S., Duncan, E. L., and Martin, J. H. (2010). Marked increase in proton pump inhibitors use in Australia. *Pharmacoepidemiol. Drug Saf.* 19, 1019–1024. doi: 10.1002/pds.1969
- Hu, W., Tong, J., Kuang, X., Chen, W., and Liu, Z. (2018). Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: a meta-analysis. *Med. (Baltimore)* 97, e9638. doi: 10.1097/MD.00000000000009638
- Igaz, I., Simonyi, G., Balogh, S., and Szathmári, M. (2018). [Adverse effects of long-term proton-pump inhibitor therapy on adults]. *Orv. Hetil.* 159 (19), 735–740. doi: 10.1556/650.2018.31057
- Iwakiri, K., Kinoshita, Y., Habu, Y., Oshima, T., Manabe, N., Fujiwara, Y., et al. (2016). Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. *J. Gastroenterol.* 51, 751–767. doi: 10.1007/s00535-016-1227-8
- Juntunen, H., Taipale, H., Tanskanen, A., Tolppanen, A.-M., Tiihonen, J., Hartikainen, S., et al. (2017). Long-term use of proton pump inhibitors among community-dwelling persons with and without Alzheimer's disease. *Eur. J. Clin. Pharmacol.* 73, 1149–1158. doi: 10.1007/s00228-017-2273-8
- Kahrilas, P. J., Shaheen, N. J., Vaezi, M. F., Hiltz, S. W., Black, E., Modlin, I. M., et al. (2008). American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 135 (4), 1383–1391, 1391.e1–5. doi: 10.1053/j.gastro.2008.08.045
- Kelly, O. B., Dillane, C., Patchett, S. E., Harewood, G. C., and Murray, F. E. (2015). The inappropriate prescription of oral proton pump inhibitors in the hospital setting: a prospective cross-sectional study. *Dig. Dis. Sci.* 60, 2280–2286. doi: 10.1007/s10620-015-3642-8
- Lanas, A. (2016). We are using too many PPIs, and we need to stop: a european perspective. *Am. J. Gastroenterol.* 111, 1085–1086. doi: 10.1038/ajg.2016.166
- Lanas-Gimeno, A., Hijos, G., and Lanas, A. (2019). Proton pump inhibitors, adverse events and increased risk of mortality. *Expert Opin. Drug Saf.* 18, 1043–1053. doi: 10.1080/14740338.2019.1664470
- Larsen, M. D., Schou, M., Kristiansen, A. S., and Hallas, J. (2014). The influence of hospital drug formulary policies on the prescribing patterns of proton pump inhibitors in primary care. *Eur. J. Clin. Pharmacol.* 70, 859–865. doi: 10.1007/s00228-014-1681-2
- Lassen, A., Hallas, J., and Schaffalitzky De Muckadell, O. B. (2004). Use of anti-secretory medication: a population-based cohort study. *Aliment Pharmacol. Ther.* 20, 577–583. doi: 10.1111/j.1365-2036.2004.02120.x
- Lodato, F., Poluzzi, E., Raschi, E., Piccinni, C., Koci, A., Olivelli, V., et al. (2016). Appropriateness of Proton Pump Inhibitor (PPI) prescription in patients admitted to hospital: attitudes of general practitioners and hospital physicians in Italy. *Eur. J. Intern. Med.* 30, 31–36. doi: 10.1016/j.ejim.2016.01.025
- Luo, H., Fan, Q., Xiao, S., and Chen, K. (2018). Changes in proton pump inhibitor prescribing trend over the past decade and pharmacists' effect on prescribing practice at a tertiary hospital. *BMC Health Serv. Res.* 18, 537. doi: 10.1186/s12913-018-3358-5
- Maes, M. L., Fixen, D. R., and Linnebur, S. A. (2017). Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Ther. Adv. Drug Saf.* 8, 273–297. doi: 10.1177/2042098617715381
- Maléth, J., and Hegyi, P. (2013). [Long-term proton pump inhibitor therapy and osteoporosis. Is there a real danger?]. *Orv. Hetil.* 154, 1005–1009. doi: 10.1556/OH.2013.29656
- Meli, M., Raffa, M. P., Malta, R., Morreale, I., Aprea, L., and D'Alessandro, N. (2015). The use of proton pump inhibitors in an Italian hospital: focus on oncologic and critical non-ICU patients. *Int. J. Clin. Pharm.* 37, 1152–1161. doi: 10.1007/s11096-015-0178-0
- National Institute for Health and Care Excellence (NICE) (2014). *Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management*. NICE. Available at: <https://www.nice.org.uk/guidance/cg184>.
- Pillans, P. I., Kubler, P. A., Radford, J. M., and Overland, V. (2000). Concordance between use of proton pump inhibitors and prescribing guidelines. *Med. J. Aust.* 172, 16–18. doi: 10.5694/j.1326-5377.2000.tb123871.x
- Pottgärd, A., Broe, A., Hallas, J., de Muckadell, O. B. S., Lassen, A. T., and Lodrup, A. B. (2016). Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. *Therap. Adv. Gastroenterol.* 9, 671–678. doi: 10.1177/1756283X16650156
- Pujal Herranz, M. (2016). Is there an overprescription of proton pump inhibitors in oncohematologic patients undergoing ambulatory oncospecific treatment? *Farm Hosp.* 40, 436–446. doi: 10.7399/fh.2016.40.5.9819
- Ronkainen, J., Aro, P., Storskrubb, T., Johansson, S.-E., Lind, T., Bolling-Sternevald, E., et al. (2005a). High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand. J. Gastroenterol.* 40, 275–285. doi: 10.1080/003655205100011579
- Ronkainen, J., Aro, P., Storskrubb, T., Johansson, S.-E., Lind, T., Bolling-Sternevald, E., et al. (2005b). Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 129, 1825–1831. doi: 10.1053/j.gastro.2005.08.053
- Savarino, V., Dulbecco, P., de Bortoli, N., Ottonello, A., and Savarino, E. (2017). The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal. *Eur. J. Intern. Med.* 37, 19–24. doi: 10.1016/j.ejim.2016.10.007
- Savarino, V., Marabotto, E., Zentilin, P., Furnari, M., Bodini, G., De Maria, C., et al. (2018a). Proton pump inhibitors: use and misuse in the clinical setting. *Expert Rev. Clin. Pharmacol.* 11, 1123–1134. doi: 10.1080/17512433.2018.1531703
- Savarino, V., Marabotto, E., Zentilin, P., Furnari, M., Bodini, G., De Maria, C., et al. (2018b). The appropriate use of proton-pump inhibitors. *Minerva Med.* 109, 386–399. doi: 10.23736/S0026-4806.18.05705-1
- Schubert, M. L. (2018). Adverse effects of proton pump inhibitors: fact or fake news? *Curr. Opin. Gastroenterol.* 34, 451–457. doi: 10.1097/MOG.0000000000000471
- Schubert, M. L. (2019). Proton pump inhibitors: placing putative adverse effects in proper perspective. *Curr. Opin. Gastroenterol.* 35 (6), 509–516. doi: 10.1097/MOG.0000000000000580

- Strand, D. S., Kim, D., and Peura, D. A. (2017). 25 years of proton pump inhibitors: a comprehensive review. *Gut Liver* 11, 27–37. doi: 10.5009/gnl15502
- Tett, S. E., Sketris, I., Cooke, C., van Zanten, S. V., and Barozzi, N. (2013). Differences in utilisation of gastroprotective drugs between 2001 and 2005 in Australia and Nova Scotia, Canada. *Pharmacoepidemiol. Drug Saf.* 22, 735–743. doi: 10.1002/pds.3442
- van den Bemt, P. M. L. A., Chaaouit, N., van Lieshout, E. M. M., and Verhofstad, M. H. J. (2016). Noncompliance with guidelines on proton pump inhibitor prescription as gastroprotection in hospitalized surgical patients who are prescribed NSAIDs. *Eur. J. Gastroenterol. Hepatol.* 28, 857–862. doi: 10.1097/MEG.0000000000000634
- van Pinxteren, B., Numans, M. E., Bonis, P. A., and Lau, J. (2006). Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst. Rev.* 3, CD002095. doi: 10.1002/14651858.CD002095.pub3
- World Health Organisation (WHO). (2020). “ATC/DDD Index (version 2020),” in *WHO Collaborating Centre for Drug Statistics Methodology*. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. Available at: <http://www.whocc.no/>.
- Ying, J., Li, L.-C., Wu, C.-Y., Yu, Z.-W., and Kan, L.-D. (2019). The status of proton pump inhibitor use: a prescription survey of 45 hospitals in China. *Rev. Esp. Enferm. Dig.* 111 (10), 738–743. doi: 10.17235/reed.2019.6155/2019
- Yu, L.-Y., Sun, L.-N., Zhang, X.-H., Li, Y.-Q., Yu, L., Yuan, Z.-Q.-Y., et al. (2017). A review of the novel application and potential adverse effects of proton pump inhibitors. *Adv. Ther.* 34, 1070–1086. doi: 10.1007/s12325-017-0532-9
- Zeng, W., Finlayson, A. E., Shankar, S., de Bruyn, W., and Godman, B. (2015). Prescribing efficiency of proton pump inhibitors in China: influence and future directions. *BMC Health Serv. Res.* 15, 11. doi: 10.1186/s12913-014-0638-6

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO): Construct Validity Study

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Background: Validity is the ability of an instrument to measure what it claims to measure. It means the degree to which the empirical evidence supports the trustworthiness of interpretations based on the calculated scores. The hematological malignancy (HM) specific patient reported outcome measure (HM-PRO), is a newly developed instrument for use in daily clinical practice as well as in research. This study, provides the evidence for construct validity of the HM-PRO, specifically focusing on the convergent and divergent validity compared to the other established instruments used in hematology.

Methods: This validation study adopted a prospective cross-sectional design where a heterogeneous group of patients diagnosed with different HMs and different disease state were recruited. A total of 905 patients were recruited from seven secondary care hospitals in the UK and online through five patient organizations. Patients were asked to complete the HM-PRO and other cancer specific PRO's, FACT-G and EORTC QLQ C-30. Data analysis was performed using IBM SPSS 23 statistical software.

Results: A total of 486 males (53.7%) and 419 females (46.3%), with a mean age of 64.3 (± 12.4) years and mean time since diagnosis of 4.6 (± 5.2) were recruited. The total score of Part A of the HM-PRO highly correlated with the five functional scales of the EORTC QLQ-C30 (Physical = -0.71 , Role = -0.72 , Emotional = -0.64 , Cognitive = -0.58 , Social = -0.74 — $p < 0.001$). With respect to correlation with FACT-G, the total score of Part A of the HM-PRO highly correlated with Physical (-0.74), Emotional (-0.57), Functional (-0.66) domains and overall score of FACT-G (-0.74). Similarly, the total score of Part B of the HM-PRO highly correlated with three symptoms scales of EORTC QLQ-C30 (Fatigue scale = -0.74 , Nausea and Vomiting = -0.52 , Pain = -0.59 — $p < 0.001$) and individual symptom items (Dyspnea = 0.51 , Insomnia = 0.43 , Appetite loss = 0.54 — $p < 0.001$).

Conclusion: The construct validity evidence presented in this research is a testimony to the HM-PRO's ability to measure HRQoL issues which it intends to measure. This is of utmost importance when a PRO is used in routine clinical practice so that the interpretation of the scores or response to an individual item is understood by the clinicians/nurses as intended by the patients.

Keywords: hematological malignancy, HM-PRO, quality of life, symptoms, construct validity, clinical practice, clinical research

INTRODUCTION

Hematological malignancies are a cause of morbidity and mortality. Although, treatments have the potential to cure or prolong life, both the disease and the treatment may cause substantial suffering. The main goal has been “cure” for many years, however, more recently, equal emphasis has been placed on patients’ “quality of life.” Measuring quality of life is not only a new clinical end-point for cancer treatments (Kosmidis, 1996; Allart-Vorelli et al., 2015), but is also used to guide the decision-making in daily clinical practice (Esser et al., 2018). The rapid growth in terms of the availability of the new treatments for hematological malignancies has added more complexity in the decision-making process. The use of patient-reported outcomes (PROs) both in clinical research and routine practice can help to collect this complex information from patients in a systematic manner to be used as an aid to treatment decision-making process (Efficace et al., 2017; Esser et al., 2018). With such an importance attached to PROs both in clinical research and routine practice, special attention should be paid to the development and validation of such instruments.

Validity, reliability, and responsiveness are the three measurement properties which should be assessed according to the COSMIN study conducted by Mokkink et al. (2010) to reach international consensus, to prove that a newly developed health-related quality of life instrument (HRQoL) possesses strong psychometric measurement properties (Mokkink et al., 2010). Validity is the ability of an instrument to measure what it claims to measure (Wan, 2002; Roberts and Priest, 2006; Mokkink et al., 2010; Fayers and Machin, 2013). It means the degree to which the empirical evidence supports the trustworthiness of interpretations based on the calculated scores (Messick, 1994). To provide evidence for validity is one of the essential steps in the development of an instrument for quantifying HRQoL and to prove the legitimacy of the instrument. The validity attribute relates to particular use of the scale and is not an inherent trait of the instrument (Messick, 1988; Zamanzadeh et al., 2015). There are different ways to assess construct validity including demonstration of moderate to high correlation with a standardized instrument

measuring the same concept to show “convergent validity,” or low correlation with an instrument measuring different concept to show “divergent validity.”

The hematological malignancy specific patient reported outcome measure (HM-PRO), is a newly developed instrument for use in daily clinical practice as well as in research (Goswami et al., 2016; Goswami et al., 2018a; Goswami et al., 2018b; Goswami et al., 2019a; Goswami et al., 2019b; Goswami et al., 2020). The HM-PRO is undergoing all necessary assessments to meet the minimum standards set out by regulatory authorities such as the FDA. This study, provides the evidence for construct validity of the HM-PRO, specifically focusing on the convergent and divergent validity compared to the other established instruments used in hematology.

METHODS

Ethics

Multicenter ethics approval was obtained from the National Research Ethics Service (NRES) South West Bristol, UK (ref 14/SW/0033) followed by individual “research and development” approvals from all the participating centers. A signed informed consent was obtained from all the study participants.

Study Design

This validation study adopted a prospective cross-sectional design to which a heterogeneous group of patients diagnosed with different HMs and different disease state were recruited. In the absence of a gold standard, the study design for carrying-out the HM-PRO validity, hypothesis testing approach was adopted. The patients were recruited from inpatient and outpatient clinics of seven secondary care hospitals in the United Kingdom and gave informed written consent in person or online if they were recruited through hematology/oncology patient organizations (Myeloma UK, Leukemia Care, Lymphoma Association, MDS support group, and MPN foundation). The patient organization posted the summary of the project on their news page, trial page, and other social media. The summary was provided with the link to the patient information sheet and contact details of the research team. Those who were interested gave online consent and provided their demographic information together with contact details. All patients were then sent a set of three questionnaires with a free post envelope to return the completed instruments. The inclusion criteria for the participants were: adult patients diagnosed with any HM as per latest WHO classification; at any

Abbreviations: ALL, Acute Lymphoid Leukemia; AML, Acute Myeloid Leukemia; ANHL, Aggressive Non-Hodgkin Lymphoma; CI, Confidence Interval; CLL, Chronic Lymphoid Leukemia; CML, Chronic Myeloid Leukemia; HL, Hodgkin Lymphoma; HM, Hematological Malignancy; HRQoL, Health-Related Quality of life; INHL, Indolent Non-Hodgkin Lymphoma; MDS, Myelodysplastic Syndromes; MM, Multiple Myeloma; MPN, Myeloproliferative Neoplasm; n, Number of Patients Recruited; QoL, Quality of Life; SD, Standard Deviation.

stage of the disease; at any stage of the treatment; and able to read and understand English. The exclusion criteria were: unable to read and understand English and unable to give written informed consent.

Instruments

HM-PRO

The hematological malignancy–patient reported outcome measure (HM-PRO) is a newly developed composite measure consisting of two scales: Part A (Impact); and Part B (Signs and Symptoms). Part A measures the impact of the HM and its treatment on a patient's HRQoL, and Part B captures the severity of disease or treatment related signs and symptoms (Goswami et al., 2016; Goswami et al., 2017; Goswami et al., 2020). Part A has a total of 24 items in four domains: physical behavior (7); social behavior (3); emotional behavior (11); and eating and drinking habits (3). Patients' responses are recorded on a three-point Likert scale (Not at all, A little, A lot) and "not applicable" as a separate response option. Part B consists of 18 items in a single domain and the responses are captured on a three-point severity Likert scale (Not at all, Mild, Severe). The third item of the "Eating and Drinking habits" domain in Part A i.e. "My drinking habits have changed," and ninth item of Part B related to "skin problems" are not included in the scoring system but collected for additional information. The HM-PRO has shown good reliability with Cronbach's alpha and ICC with coefficient greater than 0.8 for all four domains of Part A and for Part B (Goswami et al., 2016; Goswami et al., 2017; Goswami et al., 2020).

EORTC QLQ C-30

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is one of the most widely used cancer specific HRQoL instruments including for patients with HM (Kvam et al., 2010; Kvam et al., 2011). This instrument has a total of 30 items in five multiple item functional scales: Physical (5), role (2); emotional (4), cognitive (2), and social (2); two global health and quality of life (QoL) items, three symptom scales (Fatigue—3, Nausea and Vomiting—2, and Pain—2); and six single items (Dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Responses are recorded on a four-point Likert scale (Not at all–Very much). All the scales and single items are measured on linear scores ranging from 0 to 100 (Aaronson et al., 1993; Knobel et al., 2003).

FACT-G

Functional Assessment of Cancer Therapy- General (FACT-G) is another widely used cancer specific HRQoL including for patients with HM (Yost et al., 2013). This instrument has a total of 27 items in four domains: physical well-being (7); social/family well-being (7); emotional well-being (6); and functional well-being (7). Responses for all the items are recorded using a five-point Likert scale (Not at all–Very much). The total score for all the items is calculated on a linear scale ranging from 0 to 100 (McQuellon et al., 1997; Cella et al., 2012; Hlubocky et al., 2013; Yost et al., 2013).

Global Question

Global Question (GQ) is a general question which assesses the overall impact on HRQoL from a patient's perspective. The response to the question is captured using a five-point Likert scale (extremely large effect on my life to no effect on my life).

Data Processing and Analysis

The data collected from the in-patient and out-patient clinics of the seven secondary care hospitals in the UK were manually entered and 20% of the entered data were randomly selected and cross validated. For the remaining data collected through online platform, it was possible to have the direct data entry to the database minimizing the potential human error (Dillman, 2006). Data analyses were carried out with IBM SPSS 2, statistical software. The following tests were performed on the data collected: descriptive statistics to explore distribution of the variables and the HM-PRO scores; Spearman's Rank correlation coefficient was calculated to establish the relationships between the scores of both Part A and Part B of the HM-PRO and other measures. According to Fayers and Machin (2007), a correlation coefficient of greater than 0.3–0.4 supports convergent validity (Fayers and Machin, 2007). Furthermore, univariate Ordinary Least Squares (OLS) regression analysis was performed to assess the relationship between scores of the HM-PRO and the other two instruments. To assess how much of the variance in the independent variable is explained by the predictor variable, R^2 , the coefficient of determination was used (Streiner et al., 2015); and to determine the predictors of the HRQoL in hematological malignant patients, multivariate OLS regression was performed. The score of HM-PRO was the dependent variable, and patient demographics, diagnosis, and disease state were the independent variables.

RESULTS

Patient Demographics

A total of 905 patients were recruited from seven secondary care hospitals in the UK. This included 486 males (53.7%) and 419 females (46.3%), with a mean age of 64.3 ($\pm$ 12.4) years and mean time since diagnosis of 4.6 ($\pm$ 5.2) (Table 1). The diagnoses were: acute leukemias—lymphoblastic (n = 29) and myeloid (n = 67); chronic leukemias—lymphoid (n = 64) and myeloid (n = 45); multiple myeloma (n = 296); Non Hodgkin Lymphomas—indolent (n = 41) and aggressive (n = 54); Hodgkin Lymphoma (n = 37); myelodysplastic syndromes (n = 158); and myeloproliferative neoplasms (n = 114) (Table 1). The highest number of patients with MM (10) and ANHL (10) were in the age group of 60–70 years. Fifty-nine percent of patients did not report any comorbidities. With respect to the employment status, the highest percentage of patients (61.7%) were retired, followed by 27.88% who were employed and working fulltime (Table 1), and ten were students.

HM-PRO Scores

The summary scores for the four domains and both scales (Part A: Impact, and Part B: signs and symptoms) are presented in Table 2.

TABLE 1 | Sociodemographic characteristics of the study participants.

n = 905				
Age (Years)	Median		66.4	
	Mean (SD)		64.3 (± 12.4)	
	IQR		57.11–72.6	
Time since Diagnosis (Years)	Median		2.08	
	Mean (SD)		4.6 (5.2)	
	IQR		0.89–6.85	
		n		%
Gender	Male	486		53.7
	Female	419		46.3
Ethnic Origin	White	870		96.1
	Asian or Asian British	26		2.9
	Black British or Black British	7		0.8
	Unknown	2		0.02
Disease Type	ALL	29		3.2
	AML	67		7.4
	ANHL	54		6
	CLL	64		7.1
	CML	45		5
	HL	37		4.1
	INHL	41		4.5
	MDS	158		17.5
	MM	296		32.7
	MPN	114		12.6
Stage of Disease	Stable	399		44.1
	Remission	277		30.6
	Progressing	229		25.3
Employment	Employed	252		27.8
	Self-Employed	9		1
	Unemployed	41		4.5
	Homemaker	5		0.6
	Retired	558		61.7
	Student	10		1.1
	Other	6		0.7
	Unknown	24		2.6
Comorbidities	No Other Cases	533		58.9
	Other Comorbidities Cases	319		35.2
	Other Cancer	53		5.9

IQR, Inter-quartile range.

The mean linear score of Part A was 31.7 (95% CI = 29.6–33.8, SD = 21.6, and range 0 to 95.5) and for Part B was 20.9 (95% CI = 19.9–21.8, SD = 14.2, and range 0 to 76.5). In addition, the scores for the four domains of Part A were: Physical behavior 32.1 (95% CI = 30.4–33.8, SD = 26.2, and range 0 to 100); Social well-being was 24.9 (95% CI = 23.2–26.7, SD = 27.2, and range 0 to 100); Emotional behavior

38.2 (95% CI = 36.7–39.7, SD = 22.8, and range 0 to 100); and Eating and drinking 31.7 (95% CI = 29.6–33.8, SD = 31.9, and range 0 to 100). A total of 19 (2.1%) patients for Part A and 47 (5.2%) for Part B, achieved minimum score (zero) showing floor effect, however none achieved the maximum score of hundred for either part, confirming absence of ceiling effect.

TABLE 2 | HM-PRO scores for the four domains, total Parts A and B.

Statistics		Physical Behavior	Social Well-being	Emotional Behavior	Eating & Drinking	Part A	Part B
Mean		32.1	24.9	38.2	31.7	31.7	20.9
95% Confidence Interval for Mean	Lower Bound	30.4	23.2	36.7	29.6	30.3	19.9
	Upper Bound	33.8	26.7	39.7	33.8	33.1	21.8
5% Trimmed Mean		30.7	22.6	37.4	29.6	30.7	20.0
Median		28.6	16.7	36.4	25.0	28.3	17.6
Variance		684.0	741.9	518.2	1,020.1	466.3	202.0
Std. Deviation		26.2	27.2	22.8	31.9	21.6	14.2
Minimum		0.0	0.0	0.0	0.0	0.0	0.0
Maximum		100.0	100.0	100.0	100.0	95.5	76.5
Interquartile Range		42.9	33.3	31.8	50.0	32.7	20.6

Convergent Validity

The Assessment of convergent validity of both parts of the HM-PRO was performed using correlation analysis with the EORTC QLQ-C30 and FACT-G scores. Totals scores of Part A and Part B of the HM-PRO were first correlated with individual domains of EORTC QLQ-C30 and FACT-G and total Scores of FACT-G. This included correlating total score of: 1) Part A (Impact) with: five functional domains of EORTC QLQ-C30 (Physical, Role, Emotional, Cognitive, and social) and three symptom scales (Fatigue, Nausea and Vomiting, and Pain); and four domains of Fact-G (Physical, Social, Emotional, Functioning) and total Score of Fact-G; 2) Part B (Signs and Symptoms) with three symptoms scales of EORTC QLQ-C30 and three individual items (Dyspnea, Insomnia, Appetite loss); and four domains and total Score of FACT-G. The Spearman's rank correlation coefficient estimates from this analysis are presented in **Table 3**.

The total score of Part A of HM-PRO highly correlated with the five functional scales of the EORTC QLQ-C30 (Physical = -0.71 , Role = -0.72 , Emotional = -0.64 , Cognitive = -0.58 , Social = -0.74 — $p < 0.001$). The three symptoms scales of EORTC QLQ-C30 also showed moderate to high correlation (Nausea and Vomiting = -0.41 , Pain = -0.55 , Fatigue = -0.71). With respect to correlation with FACT-G, the total score of Part A of the HM-PRO highly correlated with Physical (-0.74), Emotional (-0.57), Functional (-0.66) domains and overall score of

FACT-G (-0.74) (**Table 3**). The correlation with Social well-being domain of FACT-G was moderate (-0.38). The negative correlation between the score of the HM-PRO and the other two instruments is observed because in EORTC QLQ-C30 and FACT-G higher scores reflect improving “Quality of life” of the patients, whereas the opposite is the case with the HM-PRO scores.

Similarly, the total score of Part B of HM-PRO highly correlated with three symptoms scales of EORTC QLQ-C30 (Fatigue scale = -0.74 , Nausea and Vomiting = -0.52 , Pain = -0.59 — $p < 0.001$) and individual symptom items (Dyspnea = 0.51 , Insomnia = 0.43 , Appetite loss = 0.54 — $p < 0.001$). The correlations with the four domains and total score of FACT-G were moderate to high but demonstrated weak correlation with social well-being domain (-0.28 , $p < 0.001$) (**Table 3**). The high overall correlation between the total scores of the HM-PRO and domain/scales of EORTC QLQ-C30 and FACT-G confirmed the convergent validity of the HM-PRO.

Furthermore, the correlation between the individual domains of Part A, individual items of the HM-PRO and domains and individual items of EORTC QLQ-C30 and FACT-G was assessed. The Spearman's rank correlation coefficient estimates from this analysis are presented in **Table 4**. The Physical behavior domain of the HM-PRO showed strong correlation of -0.79 with Physical function domain of EORTC QLQ-C30 and -0.73 with Physical well-being domain of FACT-G. The correlation of the emotional and social well-being domain of the HM-PRO with emotional and social domain of EORTC QLQ-C30 and FACT-G was also strong.

With respect to the individual items, constipation item of the HM-PRO and EORTC QLQ-C30 showed highest correlation of 0.88 . The correlations between all other similar items were above 0.5 showing strong correlation and confirming that the items of the HM-PRO measure the same construct as that of the EORTC QLQ-C30 and FACT-G items (**Table 4**).

Univariate Regression Analysis

The univariate regression analysis to assess the relationship between the HM-PRO and other measure was performed in two steps: first at domain level; and second at individual item level. At the domain level the univariate regression analysis showed that the model was statistically significant indicating strong relationship between the HM-PRO domains and EORTC domains (Physical: $F = 1455.13$, $p < 0.001$, $R^2 = 62\%$, Emotional: $F = 1,180.045$, $p < 0.001$, $R^2 = 56\%$, Social: $F = 360.884$, $p < 0.001$, $R^2 = 28\%$, Eating and Drinking: $F = 975.71$, $p < 0.001$, $R^2 = 52\%$) and FACT-G (Physical: $F = 937.406$, $p < 0.001$, $R^2 = 62\%$, Emotional: $F = 1,261.29$, $p < 0.001$, $R^2 = 58.5\%$, and Social: $F = 161.42$, $p < 0.001$, $R^2 = 15.2\%$) (**Table 5**). The scatter plot showing the relationship between the emotional behavior domain of the HM-PRO and emotional function scale of the EORTC and emotional well-being domain of FACT-G is presented in **Figure 1**. The R^2 value determines the strength of the relationship between the two variables i.e. “emotional well-being” domain of the HM-PRO and the respective emotional domains of the FACT-G and EORTC. Almost 60% of the

TABLE 3 | Correlation of total HM-PRO scores (Parts A and B) with EORTC QLQ-C30 and FACT-G domains, symptoms scale, and individual items.

Total Score of HM-PRO	EORTC QLQ C-30	Spearman's Correlation	p Value
Part A	Physical Function	-0.71	<0.001
	Role Function	-0.72	<0.001
	Emotional Function	-0.64	<0.001
	Cognitive Function	-0.58	<0.001
	Social Function	-0.74	<0.001
	Fatigue Scale	-0.71	<0.001
	Nausea and Vomiting	-0.41	<0.001
Part B	Pain	-0.55	<0.001
	Fatigue Scale	-0.74	<0.001
	Nausea and Vomiting	-0.52	<0.001
	Pain	-0.59	<0.001
	Dyspnea	0.51	<0.001
	Insomnia	0.43	<0.001
	Appetite Loss	0.54	<0.001
FACT-G			
Part A	Physical Well-being	-0.74	<0.001
	Social Well-being	-0.38	<0.001
	Emotional Well-being	-0.57	<0.001
	Functional Well-being	-0.66	<0.001
	FACT-G Total score	-0.74	<0.001
Part B	Physical Well-being	-0.79	<0.001
	Social Well-being	-0.28	<0.001
	Emotional Well-being	-0.45	<0.001
	Functional Well-being	-0.57	<0.001
	FACT-G Total score	-0.65	<0.001

TABLE 4 | Correlation of HM-PRO total scores (Parts A and B) with EORTC QLQ-C30 and FACT-G domains, symptoms scale, and individual items.

HM-PRO		EORTC QLQ C-30	Spearman's Correlation	p Value
Part A	Domains			
	Physical Behavior	Physical Function	−0.79	<0.001
	Emotional Behavior	Emotional Function	−0.76	<0.001
	Social Well-being	Social Function	−0.55	<0.001
	Eating and Drinking	Appetite	−0.71	<0.001
Part B	Individual items			
	Energy level	Fatigue Scale	−0.73	<0.001
	Tiredness	Fatigue Scale	−0.72	<0.001
	Back Pain	Pain Scale	−0.59	<0.001
	Body Pain	Pain Scale	−0.70	<0.001
	Breathing	Dyspnea	0.73	<0.001
	Constipation	Constipation	0.88	<0.001
	Diarrhea	Diarrhea	0.79	<0.001
	Nausea	Nausea and Vomiting Scale	−0.80	<0.001
	Sleeping	Insomnia	0.64	<0.001
		FACT-G		
Part A	Domains			
	Physical Behavior	Physical Well-being	−0.73	<0.001
	Emotional Behavior	Emotional Well-being	−0.75	<0.001
	Social Well-being	Social Well-being	−0.44	<0.001
Part B	Individual items			
	Energy level	Energy	−0.75	<0.001
	Back Pain	Pain	−0.62	<0.001
	Body Pain	Pain	−0.73	<0.001
	Nausea	Nausea	−0.82	<0.001
	Sleeping	Sleeping	−0.54	<0.001

variability in the FACT-G and EORTC emotional domain score is explained by the HM-PRO emotional well-being score.

Univariate regression analysis at the individual item level showed similar results with the HM-PRO items explaining more than 50% of variability when compared with all the items of the EORTC and FACT-G, except for “back pain” item of the HM-PRO with pain item of the EORTC and “sleeping” item of the HM-PRO with sleeping item of Fact-G (Table 6). The “constipation” item of the HM-PRO explained 74.2% of the variance of constipation item of EORTC. The models for all the compared items were statistically significant, showing strong relationship between the items of the HM-PRO and the other

two instruments, confirming that they measure similar construct (Table 6).

Predictors of HRQoL in Hematological Malignancy

It is of importance to determine and understand the determinants of the HRQoL in patients with HMs in both research and clinical practice settings, in particular in the clinical setting where the HRQoL information might guide clinical decision-making. Multivariate regression analysis was carried out using stepwise and hierarchical regression technique to identify these predictive factors. The overall score of the Parts

TABLE 5 | Univariate regression analysis of HM-PRO domains of Part A against domains of EORTC QLQ-C30 and FACT-G.

	Ind. Var (HM-PRO)	F	df	P	R2	Adj R ²	Dep. Var	B	SE	Beta	t	p
1	Physical Behavior	1,455.1	1	0.0001	0.6	0.6	EORTC_PF Constant	−0.7 93.4	0.02 0.8	−0.8	−38.2 122.5	0.001 0.001
2	Physical Behavior	937.4	1	0.0001	0.5	0.5	FACT_G_PWB Constant	−0.2 26.1	0.01 0.2	−0.7	−30.6 119.8	0.001 0.001
3	Emotional Behavior	1,180.1	1	0.0001	0.6	0.6	EORTC_EF Constant	−0.8 104.9	0.02 0.9	−0.8	−34.4 105.9	0.001 0.001
4	Emotional Behavior	1,261.3	1	0.0001	0.6	0.6	FACT_G_EWB Constant	−0.2 23.8	0.01 0.2	−0.8	−35.5 117.7	0.001 0.001
5	Social Well-being	360.9	1	0.0001	0.3	0.3	EORTC_SF Constant	−0.6 81.6	0.3 1.2	−0.5	−18.9 66.8	0.001 0.001
6	Social Well-being	161.4	1	0.0001	0.2	0.2	FACT-SWB Constant	−0.09 22.8	0.01 0.3	−0.4	−12.7 88.8	0.001 0.001
7	Eating and Drinking	975.7	1	0.0001	0.5	0.5	EORTC_AP Constant	0.6 −2.3	0.02 0.9	0.72	31.2 −2.5	0.001 0.001

PB, Physical behavior; EB, Emotional behavior; SWB, Social well-being; PF, Physical Function; PWB, Physical well-being; EF, Emotional function; EWB, Emotional well-being; ED, Eating and Drinking; AP, Appetite.

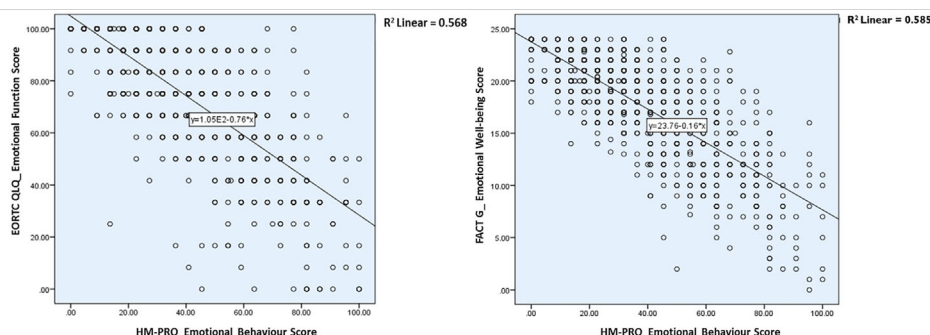


FIGURE 1 | Relationship between the emotional behavior domain of the HM-PRO and emotional function scale of the EORTC and emotional well-being domain of FACT-G.

TABLE 6 | Univariate regression analysis of individual items of HM-PRO Part B against individual items of EORTC QLQ-C30 and FACT-G.

Ind. Var(HM-PRO)	F	df	P	R2	Adj R2	Dep. Var	B	SE	Beta	T	P
1 Energy Level	1,121.9	1	0.0001	0.6	0.6	FACTG- Energy	-1.4	0.04	-0.8	-33.5	0.001
						Constant	3.6	0.04		66.9	0.001
2 Tiredness	980.1	1	0.0001	0.5	0.5	EORTC_ Fatigue	-30.9	0.1	-0.7	-31.3	0.001
						Constant	93.6	1.3		73.6	0.001
3 Back Pain	507.9	1	0.0001	0.4	0.4	EORTC_ Pain	-25.3	1.1	-0.6	-22.5	0.001
						Constant	87.7	0.9		88.2	0.001
4 Body Pain	985.1	1	0.0001	0.5	0.5	EORTC_ Pain	-31.5	1.0	-0.7	-31.4	0.001
						Constant	91.8	0.9		104.1	0.001
5 Body Pain	1,173.1	1	0.0001	0.6	0.6	FACTG-Pain	-1.4	0.04	-0.8	-34.3	0.001
						Constant	3.7	0.04		102.9	0.001
6 Breathing	1,075.7	1	0.0001	0.6	0.6	EORTC_ Dyspnea	35.8	1.1	0.7	32.8	0.001
						Constant	9.4	0.8		11.7	0.001
7 Constipation	2,575.4	1	0.0001	0.7	0.7	EORTC_ Constipation	36.7	0.7	0.9	50.8	0.001
						Constant	1.2	0.5		2.5	0.01
8 Diarrhea	1,701.9	1	0.0001	0.7	0.7	EORTC_ Diarrhea	33.9	0.8	0.8	41.3	0.001
						Constant	2.3	0.5		4.6	0.001
9 Nausea	1,145.9	1	0.0001	0.6	0.6	EORTC_ Nausea Vomiting	-25.1	0.7	-0.7	-33.9	0.001
						Constant	98.9	0.4		230.9	0.001
10 Nausea	1,673.5	1	0.0001	0.6	0.7	FACTG- Nausea	-1.3	0.03	-0.8	-40.9	0.001
						Constant	3.9	0.2		214.9	0.001
11 Sleeping	362.9	1	0.0001	0.3	0.3	FACTG- Sleeping	-0.9	0.04	-0.5	-19.1	0.001
						Constant	3.1	0.1		51.7	0.001

Ind Var, Independent variable; Dep Var, Dependent variable; F, F-Statistics; df, Degree of freedom; AdjR2, Adjusted R square value; SE, Standard error.

A and B of the HM-PRO were the dependent variable, and independent variables in the model included: Age; gender; time since diagnosis; comorbidities; occupation; ethnicity; disease diagnosed; disease state; and global question (GQ).

Hierarchical Regression Analysis

In the hierarchical regression analyses, two separate analysis were performed with Parts A and B as dependent variable. The independent variables were then sequentially added to the regression, one at a time, to have clear understanding on how each variable contributed to explain the variance in patient HRQoL. For Part A of the HM-PRO, the disease state explained the most variance in the HRQoL score (4.3%). Other variables making significant contribution to explaining the

HRQoL included: age (2.7%); comorbidities (2.1%); and Ethnicity (0.8%). Overall the model explained 34.4% of the variance in the total score (**Table 7**). With respect to Part B, comorbidity cases explained the most variance in the HRQoL (2.2%). Other variables making significant contribution to explaining the HRQoL included: age (0.7%); and disease state (2%) (**Table 8**).

Backward Stepwise Regression

In the backward stepwise regression, the regression model was estimated sequentially, first all the variables were entered into the model and then the subsequent models were estimated by eliminating the least significant regressor if its significance level was ≥ 0.1 at each step, until there was no variable to be removed

TABLE 7 | Contribution of predictors explaining variance in the HM-PRO Part A scores; with hierarchical inclusion of variables.

Model	R	R Square	Adjusted R Square	SE of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.163 ^a	.03	.03	21.4	.027	23.7	1	863	.00
2	0.167 ^b	.03	.03	21.4	.001	0.9	1	862	.33
3	0.171 ^c	.03	.03	21.4	.001	1.3	1	861	.26
4	0.224 ^d	.05	.05	21.2	.021	18.9	1	860	.00
5	0.224 ^e	.05	.05	21.2	.000	0.2	1	859	.63
6	0.242 ^f	.06	.05	21.1	.008	7.3	1	858	.01
7	0.242 ^g	.06	.05	21.2	.000	0.04	1	857	.83
8	0.318 ^h	.10	.10	20.7	.043	40.8	1	856	.00
9	0.344 ⁱ	.12	.10	20.5	.017	16.3	1	855	.00

^aPredictors: (Constant), Age.^bPredictors: (Constant), Age, Gender.^cPredictors: (Constant), Age, Gender, Time Since Diagnosis.^dPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases.^ePredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation.^fPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity.^gPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity, Disease Diagnosis.^hPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity, Disease Diagnosis, Stage of the Disease.ⁱPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity, Disease Diagnosis, Stage of the Disease, Global Question.

(Pope and Webster, 1972). The following predictors were retained in the final model for Part A: Disease state, ethnicity, comorbidities cases, and age. These four predictors were jointly significant in explaining Part A score of the HM-PRO by 11.5% (Table 9).

With respect to Part B of the HM-PRO, the following predictors were retained after eliminating the variable based on backward regression: Disease state, comorbidities cases, gender, and age. These five predictors were jointly significant in explaining the variance of Part B score of the HM-PRO by 5.6% (Table 10). Compared to the predictors retained for Part A, Part B has gender instead of ethnicity. That means patients

gender is contributing to explaining the variability in score for signs and symptoms.

DISCUSSION

The validity of an instrument explains the degree to which the instrument measures what it claims to measure and is an essential step to prove the legitimacy of the instrument. An instrument lacking validity will not answer the research question, and the outcome will be misleading. This in the

TABLE 8 | Contribution of predictors explaining variance in the HM-PRO Part B scores; with hierarchical inclusion of variables.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.081 ^a	.01	.01	14.3	.007	5.7	1	863	0.02
2	.103 ^b	.01	.01	14.3	.004	3.5	1	862	0.06
3	.110 ^c	.01	.01	14.3	.001	1.3	1	861	0.26
4	.185 ^d	.03	.03	14.1	.022	19.8	1	860	0.00
5	.187 ^e	.04	.03	14.1	.001	0.4	1	859	0.49
6	.187 ^f	.04	.03	14.1	.000	0.1	1	858	0.72
7	.188 ^g	.04	.03	14.1	.001	0.4	1	857	0.50
8	.236 ^h	.06	.05	13.9	.020	18.4	1	856	0.00
9	.257 ⁱ	.07	.06	13.9	.010	9.2	1	855	0.00

^aPredictors: (Constant), Age.^bPredictors: (Constant), Age, Gender.^cPredictors: (Constant), Age, Gender, Time Since Diagnosis.^dPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases.^ePredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities cases, Occupation.^fPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities cases, Occupation, Ethnicity.^gPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity, Disease Diagnosis.^hPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities cases, Occupation, Ethnicity, Disease Diagnosis, Stage of the Disease.ⁱPredictors: (Constant), Age, Gender, Time Since Diagnosis, Comorbidities Cases, Occupation, Ethnicity, Disease Diagnosis, Stage of the Disease, Global Question.

TABLE 9 | Predictors of HM-PRO Part A score based on stepwise backward regression.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.344 ^a	.12	.11	20.5	.118	12.7	9	855	0.000
2	.344 ^b	.12	.11	20.5	.000	0.01	1	855	0.95
3	.343 ^c	.12	.11	20.5	.000	0.3	1	856	0.57
4	.342 ^d	.12	.11	20.5	-.001	1.1	1	857	0.29
5	.340 ^e	.12	.11	20.5	-.001	1.3	1	858	0.25

^aPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Ethnicity, Comorbidities Cases, Gender, Occupation, Disease Diagnosis, Age.

^bPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Ethnicity, Comorbidities Cases, Gender, Disease Diagnosis, Age.

^cPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Ethnicity, Comorbidities Cases, Gender, Age.

^dPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Ethnicity, Comorbidities Cases, Age.

^ePredictors: (Constant), Global Question, Stage of the Disease, Ethnicity, Comorbidities Cases, Age.

TABLE 10 | Predictors of HM-PRO Part B score based on stepwise backward regression.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.257 ^a	.066	.056	13.9	.066	6.7	9	855	.000
2	0.256 ^b	.066	.057	13.9	.000	0.3	1	855	.616
3	0.254 ^c	.065	.057	13.9	-.001	0.8	1	856	.368
4	0.252 ^d	.063	.057	13.9	-.001	1.1	1	857	.284
5	0.248 ^e	.061	.056	13.9	-.002	1.8	1	858	.179

^aPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Ethnicity, Comorbidities Cases, Gender, Occupation, Disease Diagnosis, Age.

^bPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Comorbidities Cases, Gender, Occupation, Disease Diagnosis, Age.

^cPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Comorbidities Cases, Gender, Occupation, Age.

^dPredictors: (Constant), Global Question, Stage of the Disease, Time Since Diagnosis, Comorbidities Cases, Gender, Age.

^ePredictors: (Constant), Global Question, Stage of the Disease, Comorbidities Cases, Gender, Age.

context of patients with hematological malignancies might be detrimental. A non-calibrated diagnostic instrument may lead to misdiagnosis, or a non-valid HRQoL instrument may lead to under or over estimation of the impact on a patient's functional ability, both physical and psychosocial. Thus, establishing the validity of a PRO instrument is of utmost importance. This study has provided evidence to support the validity of the HM-PRO. The majority of items, in both Parts A and B of the HM-PRO received more than 80% of affirmative responses, suggesting that the content of the instrument is relevant and important to the target patient population.

The aim of construct validity is to establish a relation with variables of other measures with which theoretically it should be associated either in a positive or a negative relation or not at all. For demonstrating the construct validity of the HM-PRO, convergent validity was examined by assessing the correlation of the similar constructs in other instrument (Streiner et al., 2015; DeVellis, 2016). The HM-PRO scores correlated with the scores of EORTC QLQ-C30 and FACT-G, at both the scale level and individual item level. The correlation coefficient had the negative value because the HM-PRO measures the impact on a patient's HRQoL, whereas, EORTC QLQ-C30 and FACT-G measure the HRQoL.

The individual items of EORTC on constipation, diarrhea, or symptom scale like dyspnea, insomnia, and appetite loss showed positive correlation with the HM-PRO because they measure the construct in the same direction i.e. measuring the impact. The

HM-PRO showed strong and significant correlation with functional scales of the EORTC and FACT-G. The individual items related to tiredness, sleeping, pain, breathing, constipation, diarrhea, nausea, and vomiting of the HM-PRO, showed strong correlation with the respective items in EORTC and FACT-G.

The univariate regression analysis conducted both at the domain and item level confirmed the strong relationship between the HM-PRO and the other two measures. For the majority of the regression models, the HM-PRO domains and individual items explained more than 50% of the variance in domain and item scores of EORTC QLQ-C30 and FACT-G, showing strong relationship and confirming the construct validity of the HM-PRO.

The HM-PRO has been developed in accordance to FDA PRO guidelines. It has shown evidence of good content validity, meaning that it captures what is important to patients with different hematological malignancies (Goswami et al., 2020). The evidence on the construct validity presented in this research is a testimony of the HM-PRO's ability to measure HRQoL issues which it intends to measure. This is of utmost importance when a PRO is used in routine clinical practice, so that the interpretation of the score or response to an individual item is understood by the clinicians/nurses as intended by the patients. Further, the evidence supports that the HM-PRO can be used for the purpose of focusing on a specific functional area for which patient is mostly affected and might benefit from more patient-centered consultation. The clinicians have the tendency to trust

their own *ad-hoc* assessment of patient HRQoL, but they are not always able to do this accurately and systematically (Basra and Shahrukh, 2009). Therefore, the HM-PRO might be useful to identify specific functional issues on individual basis early in the course of the disease and treatment.

A randomized controlled trial conducted by Basch E et al. assessed the overall survival associated with electronic patient-reported symptoms monitoring *versus* usual care (Basch et al., 2017). The authors concluded that integration of a PRO into routine care was associated with increased survival compared to usual care in patients with metastatic cancer. The potential mechanism proposed by the authors in regard to the findings is early responsiveness to patient symptoms preventing adverse consequences. The individual items of HM-PRO in Part B measuring impact of signs and symptoms have the potential to capture and monitor the responsiveness of the treatments towards these signs and symptoms across different hematological malignancies. The implementation of a PRO in routine clinical practice have shown positive outcomes in the past and with strong evidence on the content and construct validity of the HM-PRO, it has potential to focus on person-centered care and measure what is important to patients with different hematological malignancies.

STRENGTHS AND LIMITATION

The HM-PRO has been developed with strong involvement of patients not only as study participants but also as a research partner and adviser. The intensive qualitative phase and robust cognitive debriefing phase ensured the content of instruments assessed for construct validity are comprehensive and covers all important aspects of HRQoL for patients with HMs. Due to the lack of a “gold standard” instrument which has been validated to be used in clinical practice for all types of HMs, the construct validation of the HM-PRO was carried out using instruments which have been developed and validated, primarily for use in clinical trials. Furthermore, most of the internationally recognized patient-reported outcome measures which are used in oncology have been developed and validated by an international patient population. Since the HM-PRO has been developed only with the UK patient population, it might not have captured certain different culture specific HRQoL issues important to such patients. Although, certain aspects of translatability and universality were taken into account during relevant stages of development, such issues should be considered while translating and cross-culturally adapting the HM-PRO into different languages/cultures.

REFERENCES

- Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* 85, 365–376. doi: 10.1093/jnci/85.5.365
- Allart-Vorelli, P., Porro, B., Baguet, F., Michel, A., and Cousson-Gelie, F. (2015). Haematological cancer and quality of life: a systematic literature review. *Blood Cancer J.* 5, e305. doi: 10.1038/bcj.2015.29

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NRES South West Bristol, UK (ref 14/SW/0033). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PG collected the data, developed the analysis policy, liaised with hospitals for patient recruitment, analyzed the data, interpreted results, and wrote the first draft of the manuscript. RE contributed to data collection as a patient research partner and reviewed the draft manuscript. SS generated the original idea, developed the study protocol, supervised the study, liaised with study centers as part of patient recruitment, developed the analysis policy, interpreted results, and reviewed the draft manuscript. EO and TI contributed to the design of the study, interpreted results, and reviewed the draft manuscript. JK, AF, DJ, MK, SA-I, MA-O, MA, GC, SM, CL, MA, and MO contributed to patient recruitment from their respective center and reviewed the draft manuscript. All authors contributed to the article and approved the submitted version.

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- Basch, E., Deal, A. M., Dueck, A. C., Scher, H. I., Kris, M. G., Hudis, C., et al. (2017). Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA* 318, 197–198. doi: 10.1001/jama.2017.7156
- Basra, M. K. A., and Shahrukh, M. (2009). Burden of skin diseases. *Expert Rev. Pharmacoecon. Outcomes Res.* 9, 271–283. doi: 10.1586/erp.09.23
- Cella, D., Jensen, S. E., Webster, K., Hongyan, D., Lai, J. S., Rosen, S., et al. (2012). Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) questionnaire. *Value Health* 15, 1051–1058. doi: 10.1016/j.jval.2012.08.2210

- DeVellis, R. F. (2016). *Scale Development: Theory and Applications* (California, USA: Sage Publishing).
- Dillman, D. A. (2006). *Mail and Internet Surveys: The Tailored Design Method - 2007 Update with New Internet, Visual, and Mixed-Mode Guide* (Hoboken (NJ): John Wiley & Sons).
- Efficace, F., Gaidano, G., and Lo-Coco, F. (2017). Patient-reported outcomes in hematology: is it time to focus more on them in clinical trials and hematology practice? *Blood* 130, 859–866. doi: 10.1182/blood-2017-03-737403
- Esser, P., Kuba, K., Mehnert, A., Johansen, C., Hinz, A., Lordick, F., et al. (2018). Quality of life in survivors of hematological malignancies stratified by cancer type, time since diagnosis and stem cell transplantation. *Eur. J. Haematol.* 101 (3), 340–348. doi: 10.1111/ejh.13104
- Fayers, P., and Machin, D. (2007). *Quality of Life: The assessment, analysis and interpretation of patient-reported outcomes* (Chichester: John Wiley & Sons).
- Fayers, P. M., and Machin, D. (2013). *Quality of Life: The Assessment, Analysis and Interpretation of Patient-reported Outcomes* (West Sussex: John Wiley & Sons).
- Goswami, P., Salek, S., Fielding, A. K., Kell, J., Al-Ismaïl, S., Oliva, E., et al. (2016). Development of a Novel Patient-Reported Outcome Measure in Hematological Malignancy for Use in Routine Clinical Practice: Item Generation. *Blood* 128, 5985. doi: 10.1182/blood.V128.22.5985.5985
- Goswami, P., Salek, S., Ionova, T., Oliva, E. N., Fielding, A. K., Karakantza, M., et al. (2017). HM-PRO: A Novel Patient-Reported Outcome Measure in Hematological Malignancy for Use in Clinical Practice. *Blood* 130, 2176. doi: 10.1182/blood.V130.Suppl_1.2176.2176
- Goswami, P., Oliva, E. N., Ionova, T., and Salek, S. (2018a). Responsiveness and the Minimal Clinically Important Difference for HM-PRO in Patients with Hematological Malignancies. *Blood* 132, 2294. doi: 10.1182/blood-2018-99-117094
- Goswami, P., Oliva, E. N., Ionova, T., and Salek, S. (2018b). Translating the Science of Patient Reported Outcomes into Practice: Meaningfulness of HM-PRO Scores in Patients with Hematological Malignancies. *Blood* 132, 4860. doi: 10.1182/blood-2018-99-117180
- Goswami, P., Khatib, Y., and Salek, S. (2019a). Haematological malignancy: Are we measuring what is important to patients? A systematic review of quality-of-life instruments. *Eur. J. Haematol.* 102, 279–311. doi: 10.1111/ejh.13203
- Goswami, P., Oliva, E. N., Ionova, T., Else, R., Kell, J., Fielding, A. K., et al. (2019b). Paper and electronic versions of HM-PRO, a novel patient-reported outcome measure for hematology: an equivalence study. *J. Comp. Eff. Res.* 8, 523–533. doi: 10.2217/ce-2018-0108
- Goswami, P., Oliva, E. N., Ionova, T., Else, R., Kell, J., Fielding, A. K., et al. (2020). Development of a Novel Hematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO): Content Validity. *Front. Pharmacol.* 11, 209. doi: 10.3389/fphar.2020.00209
- Hlubocky, F. J., Webster, K., Cashy, J., Beaumont, J., and Cella, D. (2013). The Development and Validation of a Measure of Health-Related Quality of Life for Non-Hodgkin's Lymphoma: The Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym). *Lymphoma* 2013, 9. doi: 10.1155/2013/147176
- Knobel, H., Loge, J. H., Brenne, E., Fayers, P., Hjermstad, M. J., and Kaasa, S. (2003). The validity of EORTC QLQ-C30 fatigue scale in advanced cancer patients and cancer survivors. *Palliat. Med.* 17, 664–672. doi: 10.1191/0269216303pm8410a
- Kosmidis, P. (1996). Quality of life as a new end point. *Chest* 109, 110s–112s. doi: 10.1378/chest.109.5_Supplement.110S
- Kvam, A. K., Wisloff, F., and Fayers, P. M. (2010). Minimal important differences and response shift in health-related quality of life: a longitudinal study in patients with multiple myeloma. *Health Qual. Life Outcomes* 8, 79. doi: 10.1186/1477-7525-8-79
- Kvam, A. K., Fayers, P. M., and Wisloff, F. (2011). Responsiveness and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. *Eur. J. Haematol.* 87, 330–337. doi: 10.1111/j.1600-0609.2011.01665.x
- McQuellon, R. P., Russell, G. B., Cella, D. F., Craven, B. L., Brady, M., Bonomi, A., et al. (1997). Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant.* 19, 357–368. doi: 10.1038/sj.bmt.1700672
- Messick, S. (1988). The once and future issues of validity: Assessing the meaning and consequences of measurement. In: Test validity. Eds. H. Wainer and H. I. Braun (Lawrence Erlbaum Associates, Inc), p. 33–48.
- Messick, S. (1994). Validity of Psychological Assessment: Validation of Inferences from Persons' Responses and Performances as Scientific Inquiry into Score Meaning. *Am. Psychol.* 50, 741–749. doi: 10.1037/0003-066X.50.9.741
- Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., et al. (2010). The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J. Clin. Epidemiol.* 63, 737–745. doi: 10.1016/j.jclinepi.2010.02.006
- Pope, P. T., and Webster, J. T. (1972). The Use of an F-Statistic in Stepwise Regression Procedures. *Technometrics* 14, 327–340. doi: 10.2307/1267425
- Roberts, P., and Priest, H. (2006). Reliability and validity in research. *Nurs. Stand.* 20, 41–45. doi: 10.7748/ns.20.36.41.s58
- Streiner, D., Norman, G., and Cairney, J. (2015). *Health Measurement Scales: A Practical Guide To Their Development and Use (5th ed.)*. Oxford University Press. doi: 10.1093/med/9780199685219.001.0001
- Wan, T. T. (2002). *Evidenced-Based Health Care Management. Multivariate Modeling Approaches* (Norwell, MA: Kluwer Academic Publishers).
- Yost, K. J., Thompson, C. A., Eton, D. T., Allmer, C., Ehlers, S. L., Habermann, T. M., et al. (2013). The Functional Assessment of Cancer Therapy - General (FACT-G) is valid for monitoring quality of life in patients with non-Hodgkin lymphoma. *Leuk. Lymphoma* 54, 290–297. doi: 10.3109/10428194.2012.711830
- Zamanzadeh, V., Ghahramanian, A., Rassouli, M., Abbaszadeh, A., Alavi-Majd, H., and Nikanfar, A. R. (2015). Design and Implementation Content Validity Study: Development of an instrument for measuring Patient-Centered Communication. *J. Caring Sci.* 4, 165–178. doi: 10.15171/jcs.2015.017

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Sixteen-Year Cohort of Liver Transplantation in the National Health System in Brazil: Analysis of Immunosuppression Maintenance Therapies

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Objective: To evaluate factors related to liver graft survival with a focus on immunosuppressive schemes based on calcineurin inhibitors (tacrolimus or cyclosporine).

Methodology: This study was carried out through an open cohort constructed by deterministic and probabilistic matching through three databases of the SUS with assessment of liver graft survival from 2000 to 2015 in Brazil. From this first cohort, a second cohort was constructed by pairing 1: 1 to more precisely assess the effect of the immunosuppressive scheme on graft survival. The Kaplan-Meier method and was used to estimate the probability of survival. Cox's model of proportional risks was used to assess factors related to graft loss.

Result: We found 12,687 patients in the Full cohort and 470 patients in the Matched cohort. The overall graft survival rates at 1, 5, 10, and 16 years were 72.6, 63.3, 52.8, and 45.3%, respectively. Patients younger had a longer graft survival than older ones. In the Full cohort, male patients had a higher survival rate than female ones. Therapeutic schemes based on tacrolimus were more prevalent and had a better survival rate when compared to schemes that used cyclosporine. Tacrolimus without association with antiproliferative agents or rapamycin inhibitors was the therapeutic scheme associated with greater survival rate in both cohorts (HR = 0.81, 95% CI = 0.72–0.91), (HR = 0.50, 95% CI = 0.30–0.85). In addition, white-skinned patients had longer survival rate in both cohorts (HR = 0.55, 95% CI = 0.50–0.61 and HR = 0.50, 95% CI = 0.34–0.75). On the other hand, patients who a greater time ratio without using an immunosuppressant had lower graft survival rate (HR = 6.46, 95% CI = 5.05–8.27 and HR = 6.57, 95% CI = 2.66–16.22).

Conclusion: This 16-year cohort showed that the older age and the greater time ratio without using an immunosuppressant are risk factors for liver graft loss. White-skinned patients and tacrolimus-based regimens, especially tacrolimus without other immunosuppressants, are factors of better prognosis to the graft.

Keywords: graft survival, cyclosporine, tacrolimus, National Health Service, survival analysis, calcineurin inhibitor, immunosuppression, liver transplantation

INTRODUCTION

Currently, liver transplantation (LT) is well established in Brazil and worldwide. Since the first LT in 1963 in the United States, as well as the first operation in 1968 in Brazil, patients' survival rate has progressively improved. This was possible due to advances in surgical methods, preservation solutions, early diagnosis, peritransplant intensive care, and immunosuppressive regimens (Starzl et al., 1968; Song et al., 2014; Burra et al., 2016).

The progress of immunosuppressive treatment was an important step towards success in LT. After the 1980s, calcineurin inhibitors (CIs) became the standard for immunosuppressives in LT. During this decade, cyclosporine was introduced as an immunosuppressive and there was a large increase in LT survival rates. In the following decade, tacrolimus, another CI, was used with patients who experienced rejection while taking cyclosporine. From that time on, tacrolimus became the standard drug for immunosuppression in LT (Korayem et al., 2017).

Brazil has one of the largest LT programs in the world, with public and free access, both for hospital treatment (surgery and hospital care) and outpatient immunosuppression with no need for co-payment (Guerra Junior et al., 2010; Meirelles Júnior et al., 2015). In 2016, Brazil was the third country in the world in the number of LTs performed, behind only the United States and China, which ranked first and second, respectively. However, in that same year, Brazil was the 21st in the number of liver transplants per million people in a ranking of 44 countries (Associação Brasileira de Transplante, 2018; Manyalich et al., 2018; Ming et al., 2019).

In the current transplant era the factors that impact survival rates depend on donor, recipient, perioperative and post-operative parameters. Recipient age is a very important aspect of survival rate. Pediatric recipients have a better survival rate than the adult population and adults above 55 years have poor outcomes than youngsters (Agopian et al., 2013). Previous study in Brazil shows the same results, recipient older than 65 have a shorter survival rate than youngsters (Brandão et al., 2009). Gender influence in the outcome of LT is still controversial. Some works show females with a better survival rate and others show no sex effect in survival rate (Watt et al., 2010; Sarkar et al., 2015). Recipients white race seems to be a protective factor in LT (Roberts et al., 2004; Tae et al., 2007). Many other characteristics influence directly survival rate in LT like previous liver diagnosis—cancer has a poor survival rate—graft type, donor age, and number of transplants (Adam et al., 2018).

There is strong evidence that the use of tacrolimus improves the transplanted patient's survival rate from one to three years

when compared to cyclosporine (Haddad et al., 2006). When these immunosuppressants are compared over longer periods, evidence shows no difference in patients' survival. However, it is known that cyclosporine presents a higher rate of graft loss than tacrolimus (Rodríguez-Perálvarez et al., 2017).

Our study's goal was to analyze the data from the 12,687 LTs found in the cohort and identifying the factors, which influenced the long-term graft survival, as well as to compare the survival rate of the liver graft on the therapeutic regimens with tacrolimus and cyclosporine during an observation of up to sixteen years.

METHODS

Study Design and Population

We conducted a historical open cohort study, including SUS patients undergoing LT in Brazil from January 2000 to December 2014 with sequence until December 2015. This cohort was obtained using deterministic and probabilistic pairing of three different SUS administrative databases: mortality information system (SIM), hospital information system (SIH/SUS), and high complexity procedure system (SIA/SUS). The date of the LT recorded in SIH was the first of the cohort. This same model was used in other studies published by our group in Brazil (Cherchiglia et al., 2007; Guerra et al., 2010; Gomes et al., 2016; Junior et al., 2018).

Initially, a cohort including all 12,687 liver transplanted patients found by the method was constructed in this period and this cohort was called Full cohort. Afterward, from the Full cohort, a new 1:1 Matched cohort was constructed using CI, sex of the recipient, age in years at the time of transplantation and the period of transplantation, named as Matched cohort. When more than one patient met the matching criteria, the allocation of pairs was done randomly. In the Matched cohort, the inclusion criterion was the age of the recipient over 18 years. Patients under 18 submitted to LT have peculiar characteristics that may interfere in the data analysis. The exclusion criteria were the absence of CI in the immunosuppressive scheme and the absence of registration of immunosuppressive treatment (Moreno and Berenguer, 2006; Watt et al., 2010; Daniel et al., 2017). We built the Matched cohort to reduce misleading factors and filter the role of immunosuppressants in graft survival.

The event used for survival analysis was the loss of the graft, defined as death or liver retransplantation. The right censoring was established on December 31, 2015. In Brazil, mortality reporting is mandatory, and continuous immunosuppressive treatment is given to SUS patients monthly.

The graphical representation of the cohort selection flowchart can be seen in **Figure 1**. The patient's therapeutic regimen was defined as the first time the patient was treated with the same regimen lasting at least 90 days. All therapeutic regimens were listed in the Full cohort. In the Matched cohort, the therapeutic regimens were stratified by the use of cyclosporine or tacrolimus associated or not with azathioprine or mycophenolate. The other associations to the CI used by the patients in the Matched cohort were included in the infrequent schemes category. It was considered that all patients of both cohorts used corticosteroids concomitantly, because it was not possible to track the

dispensation of this drug by our database, since it is not a high-cost drug.

Baseline Variables

The descriptive analysis of all variables used in the study was performed, with frequency distribution for categorical variables and a central tendency for continuous variables. The variables included therapeutic regimens; the geographical region of the hospital where the transplantation was performed; year of transplantation; the periods of transplantations, categorized in 2000 to 2003, 2004 to 2007, 2008 to 2011, and 2012 to 2014; the

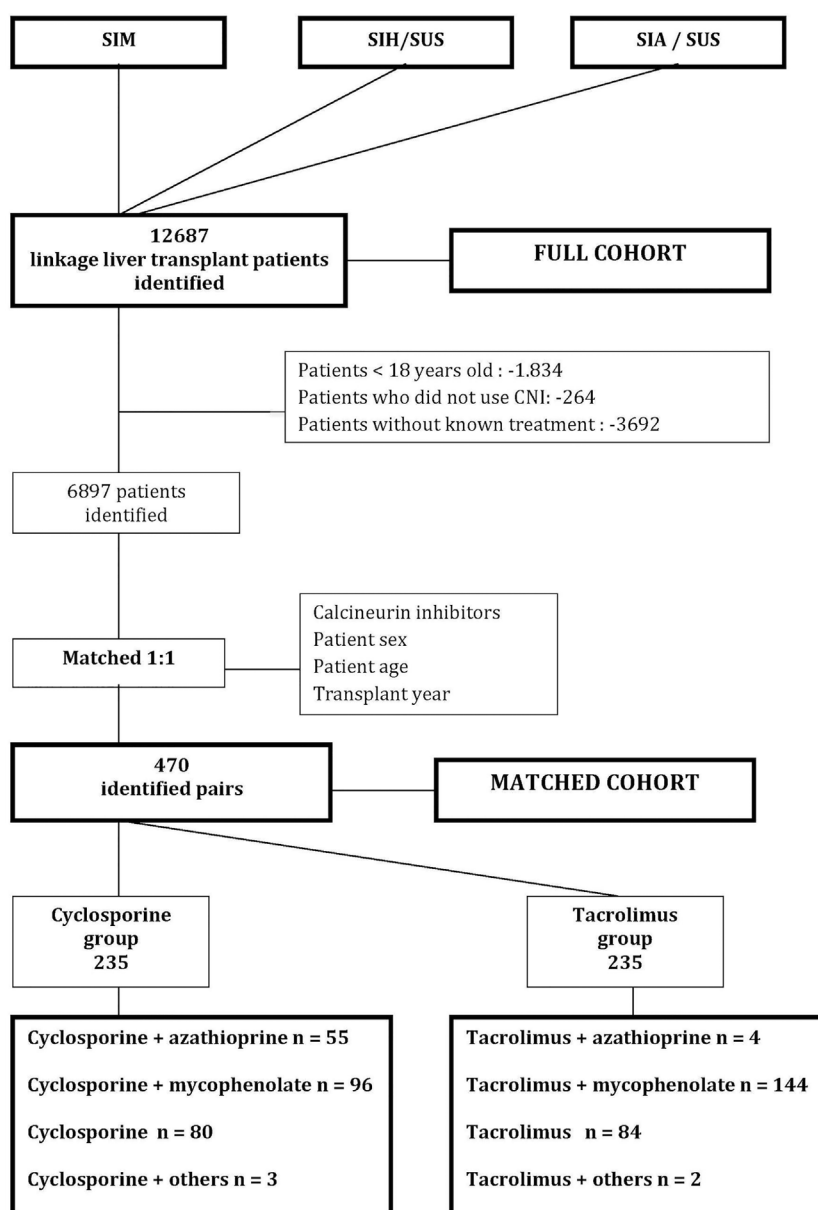


FIGURE 1 | Cohort selection flowchart. CI, calcineurin inhibitor; SUS, Brazilian Unified Health System; SIM, Mortality Information System; SIH/SUS, Hospital Information System, SIA/SUS Outpatient Information System; Others: sirolimus or everolimus.

sex of the recipient; the age of the recipient at the time of transplantation; the age group of the recipient characterized by children and teenagers (under 18), adults (over 18 and under 65) and elders (over 65 years); the type of transplant (living or deceased donor); skin color, this variable was included in the database only in 2008; liver disease causes; the duration of liver diseases prior to the transplantation (greater or lesser than the median); the time ratio use of immunosuppressant; and the time ratio lacking immunosuppressants. The penultimate criterion was calculated dividing the number of months in which the medication was dispensed by the time of the patient in the cohort. The last criterion was calculated dividing the number of months without dispensing the medication by the time of the patient in the cohort.

Statistical Analysis

The cumulative probability of graft survival over the 16-year cohort was evaluated by the Kaplan-Meier method and the survival curves according to immunosuppressants were compared by the log-rank test. Several factors that could affect the survival of the graft were initially evaluated by univariate analysis. The level of significance was set at 5%. The variables with a p-value less than 0.20 in the univariate analysis and those clinically relevant were included in the multivariate model. The relative risk of progression to the event adjusted for the multivariate model was calculated by the Cox proportional risk model and presented considering a 95% confidence interval (95% CI). The suitability of the multivariate model was measured by residue analysis. The statistical analysis was performed with the RStudio software, version 1.1.463, R Foundation for Statistical Computing.

Ethics Statement

The research was approved by the Ethics Research Committee of Federal University of Minas Gerais (report no. 16334413.9.0000.5149). All subjects were anonymized; thus, the provision of informed consent was not required.

RESULTS

Characteristics of the Patient

We identified 12,687 patients submitted to LT in the Full cohort and 470 patients in the Matched cohort, with an average follow-up of 34.5 and 61.1 months, respectively. The Full cohort included 859 elders (over 65 years), 9994 adults, and 1834 transplanted under 18 years of age, being the majority of patients male, with a male-female ratio of 1.89:1.

Most of the grafts came from deceased donors and the transplantations occurred predominantly in southeastern Brazil in both cohorts. White skin patients were majority among those who informed their skin color in both cohorts. Among the diagnosis of liver disease prior to the transplant, viral hepatitis corresponded to about 25% of them. All data with the characteristics of the patients are summarized in **Table 1**.

Graft Survival in Full Cohort

During the entire follow-up, 4,308 graft losses occurred (3,533 deaths and 775 retransplants) in the Full cohort. The estimated graft survival by the Kaplan-Meier method is shown in **Figure 2**. The general graft survival rates in 1, 5, 10, and 16 years were 72.6, 63.3, 52.8, and 45.3%, respectively.

The survival rate of the graft was significantly higher in men when compared to women. The elders had a significantly worse graft survival rate compared to adults who, on the other hand, presented significantly worse results when compared to patients under 18 years old. The transplantation period from 2012 to 2014 had a significantly higher graft survival than the other ones. The length of time of liver disease prior to LT showed no difference in graft survival. The survival curves of the liver graft categorized by the characteristics of the patient can be seen in **Figure 3**.

Graft's Survival Rate in Matched Cohort

One hundred graft losses (85 deaths and 15 retransplants) occurred in the Matched cohort during the 16 years of observation. The survival rates of the graft at 1, 5, 10, and 16 years were 95.3, 82.5, 66, and 55.1%, respectively. The estimated graft survival rate by the Kaplan-Meier method is shown in **Figure 4**.

Similarly to the Full cohort, the elderly also had significantly shorter graft survival when compared to the younger patients. Male patients had a higher survival than females ones, however, not statistically significant ($p = 0.08$). The transplantation region, the transplantation period, liver disease prior to LT, and the type of transplantation did not demonstrate statistically significant differences. The graft survival curves of the Matched cohort can be seen in **Figure 5**.

Immunosuppressants

The graft survival curve by Kaplan-Meier comparing the therapeutic schemes in the Full cohort can be seen in **Figure 6**. **Figure 6A** shows the curves with the therapeutic regimens based on cyclosporine and tacrolimus with a higher survival in the tacrolimus group with $p < 0.001$. **Figure 6B** shows the composition of the most frequent therapeutic regimens and evidences that the regimens that contained tacrolimus in their composition had a higher graft survival.

We found 28 different immunosuppression schemes in the Full cohort and the most frequent was tacrolimus associated with mycophenolate, followed by tacrolimus. The tacrolimus regimens were more frequent than the cyclosporine ones. All the schemes and their frequencies in both cohorts are described in **Table 2**.

It was not identified the immunosuppressive treatment of 4,393 patients in the Full cohort. Out of these patients, 2,073 had graft loss before completing 30 days and 2,481 before completing the third month after transplantation. The majority of the patients who did not survive in this period of time were in this group, since there was a total of 2,669 graft losses by the third month after transplantation in the Full cohort.

TABLE 1 | Patient characteristics.

Parameters	Full cohort	Matched cohort	Cyclosporine	Tacrolimus
	n	n	n	n
	12,687	470	235	235
Sex				
Female	34,63%	22.12%	11.06%	11.06%
Male	65,37%	77.88%	38.94%	38.94%
Age group				
<18	14,46%	NA	NA	NA
18–65	78,77%	92.76%	46.38%	46.38%
>65	6,77%	7.24%	3.62%	3.62%
Skin color*				
Yellow	2,35%	2.55%	0.64%	1.91%
White	38,95%	57.44%	27.87%	29.57%
Brown	9,50%	5.32%	1.70%	3.62%
Black	1,70%	1.28%	0.85%	0.43%
Indigenous	0,01%	0,00%	0,00%	0,00%
Without register	47,49%	33.41%	18.94%	14.47%
Regions of liver transplant				
Southeast	56,99%	52.77%	23.83%	28.94%
South	23,53%	35.53%	25.53%	10.00%
Northeast	18,42%	11.49%	0.43%	11.06%
North	0,06%	0.00%	0.00%	0.00%
Midwest	1,01%	0.21%	0.21%	0.00%
Eras of transplantation				
2000–2003	13,83%	20.42%	10.21%	10.21%
2004–2007	19,41%	27.66%	13.83%	13.83%
2008–2011	34,31%	29.36%	14.68%	14.68%
2012–2014	32,45%	22.56%	11.28%	11.28%
Liver Disease Before LT				
≤Median	27,56%	28.94%	17.66%	11.28%
>Median	26,82%	33.62%	17.02%	16.60%
Without register	45,61%	37.45%	15.32%	22.13%
Diagnosis prior to liver transplantantion				
Alcoholic cirrhosis	9,89%	11.70%	5.53%	6.17%
Toxic liver disease	0,50%	0.42%	0.21%	0.21%
Cancer	0,28%	0.21%	0.21%	0.00%
Viral hepatitis	24,27%	27,66%	14.68%	12.98%
Others or indeterminant	65,07%	60.00%	29.36%	30.64%
Type of transplant				
Deceased donor	90,07%	97,88%	48,94%	48,94%
Living donor	9,93%	2.12%	1.06%	1.06%
Events				
Censoring	66.04%	78.72%	38.51%	40.21%
Death	27,85%	18,09%	10.00%	8.09%
Retransplant	6.11%	3.19%	1.49%	1.70%

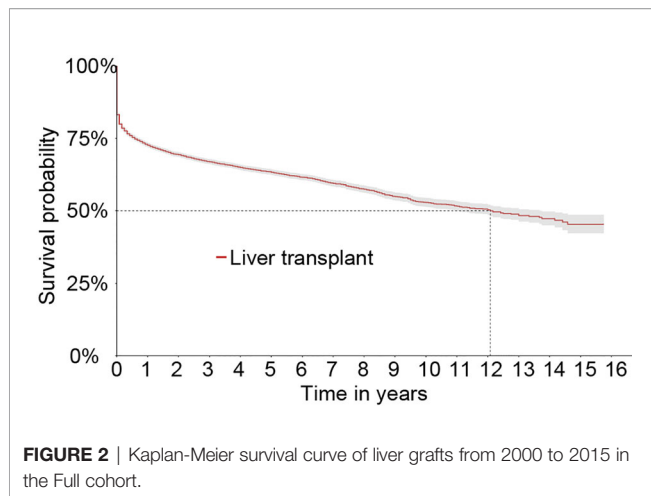
*Skin color was included in database only after 2008.

In the Matched cohort the graft survival curve by Kaplan-Meier comparing the therapeutic schemes can be seen in **Figure 7**. **Figure 7A** shows the survival curve combining the therapeutic regimens that used cyclosporine or tacrolimus. **Figure 7B** shows the survival curve of the most frequent therapeutic regimens. In both curves no statistically significant difference was observed.

Univariate Analysis

Univariate analysis indicated lower risk of graft loss in male patients in the full (HR = 0.9, 95% CI = 0.84–0.97) and matched (HR = 0.68, 95% CI = 0.44–1.05) cohorts, however, not statistically significant in the latter ($p = 0.08$). Patients under 18 (HR = 0.85, 95% CI = 0.78–0.93) had longer survival rate than

adults and elders. On the other hand, the elders had a lower survival rate than the others in the Full cohort (HR = 1.32, 95% CI = 1.18–1.48) and in the Matched cohort (HR = 2.02, 95% CI = 1.05–3.89). White skin patients had higher graft survival in the Full (HR = 0.41, 95% CI = 0.38–0.44) and matched (HR = 0.50, 95% CI = 0.34–0.75) cohorts. Patients who did not declare skin color had a lower survival compared to the others in the Full cohort (HR = 3.06, 95% CI = 2.87–3.26) and in the Matched cohort (HR = 2.01, 95% CI = 1.36–2.97). A higher proportion of tacrolimus use was a factor of higher survival in the full (HR = 0.49, 95% CI = 0.42–0.56) and matched (HR = 0.59, 95% CI = 0.35–0.98) cohorts. On the other hand, the higher the time ratio lacking the use of immunosuppressants, the lower the graft



survival rate in both the full (HR = 4.04, 95% CI = 3.3–4.94) and matched (HR = 5.56, 95% CI = 2.35–13.39) cohorts. All factors of risk are described in **Table 3**.

Multivariate Analysis

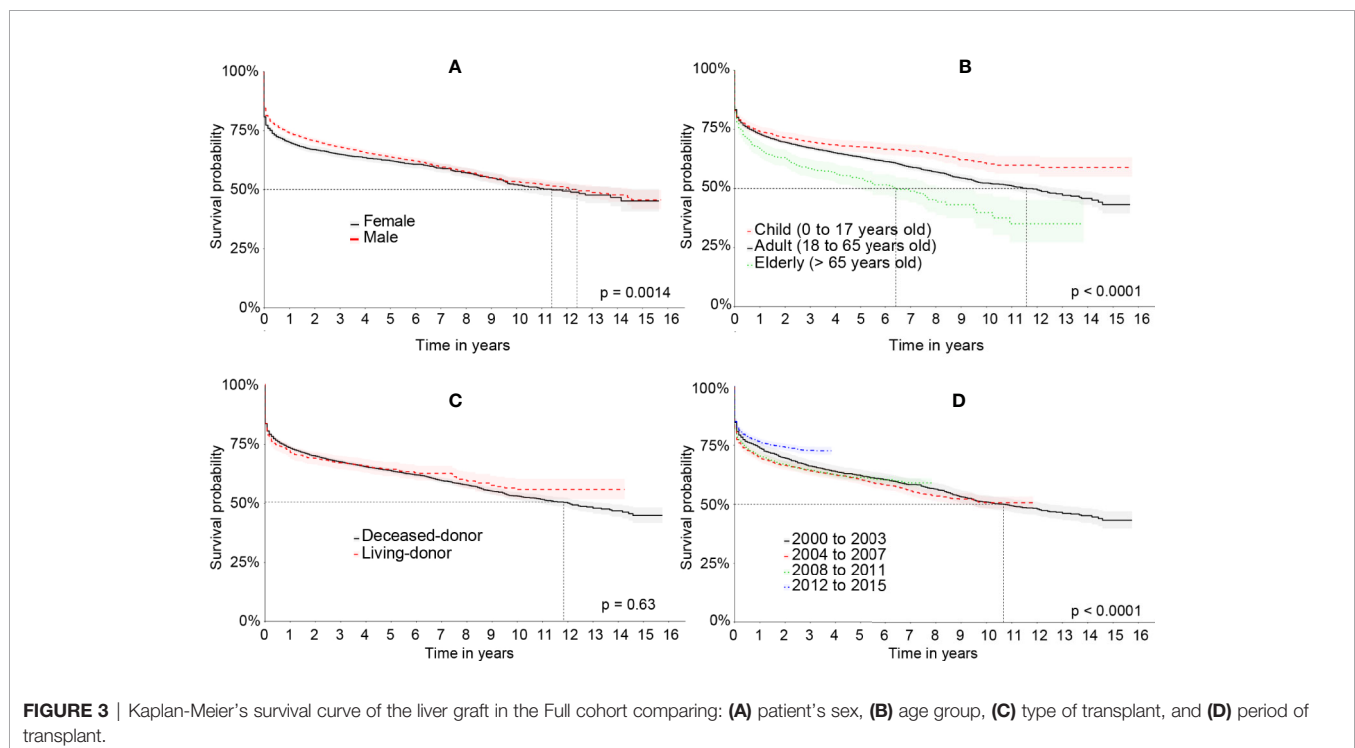
Multivariate analysis revealed that the following variables in the Full cohort were associated with a higher risk of graft loss: time ratio of azathioprine use (HR = 2.55; 95% CI = 1.72–3.80); time ratio of mycophenolate use (HR = 1.70; 95% CI = 1.41–2.04), time ratio lacking the use of immunosuppressants (HR = 6.46, 95% CI = 5.05–8.27) and age in years at the time of LT (HR = 1.01, 95% CI = 1.01–1.02). On the other hand, white skin patients (HR = 0.55, 95% CI = 0.50–0.61); yellow skin patients (HR = 0.33, 95% CI = 0.21–0.50); those who used tacrolimus (HR =

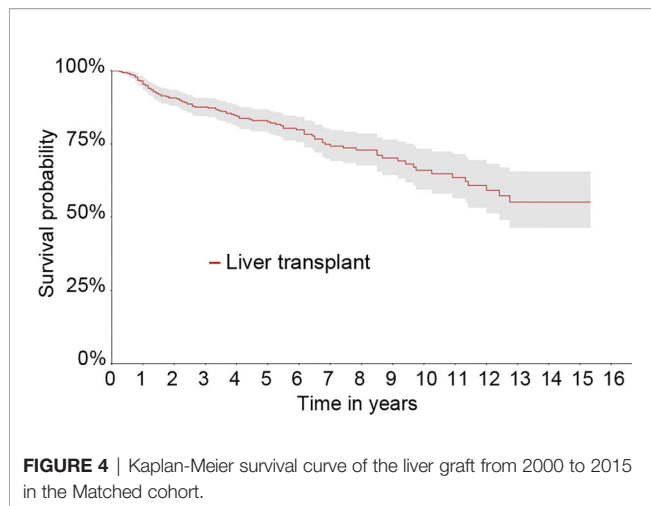
0.81, 95% CI = 0.72–0.91) and those who performed the transplantation between 2012 and 2014 (HR = 0.74, 95% CI = 0.64–0.85) had a lower risk of graft loss. Multivariate analysis in the Matched cohort showed these as graft protection factors: white skin (HR = 0.50, 95% CI = 0.34–0.75) and tacrolimus scheme (HR = 0.50, 95% CI = 0.30–0.85). On the other hand, graft loss in the Matched cohort was related to the time ratio lacking immunosuppressant use (HR = 6.57, 95% CI = 2.66–16.22). All factors of risk are described in **Table 4**.

DISCUSSION

Brazil is one of the world's largest LT performing countries and has one of the largest free public assistance programs in LT. This study is the largest cohort in Latin America which evaluated liver graft survival rate due to the immunosuppressive scheme, among other factors.

The Brazilian Unified Health System (SUS) is responsible for about 95% of LTs performed in the country. The guidelines of the Ministry of Health for Immunosuppression of Maintenance in Liver Transplantation in Adults or Children standardized behaviors for the LT treatment. These guidelines were created to ensure the best possible treatment in the Brazilian context, with the resources available in SUS. As in the rest of the world, the Brazilian guidelines chose CI as the main maintenance immunosuppressant after LT. Tacrolimus is usually the first option. CI can be used in monotherapy or with an antiproliferative agent (azathioprine or mycophenolate) or with everolimus, a rapamycin receptor inhibitor. These drugs can also be combined in maintenance treatment, depending on the patient's characteristics. Generally, all immunosuppression





schemes start in conjunction with the corticosteroid. Another inhibitor of rapamycin receptor, sirolimus, previously used in LT was excluded in the last Brazilian guideline. The induction of immunosuppression is done with methylprednisolone and/or thymoglobulin and/or basiliximab (Ministério da Saúde, 2016).

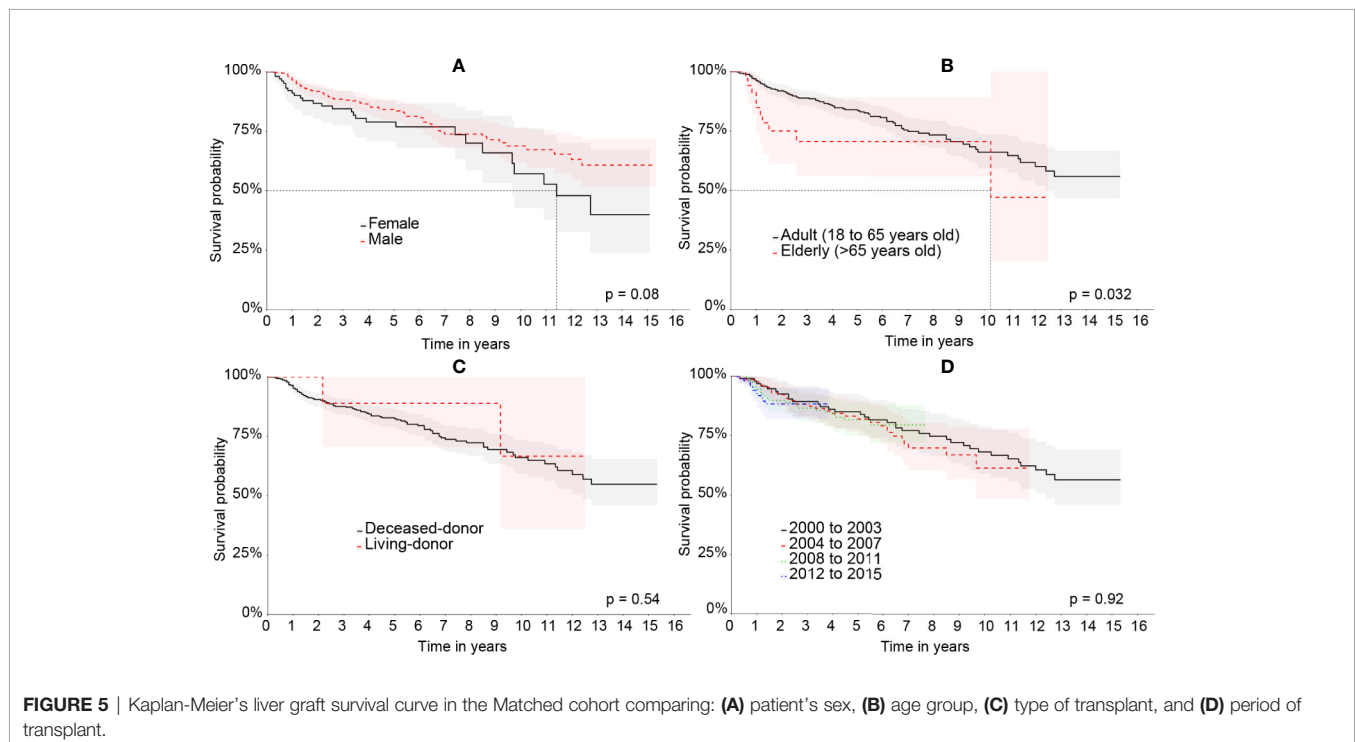
This cohort, despite not including all patients who underwent LT in Brazil in the period analyzed, presents a great representativity of the group. Patients who underwent LT outside SUS were not part of this cohort and there were also patient losses through the cohort construction method.

The graft survival in the Full cohort was different from the one shown in the Brazilian Registry of Transplants from the Brazilian Organ Transplantation Society (ABTO). The Brazilian

Transplant Registry only included data from transplant teams that voluntarily reported 100% of their results in its analysis, but in 2018, only 55% of the teams met this requirement (Associação Brasileira de Transplante, 2018). Thus, bad performances of some teams may have been omitted. In our study, differently, the mortality was evaluated through SIM, where the mandatory mortality records are and the performance of a retransplant was surely seen by SIH. Even though, in the first year, the graft survival rate was similar both in ABTO (74%) and our study (72.6%), they differed in following years. In the fifth year after transplantation the graft survival rate was 67% according to ABTO and 63.3% in the Full cohort. In the ninth year, the maximum ABTO evaluation of survival rate was 63% compared to the 54.9% in the Full cohort. Information on liver graft survival in Brazil, up to then, was scarce and fragmented (Brandão et al., 2009). This study showed a long and reliable observation of liver graft survival.

The best results in the Matched cohort occurred by including only those patients who used CI for at least 3 months. Therefore, the patients with early mortality or retransplantation were excluded from the Matched cohort. Of the 12,687 patients in the Full cohort, 2,134 did not complete one month of graft survival and 2,669 had a graft loss before reaching the third month after transplantation, which corresponds to 21.3% of the patients in the cohort. This portrays a high mortality rate on the first 90 days following surgery.

This study results fall short when compared to those published from American and European cohorts, especially in the first 5 years. Since the 2000s, the adult liver graft survival rate when coming from a deceased donor in Europe in 1, 5, and 10 years was 80, 67, and 54%, respectively, and in the United States was 85, 75, and 55%, respectively (Adam et al., 2012; Berg, 2016).



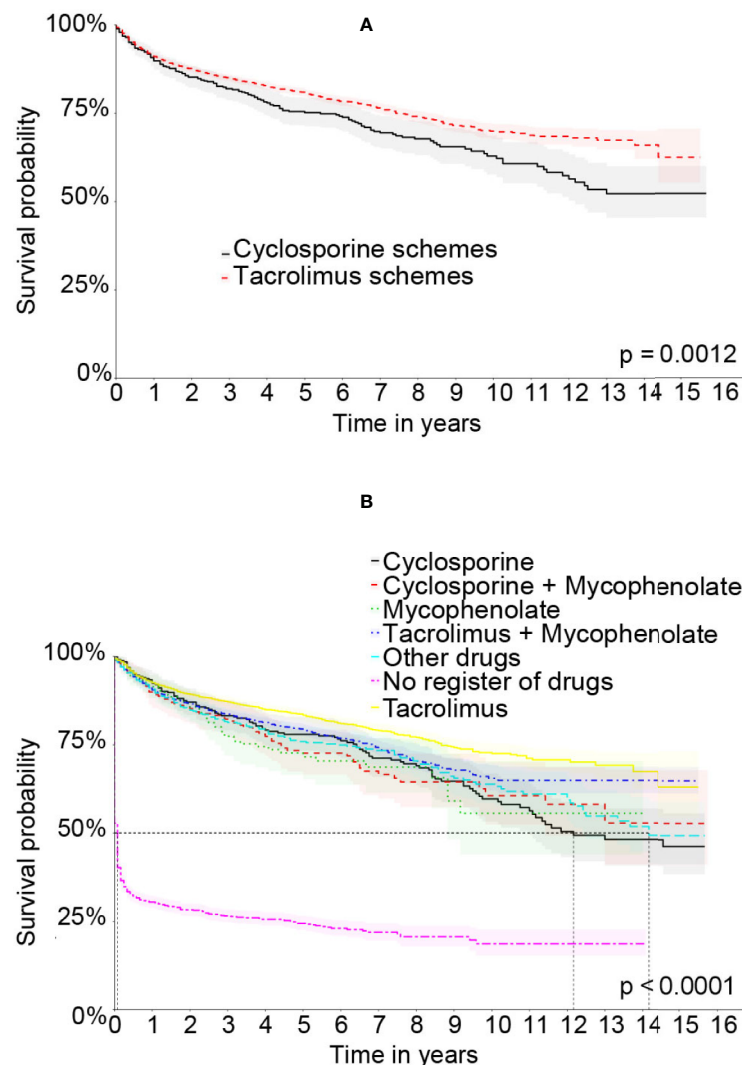


FIGURE 6 | Kaplan-Meier's liver graft survival curve in the Full cohort comparing therapeutic schemes: **(A)** Treatment based on tacrolimus or cyclosporine. **(B)** The specific therapeutic schemes.

The great difference of hepatic graft's survival rate in the Full cohort compared to the rate of Americans and Europeans occurred especially due to the low survival rate in the first year and particularly in the first months after transplantation. It was not possible to evaluate the severity criteria of the patients, since we did not have this information in the database. However, this finding suggests the need to carefully examine the surgical procedure and post-transplant intensive care in order to discover the cause of the high rate of graft loss during this period.

Tacrolimus-based treatment regimens represented almost 85% of the treatments in the Full cohort and another 12% of the regimens were based on cyclosporine, the rest being the regimens that did not use CI. The frequency of tacrolimus usage is close to the one found in literature (Burra et al., 2016).

Analyzing Kaplan-Meier's curves, it is possible to observe a higher graft survival rate on patients under tacrolimus-based

therapeutic regimens when compared to those based on cyclosporine in the Full cohort. This finding is similar to that one of another cohort (Jonas et al., 2005) and the finding of Rodríguez's meta-analysis (Rodríguez-Perálvarez et al., 2017). In multivariate analysis in the Full cohort, a higher proportion of azathioprine or mycophenolate use was related to a worse prognosis for the graft.

The Matched cohort was constructed to reduce bias in the interpretation of liver graft survival analysis specifically related to the immunosuppressive therapeutic scheme based on CI. Although the Kaplan-Meier curve showed no statistically significant difference in this cohort, possibly due sample number, the multivariate analysis in both cohorts showed that the tacrolimus therapeutic scheme was the only one related to the best graft survival rate. It is worth reinforcing that it was not possible to analyze the concomitant use of corticoids for any of

TABLE 2 | Full and Matched cohort immunosuppression therapy schemes.

Immunosuppressant schemes	n	%	% cumulative
Full cohort			
Tacrolimus + mycophenolate	4060	48.95%	48.95%
Tacrolimus	2834	34.17%	83.12%
Cyclosporine	320	3.86%	86.98%
Mycophenolate	304	3.67%	90.64%
Cyclosporine + mycophenolate	269	3.24%	93.89%
Cyclosporine + azathioprine	231	2.79%	96.67%
Tacrolimus + azathioprine	131	1.58%	98.25%
Infrequent schemes	145	1.75%	100%
Subtotal	8,294	100.00%	
Without register	4,393	34.63%	
Total - Full cohort	12,687	100%	
Matched cohort			
Tacrolimus + mycophenolate	145	30.85%	30.85%
Cyclosporine + mycophenolate	96	20.43%	51.28%
Tacrolimus	84	17.87%	69.15%
Cyclosporine	81	17.23%	86.38%
Cyclosporine + azathioprine	55	11.70%	98.09%
Infrequent schemes	9	1.91%	100%
Total - Matched cohort	470	100%	

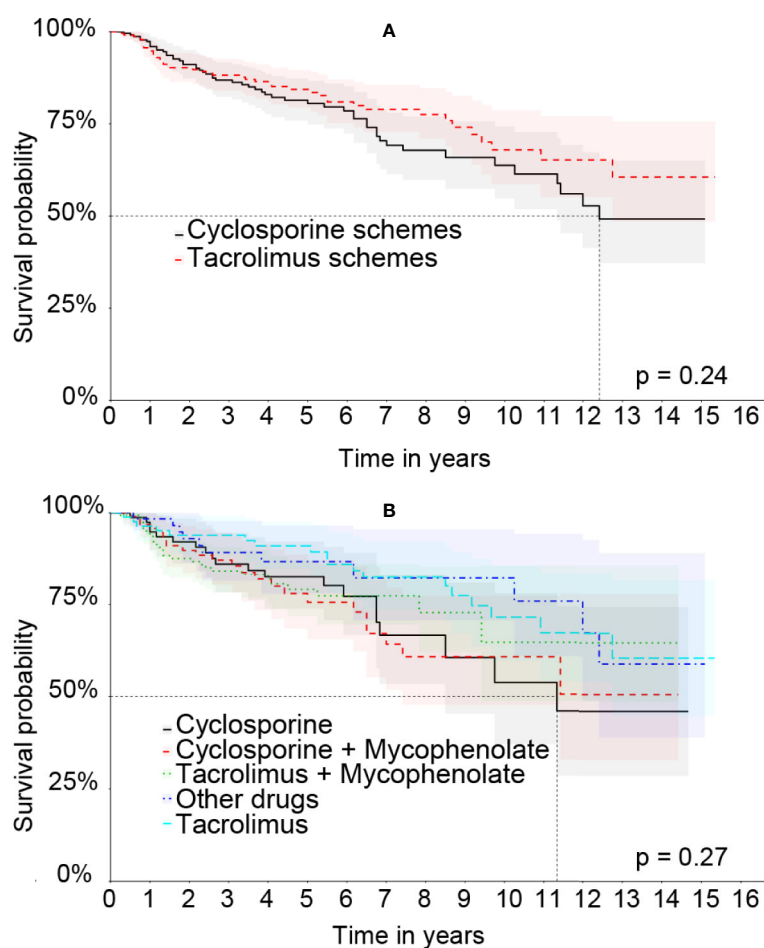
**FIGURE 7** | Kaplan-Meier's liver graft survival curve in the Matched cohort comparing therapeutic regimens: **(A)** Treatment based on cyclosporine or tacrolimus. **(B)** The specific therapeutic schemes.

TABLE 3 | Univariate analysis—Risk factors associated with graft loss.

Risk factor	Full cohort		Matched cohort	
	HR (IC 95%)	p	HR (IC 95%)	p
Male sex	0.90 (0.84–0.97)	<0.01	0.68 (0.44–1.05)	0.08
Age in years	1.005 (1.003–1.006)	<0.01	1.02 (1.0–1.04)	0.1
Age group				
<18	0.85 (0.78–0.93)	<0.01	NA	
18–65	1.01 (0.93–1.08)	0.9	0.49 (0.26–0.95)	0.03
>65	1.32 (1.18–1.48)	<0.01	2.02 (1.05–3.89)	0.03
Skin Color				
Black	0.72 (0.56–0.94)	0.01	2.14 (0.68–6.75)	0.2
Brown	0.53 (0.47–0.60)	<0.01	0.82 (0.30–2.24)	0.7
Yellow	0.25 (0.17–0.37)	<0.01	0.81 (0.20–3.22)	0.8
White	0.41 (0.38–0.44)	<0.01	0.50 (0.34–0.75)	<0.01
Without register	3.06 (2.87–3.26)	<0.01	2.01 (1.36–2.97)	<0.01
Regions of liver transplant				
Southeast	1.03 (1.0–1.06)	1	0.96 (0.65–1.43)	0.8
South	1.19 (1.11–1.27)	<0.01	0.95 (0.63–1.45)	0.8
Northeast	0.83 (0.76–0.91)	<0.01	1.25 (0.68–2.3)	0.4
North	0.58 (0.30–1.13)	0.2	NA	NA
Midwest	0.31 (0.19–0.53)	<0.01	(0–∞)	0.7
Immunosuppression scheme (basal)				
Tacrolimus + mycophenolate	0.34 (0.31–0.36)	<0.01	1.13 (0.73–1.76)	0.6
Tacrolimus	0.31 (0.28–0.34)	<0.01	0.67 (0.39–1.1)	0.1
Cyclosporine	0.66 (0.55–0.80)	<0.01	1.24 (0.76–2.02)	0.4
Mycophenolate	0.53 (0.42–0.68)	<0.01	NA	NA
Cyclosporine + mycophenolate	0.59 (0.47–0.75)	<0.01	1.36 (0.85–2.16)	0.2
Cyclosporine + azathioprine	0.57 (0.45–0.73)	<0.01	0.82 (0.44–1.54)	0.5
Infrequent schemes	0.59 (0.50–0.69)	<0.01	0.71 (0.38–1.34)	0.2
Without register	10.6 (9.91–11.35)	<0.01	NA	NA
Time ratio use of immunosuppressor				
Cyclosporine	1.14 (0.94–1.38)	0.2	1.03 (0.64–1.66)	0.9
Azathioprine	1.6 (1.12–2.28)	<0.01	0.96 (0.32–2.82)	0.9
Mycophenolate	1.05 (0.92–1.2)	0.4	1.08 (0.64–1.84)	0.8
Tacrolimus	0.49 (0.42–0.56)	<0.01	0.59 (0.35–0.98)	0.04
Everolimus	0.27 (0.05–1.45)	0.1	(0–∞)	0.7
Sirolimus	1.79 (1.08–2.96)	0.02	4.24 (0.63–28.9)	0.1
Time ratio lacking immunosuppressant	4.04 (3.3–4.94)	<0.01	5.6 (2.35–13.39)	<0.01
Type of transplant				
Living donor	0.98 (0.88–1.08)	0.7	0.65 (0.16–2.62)	0.5
Diagnosis prior to liver transplantantion				
Alcoholic cirrhosis	0.91 (0.82–1.01)	0.07	1.05 (0.55–1.95)	0.9
Toxic liver disease	1.05 (0.68–1.61)	0.8	(0–∞)	0.6
Cancer	1.17 (0.68–2.02)	0.6	(0–∞)	0.8
Viral hepatitis	1.11 (0.69–1.76)	0.7	1.01 (0.70–1.76)	0.7
Others or indeterminate	1.01 (0.95–1.08)	0.7	0.92 (0.60–1.40)	0.7
Transplant era				
2000–2003	1.04 (0.96–1.13)	0.4	0.88 (0.55–1.40)	0.6
2004–2007	1.13 (1.05–1.21)	<0.01	1.09 (0.71–1.68)	0.7
2008–2011	1.11 (1.04–1.18)	<0.01	0.97 (0.60–1.57)	0.9
2012–2014	0.76 (0.71–0.82)	<0.01	1.15 (0.59–2.24)	0.7
Year of hospitalization (t0)	0.98 (0.97–0.99)	<0.01	1.02 (0.96–1.08)	0.5
Liver disease before LT				
>Median	1.06 (0.98–1.15)	0.1	0.94 (0.57–1.55)	0.8

∞ - Infinity symbol.

the groups, nor the serum level of the CI, nor the severity of the patients in each therapeutic scheme. On the other hand, as expected, the time ratio lacking immunosuppressant was the most significant risk factor for graft loss in both cohorts. The lack of use of immunosuppressant, measured, in this case, by the absence of outpatient delivery of the drug, reflects the non-adherence to treatment or prolonged hospitalization of the patient in the period.

These findings resulted from the survival rate curve and multivariate analysis suggest that immunosuppression in LT with tacrolimus without antiproliferative agents is the most effective therapeutic scheme. A previous study indicated that tacrolimus in monotherapy or associated with corticosteroids is as effective as tacrolimus associated with antiproliferative agents (Lan et al., 2014). However, another interpretation would be that less severe patient cases did not need an association of

TABLE 4 | Multivariate analysis—Risk factors associated with graft loss.

Risk factor	HR (IC 95%)	p
Full cohort		
Transplant period from 2012 to 2014	0.74 (0.64–0.85)	<0.01
Time ratio lacking immunosuppressor	6.46 (5.05–8.27)	<0.01
Age (years)	1.01 (1.01–1.02)	<0.01
Ratio azathioprine use over time	2.55 (1.72–3.80)	<0.01
Ratio mycophenolate use over time	1.70 (1.41–2.04)	<0.01
Tacrolimus	0.81 (0.72–0.91)	<0.01
Yellow skin	0.33 (0.21–0.50)	<0.01
White skin	0.55 (0.50–0.61)	<0.01
Matched cohort		
Time ratio lacking immunosuppressor	6.57 (2.66–16.22)	<0.01
Tacrolimus	0.50 (0.30–0.85)	0.01
White skin	0.50 (0.34–0.75)	<0.01

immunosuppressants. Therefore, a better outcome could be justified.

A limiting factor in the interpretation of the graft survival's data and its association with immunosuppressants was the absence of records of immunosuppressive therapy among 4,393 patients in the Full cohort. The main causes of non-registration were the death of the patient before the outpatient delivery of the drug, failure in registration, failure in deterministic pairing and dispensation of the drug by private health plan or private consultations. We faced this limitation and reduce potential bias by paired therapeutic schemes in the Matched cohort.

Data from the current study reaffirm that age is an independent risk factor for liver graft survival which shows better survival rates for younger patients and worse rates especially for those over 65 years old (Jain et al., 2000). Unlike other studies, this one showed that male patients had a better graft survival rate when compared to female patients in the Full cohort by the Kaplan-Meier method (Brandão et al., 2009; Watt et al., 2010; Fayek et al., 2016).

Other relevant factors related to improved survival of the liver graft were the period of LT between 2012 and 2014 and the yellow or white skin patients. A variable skin color was included in the database only in 2008. Then, the patients who lose the graft before this time had not skin color declared. We understand that this is a limitation of the study but if we exclude data for the period up to 2008 it would be a much greater loss for the study. The white colored skin proved to be a protective factor of the graft in the Full and Matched cohort by multivariate analysis as previously indicated in a different studies (Nair et al., 2002; Ananthakrishnan and Saeian, 2008). It is known that people with white skin color in Brazil have, in general, better socio-educational conditions, which may justify their better survival rate (Bastos et al., 2008).

Through the database, it was possible to identify records of liver disease before transplantation in part of the patients, and from these records, we were able to infer the basic cause of transplantation for some patients. However, in the vast majority of cases, it was not possible to evaluate neither the initial diagnosis that led to the transplantation nor the cause of graft loss. The vast majority of patients had generic diagnoses such as liver failure or cirrhosis, according to the database.

Brazil has presented important advances in LT, progressively increasing the absolute number of transplants, the number of

transplant teams and the number of states that perform the transplantation, therefore improving the access and treatment of the population with terminal liver disease (Brazilian Organ Transplantation Society (ABTO), 2018). However, information on the outcome and impact of LT was either non-existent or from a disconnected source due to Brazil's reality.

Despite the limitations of both the method and the records, this study was able to connect important information regarding LT, through the joining of three important SUS databases, which may help to improve LT care.

CONCLUSION

This study evaluated liver graft through up to 16 years of observation and showed a survival rate of 72% in the first year and a mortality rate of 21% in the first 3 months following transplantation. It was shown that the transplanted patients who had an immunosuppressive scheme based on tacrolimus had less graft losses than the group that used cyclosporine. In addition, patients who were immunosuppressed with tacrolimus and had no association with antiproliferative agents or mTOR had a higher graft survival rate when compared to all other immunosuppressive schemes. In this cohort, the age and the time ratio lacking immunosuppressant were risk factors for graft losses, while white skin and time, considering the most recent transplantation, were criteria of better prognosis regarding the graft.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Research Committee of Federal University of Minas Gerais (Report No. 16334413.9.0000.5149). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

FA, JA-T, MC, and CS-F contributed conception and design of the study and manuscript revision. RG and NR contributed to manuscript revision and analyzed the results. TS and LG prepared the figures and analyzed the results. GN and AG wrote the manuscript and contributed in all parts of the research. All authors contributed to the article and approved the submitted version.

REFERENCES

- Adam, R., Karam, V., Delvart, V., O'Grady, J., Mirza, D., Klempnauer, J., et al. (2012). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J. Hepatol.* 57, 675–688. doi: 10.1016/j.jhep.2012.04.015
- Adam, R., Karam, V., Cailliez, V., Grady, J. G. O., Mirza, D., Cherqui, D., et al. (2018). 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. *Transpl. Int.* 31, 1293–1317. doi: 10.1111/tri.13358
- Agopian, V. G., Petrowsky, H., Kaldas, F. M., Zarrinpar, A., Farmer, D. G., Yersiz, H., et al. (2013). The Evolution of Liver Transplantation During 3 Decades. *Ann. Surg.* 258, 409–421. doi: 10.1097/sla.0b013e3182a15db4
- Ananthakrishnan, A. N., and Saeian, K. (2008). Racial differences in liver transplantation outcomes in the MELD era. *Am. J. Gastroenterol.* 103, 901–910. doi: 10.1111/j.1572-0241.2008.01809.x
- Associação Brasileira de Transplante (2018). Rbt, (2011–2018). Registro Brasileiro de Transplante. *Regist. Bras. Transplant.* 4, 1–88. Available at: http://www.abto.org.br/abto03/Upload/file/RBT/2018/Lv_RBT-2018.pdf.
- Bastos, J. L., Dumith, S. C., Gigante, D. P., Peres, M. A., and Peres, K. G. (2008). Socioeconomic difference between self-and interviewer-classification of color/race. *Rev. Saude Publ.* 42, 324–334. doi: 10.1590/S0034-89102008000200019
- Berg, C. L. (2016). Liver Transplantation in 2016: An Update. *N. C. Med. J.* 77, 194–197. doi: 10.18043/ncm.77.3.194
- Brandão, A., Fuchs, S., Gleisner, A., Zanotelli, M., and Cantisani, G. (2009). MELD and other predictors of survival after liver transplantation. *Clin. Transplant.* 23, 220–227. doi: 10.1111/j.1399-0012.2008.00943.x
- Brazilian Organ Transplantation Society (ABTO) (2018). Organ Transplantation in Brazil, (2011–2018). *Braz. Transplant. Regist.* 4, 1–34. Available at: http://www.abto.org.br/abto03_inlgles/Upload/file/BrazilianTransplantationRegistry/Eng_RBT2018-leitura.pdf.
- Burra, P., Burroughs, A., Graziadei, I., Pirenne, J., Valdecasas, J. C., Muiesan, P., et al. (2016). EASL Clinical Practice Guidelines: Liver transplantation. *J. Hepatol.* 64, 433–485. doi: 10.1016/j.jhep.2015.10.006
- Cherchiglia, M. L., Guerra Júnior, A. A., Andrade, E.II, Machado, C. J., de Assis Acúrcio, F., Meira Júnior, W., et al. (2007). A construção da base de dados nacional em Terapia Renal Substitutiva (TRS) centrada no indivíduo: aplicação do método de linkage determinístico-probabilístico. *Rev. Bras. Estud. Popul.* 24, 163–167. doi: 10.1590/s0102-30982007000100010
- Daniel, K. E., Eickhoff, J., and Lucey, M. R. (2017). Why do patients die after a liver transplantation? *Clin. Transplant.* 31, 1–7. doi: 10.1111/ctr.12906
- Fayek, S. A., Quintini, C., Chavin, K. D., and Marsh, C. L. (2016). The Current State of Liver Transplantation in the United States: Perspective From American Society of Transplant Surgeons (ASTS) Scientific Studies Committee and Endorsed by ASTS Council. *Am. J. Transplant.* 16, 3093–3104. doi: 10.1111/ajt.14017
- Gomes, R. M., Guerra Júnior, A. A., de Lemos, L. L. P., Costa, J., de, O., Almeida, A. M., et al. (2016). Ten-year kidney transplant survival of cyclosporine- or tacrolimus-treated patients in Brazil. *Expert Rev. Clin. Pharmacol.* 9, 991–999. doi: 10.1080/17512433.2016.1190270
- Guerra, A. A., Cesar, C. C., Cherchiglia, M. L., Andrade, E.II, De Queiroz, O. V., Silva, G. D., et al. (2010). Cyclosporine versus tacrolimus in immunosuppressive maintenance regimens in renal transplants in Brazil: Survival analysis from 2000 to 2004. *Ann. Pharmacother.* 44, 192–201. doi: 10.1345/aph.1M244
- Guerra Junior, A. A., Acúrcio, F., de, A., Andrade, E.II, Cherchiglia, M. L., Cesar, C. C., et al. (2010). Ciclosporina versus tacrolimus no transplante renal no Brasil: uma comparação de custos TT - Cyclosporine versus tacrolimus in kidney transplants in Brazil: a cost comparison. *Cad. Saude Publ.* 26, 163–174. doi: 10.1590/S0102-311X2010000100017
- Haddad, E., Mcalister, V., Renouf, E., Malthaner, R., Ms, K., Li, G., et al. (2006). Cyclosporin versus tacrolimus for liver transplanted patients (Review) Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst. Rev.* 1–92. doi: 10.1002/14651858.CD005161.pub2.Copyright
- Jain, A., Reyes, J., Kashyap, R., Dodson, S. F., Demetris, A. J., Ruppert, K., et al. (2000). Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann. Surg.* 232, 490–500. doi: 10.1097/00000658-200010000-00004
- Jonas, S., Neuhaus, R., Junge, G., Klupp, J., Theruvath, T., Langrehr, J. M., et al. (2005). Primary immunosuppression with tacrolimus after liver transplantation: 12-Years follow-up. *Int. Immunopharmacol.* 5, 125–128. doi: 10.1016/j.intimp.2004.09.014
- Junior, A. A. G., Pereira, R. G., Gurgel, E.II, Cherchiglia, M., Dias, L. V., Ávila, J., et al. (2018). Building the National Database of Health Centred on the Individual: Administrative and Epidemiological Record Linkage - Brazil 2000–2015. *Int. J. Popul. Data Sci.* 3, 1–10. doi: 10.23889/ijpds.v3i1.446
- Korayem, G., Alissa, D., Alsuhaibani, L., Alshykh, H., and Elsiey, H. (2017). “Immunosuppression in Liver Transplantation,” in *Immunosuppressive Therapy* (Riad: Avid Science), 2–40.
- Lan, X., Liu, M. G., Chen, H. X., Liu, H. M., Zeng, W., Wei, D., et al. (2014). Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis. *World J. Gastroenterol.* 20, 12330–12340. doi: 10.3748/wjg.v20.i34.12330
- Manyalich, M., Gómez, M. P., and Reis, D. L. (2018). International Registry in Organ Donation and Transplantation (IRODAT) - 2016 Worldwide Data. *Transplantation* 102, S800. doi: 10.1097/01.tp.0000543830.31611.cf
- Meirelles Junior, R. F., Salvalaggio, P., de Rezende, M. B., Evangelista, A. S., Della Guardia, B., Matielo, C. E. L., et al. (2015). Liver transplantation: history, outcomes and perspectives. *Einstein (São Paulo)* 13, 149–152. doi: 10.1590/s1679-45082015rw3164
- Ming, Y., Zhuang, Q., Tu, B., Kong, G., Li, H., Niu, Y., et al. (2019). “Liver Transplantation in China,” in *Surgical Challenges in the Management of Liver Disease*. Ed. G. Tsoulfas (Changsha: IntechOpen), 42. doi: 10.5772/intechopen.81230
- Ministério da Saúde (2016). *Protocolo Clínico e Diretrizes Terapêuticas para Imunossupressão no Transplante Hepático em Adultos* (Brasília: Ministério da Saúde).
- Moreno, R., and Berenguer, M. (2006). Post-liver transplantation medical complications. *Ann. Hepatol.* 5, 77–85. doi: 10.1016/S1665-2681(19)32022-8
- Nair, S., Eustace, J., and Thuluvath, P. J. (2002). Effect of race on outcome of orthotopic liver transplantation: A cohort study. *Lancet* 359, 287–293. doi: 10.1016/S0140-6736(02)07494-9
- Roberts, M. S., Angus, D. C., Bryce, C. L., Valenta, Z., and Weissfeld, L. (2004). Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database. *Liver Transplant.* 10, 886–897. doi: 10.1002/lt.20137
- Rodríguez-Perálvarez, M., Guerrero-Misas, M., Thorburn, D., Davidson, B. R., Tsochatzis, E., and Gurusamy, K. S. (2017). Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database Syst. Rev.* 148, 1–145. doi: 10.1002/14651858.CD011639.pub2. www.cochranelibrary.com
- Sarkar, M., Watt, K. D., Terrault, N., and Berenguer, M. (2015). Outcomes in liver transplantation: Does sex matter? *J. Hepatol.* 62, 946–955. doi: 10.1016/j.jhep.2014.11.023
- Song, A. T. W., Avelino-Silva, V.II, Pecora, R. A. A., Pugliese, V., D'Albuquerque, L. A. C., and Abdala, E. (2014). Liver transplantation: Fifty years of experience. *World J. Gastroenterol.* 20, 5363–5374. doi: 10.3748/wjg.v20.i18.5363
- Starzl, T. E., Groth, C. G., Bretschneider, L., Penn, I., Fulginiti, V. A., Moon, J. B., et al. (1968). Orthotopic homotransplantation of the human liver. *Ann. Surg.* 168, 392–415. doi: 10.1097/00000658-196809000-00009
- Tae, H. L., Shah, N., Pedersen, R. A., Kremers, W. K., Rosen, C. B., Klintmalm, G. B., et al. (2007). Survival after liver transplantation: Is racial disparity inevitable? *Hepatology* 46, 1491–1497. doi: 10.1002/hep.21830
- Watt, K. D. S., Pedersen, R. A., Kremers, W. K., Heimbach, J. K., and Charlton, M. R. (2010). Evolution of causes and risk factors for mortality post-liver transplant: Results of the NIDDK long-term follow-up study. *Am. J. Transplant.* 10, 1420–1427. doi: 10.1111/j.1600-6143.2010.03126.x

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Reliability of a Novel Hematological Malignancy Specific Patient-Reported Outcome Measure: HM-PRO

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Background: Patients' experience of symptoms often goes undetected during consultation in an outpatient clinic, and the use of a patient-reported outcome measure (PRO) in such a setting could be useful to aid treatment decision-making. A new PRO measure, the HM-PRO (Hematological Malignancy Specific Patient-Reported Outcome Measure) has been recently developed to evaluate hematological malignancy (HM) patients' health-related quality of life (HRQoL) and their symptom experience in daily clinical practice as well as in research. The objectives of the study were to assess: the internal consistency of the scores for Part A (impact) and its four domains (physical behavior; social well-being; emotional behavior; and eating and drinking habits) and Part B (signs and symptoms); and the test-retest reliability of the individual items of the newly developed hematological malignancy specific composite measure, the HM-PRO.

Methods: This was a prospective longitudinal observational study where 150 patients with different HMs and different stage of disease (male $n = 98$ (65.3%); mean age 64.9 ± 14.4 years, range 17.9–89.2 years; mean time since diagnosis 3.7 ± 4.9 years, range 0.04–25.8 years) completed the HM-PRO at baseline (assessment 1 at t1) and after 7 days (assessment 2 at t2). Data analysis was performed using IBMSPSS 23 statistical software.

Results: The Cronbach's alpha estimates of the HM-PRO for both assessment points (t1 and t2) were above 0.9 for Part A, and above 0.8 for Part B, showing strong stability of the measurement. The level of agreement for the reproducibility between the two

assessments, using intra-class correlation coefficients (ICC), was very strong with Part A: ICC = 0.93 (95% CI = 0.90–0.95), and Part B: ICC = 0.91 (0.88–0.93). The ICC for the four domains of Part A ranged from 0.85–0.91. The ICC was greater than 0.8 for overall score of Part A and Part B for all the 10 diagnoses, confirming strong reliability.

Conclusion: This study clearly indicates that the HM-PRO possesses strong test-retest reliability for both Part A and Part B. The Cronbach's alpha confirmed acceptable internal consistency. The extensive reliability testing described in this study supports the generic nature of the HM-PRO for use in hematological malignancies in both routine clinical practice, to aid treatment decisions, as well as in research.

Keywords: hematological malignancy, Hematology-Specific Patient-Reported Outcome Measure, quality of life, symptoms, reliability, internal-consistency, clinical practice, clinical research

INTRODUCTION

Hematological Malignancies (HM) include neoplasms of myeloid and lymphoid cell lines (HMRN, 2004), with an expected UK incidence rate of 38,740 per annum (HMRN, 2014). WHO defines the primary objectives of cancer diagnosis and treatment as the cure, prolongation of life and improvement of the quality of life (QoL) (WHO, 2017). With the advances in the treatment modalities, patients treated for HMs are able to survive their disease and evidence suggests that health-related QoL (HRQoL) of patients with HM is significantly affected by the disease and its treatments (Persson et al., 2001; Holzner et al., 2004; Santos et al., 2006; Mols et al., 2007; Shanafelt et al., 2007; Strasser-Weippl and Ludwig, 2008; Johnsen et al., 2009; Goswami et al., 2019a). Hence, maintaining a good QoL is of paramount importance in treating and caring for patients with HM.

A recent systematic literature review identified the health-related QoL (HRQoL) issues important to patients with HMs and the HRQoL instruments currently used in hematology (Goswami et al., 2019a). This review assessed the conceptual coverage of the identified HRQoL instruments as well as their measurement properties. It was reported that these instruments do not cover important HRQoL and highlighted the need for the development of a new PRO with a robust methodology (Goswami et al., 2019a). Similar finding were reported by another systematic reviewer which focused on patients with multiple myeloma (Osborne et al., 2012; Goswami et al., 2019a). A new PRO measure, HM-PRO (hematological malignancy specific patient-reported outcome measure), has been recently developed to evaluate the HRQoL of patients with HMs in daily clinical practice as well as in research (Goswami et al., 2017; Goswami et al., 2020b; Goswami et al., 2020c).

Reliability is a measure of reproducibility of an instrument; it is the degree to which the instrument yields the same score each time it is administered, while the underlying construct remains the same. It is a way to reflect the amount of error inherent in the measurement of the HRQoL (Mcdowell and Newell, 1996; Streiner and Norman, 2003). The use of a reliable instrument in daily clinical practice settings is crucial. An unreliable

instrument will lead to an error in the measurement of HRQoL eventually resulting in a misleading interpretation of the scores and its ultimate influence on clinical decision-making. The importance of PRO instruments in evaluating the impact of the disease and its treatment and in understanding the health outcomes is fully established (Dobrozsi and Panepinto, 2015). Patients' experience of symptoms often goes undetected during consultation in an outpatient clinic, and therefore the use of a PRO instrument in such setting could be very useful to aid treatment decision-making. An unreliable patient-reported outcome measure (PRO) instrument will have a negative impact on the measurement of such symptoms. Poor reliability of an instrument would also affect its convergent validity, i.e., it may affect the correlation of the instrument with other measures (John and Soto, 2007) in an attempt to establish its being fit for purpose. However, a PRO instrument with acceptable reliability would result in a more accurate assessment (McCrae et al., 2011) which, in turn, influences the ability of such instrument to detect change over time, i.e., its responsiveness. Hence, reliability is very central to the measurement properties of an instrument. There are three possible ways to measure the reliability: internal consistency; inter-rater reliability; and test-retest reliability.

Internal consistency is the measure of the homogeneity of the instrument. It reflects an instrument's ability to identify variability within a patient population and extent to which all the items in the scale measure the same underlying concept (Streiner and Norman, 2003; McCrae et al., 2011). The inter-rater reliability measures the agreement between the data collected from different raters. It is used to measure whether different raters are harmonious in their observations and scoring. The test-retest reliability focuses on the reproducibility of the scores. It assesses an instrument's ability to measure the same construct at two different time points while keeping all other variables constant. In an ideal situation, the scores of an instrument, completed at two different points, should be the same, proving the reproducibility reliability of the instrument. The US Food and Drug Administration (FDA) assesses the stability of scores by using evidence of intraclass correlation coefficient (ICC) and the time period of assessment for test-retest test (USFDA, 2009). The objectives of this study, therefore, were to: (1) assess the internal consistency of the scores for Part A (impact) and its four

domains, and Part B (signs and symptoms) of the HM-PRO; (2) assess the test-retest reliability of the individual items of the HM-PRO, the scores of the domains of Part A, and overall scores of Part A and Part B.

METHODS

Ethics

Multicenter ethics approval was obtained from the National Research Ethics Service (NRES) South West Bristol, UK (ref 14/SW/0033) followed by individual “research and development” approvals from all the participating centers. A signed informed consent was obtained from all the study participants.

Study Design

The study was a prospective longitudinal observational study. All study participants were assessed on two occasions, at baseline (t1—assessment 1) and after 7 days (t2—assessment 2). The time interval of 7 days between assessments was chosen to minimize the “learning effect” (Salek, 1992). The choice of 7 days period was further confirmed after discussing it with the patient research partner and the clinicians (hematologist) involved in the study design. The selection of the optimal time between the two assessments is very crucial as it will help in avoiding the overestimation (if it is shorter) and underestimation (if it is longer) of reliability. Patients who were receiving treatment or had completed their course of treatment may have a drastic change in their symptoms and HRQoL in a short period of time; hence, a slight difference in score was expected between the two assessments.

Patient Population

Patients with different hematological malignancies were recruited from seven secondary care hospitals in the UK. The inclusion criteria were: diagnosed with hematological malignancy as per the most recent WHO classification; at any stage of disease (defined as stable, progressing, and remission)—confirmed by clinical staff; at any stage of the treatment (due to start the treatment, on treatment, or finished treatment); able to read and write in English; ability to give written informed consent; and aged 17 or above. The exclusion criteria were: patients whose diagnosis was not confirmed; aged below 17; unable to read and write in English; patients with compromised mental capacity; and unavailable to complete the second assessment after 7 days.

Measurement Instrument

The HM-PRO, a hematological malignancy specific patient-reported outcome measure, is a newly developed composite measure consisting of two scales: Part A (impact) and Part B (signs and symptoms) (Goswami et al., 2016; Goswami et al., 2018a; Goswami et al., 2018b; Goswami et al., 2019b; Goswami et al., 2020c). Part A measures the impact of hematological malignancy and its treatment on a patient’s HRQoL, and Part B captures the severity of different disease symptoms and

treatment side effects. Part A has a total of 24 items in four domains: physical behavior (7); social well-being (3); emotional behavior (11); and eating and drinking habits (3) rated on a 3-point Likert scale (0 = not at all, 1 = A little, and 2 = A lot), and “not applicable” as a separate response option. Part B consists of 18 items in a single domain, with 3-point severity Likert scale (0 = not, 1 = Mild, and 2 = Severe). The third items of the “Eating and drinking habits” domain in Part A, i.e., “*My drinking habits have changed*”, and the ninth item of Part B “*I have skin problems (e.g. itching, bruises, rashes, etc.)*” are not included in the scoring system due to misfit in Rasch model but were collected for additional information (Goswami et al., 2017; Goswami et al., 2018b). The HM-PRO has demonstrated good construct validity of both convergent and divergent type comparing it with existing closely and distantly related PROs (Goswami et al., 2020a).

Procedure

During the first assessment, patients were approached by the clinic/research nurse in an out-patient/day-care or in-patient setting, who explained in brief about the study and asked their willingness to participate. Those who agreed were asked to complete the HM-PRO after reading the patient information sheet and giving written informed consent. After completing the first assessment, all the patients were provided with a package containing the HM-PRO for the second assessment and a freepost self-addressed envelope to return the completed instrument after 7 days. Other relevant patient demographic information and preferred contact details were collected. On the 6th day following the initial assessment, patients were reminded *via* text/calls/emails and asked to complete the instrument on the 7th day and use the freepost envelope provided in the pack to send it back to the research team.

Data Processing and Analysis

The data entry was performed in Microsoft Excel and 20% entries were randomly selected for cross-validation by a reviewer. Cleaning, coding, and analysis of the data were performed using SPSS Windows version 23. Cronbach’s alpha was calculated to measure the internal consistency of the scales and subscales of the HM-PRO, which is the average inter-item correlation (Cronbach, 1951; Frost et al., 2007; Tavakol and Dennick, 2011; Devellis, 2016). The alpha value reflects the extents to which the instrument measures the concept consistently. Cronbach’s alpha value greater than 0.7 was taken as reliable (Tavakol and Dennick, 2011). Spearman’s rank correlation was also calculated to assess the inter-item and item-total partial correlation. A moderate correlation ($r_s = 0.2$) is expected between items (Streiner and Norman, 2003). Intra-class correlation was calculated to assess the level of agreement between scores from the first assessment (test) and after 7 days (re-test). An ICC value of 1 means that 100% variability is because of difference between patients, and the ICC value of 0 means that all variability is due to within-patient variability and error (Studenic et al., 2016). A 2-way mixed-effects, absolute agreement, multiple raters measurement type of ICC was chosen as per McGraw and Wong convention (Mcgraw and Wong, 1996).

RESULTS

Patient Demographics

A total of 193 patients with different hematological malignancies (acute lymphoid leukemia = 12; acute myeloid leukemia = 28; chronic lymphoid leukemia = 17; chronic myeloid leukemia = 13; multiple myeloma = 33; indolent non-Hodgkin lymphoma = 16; aggressive non-Hodgkin lymphoma = 22; Hodgkin lymphoma = 14; myelodysplastic syndrome = 15; and myeloproliferative neoplasm = 23), at different stage of disease (stable = 71; remission = 64; and progressing = 58) participated

in the study and completed the first assessment (t1). The mean age of patients was 63.3 (± 15.2 , range = 18–89 years) and the mean time since diagnosis was 3.8 (± 4.9) years. However, a total of 150 patients completed the second assessment after 7 days (t2) and returned them by post, with a response rate of 77.7%. The data from these 150 patients (mean age 64.6 ± 14.4 years, range 17.9 to 89.2; mean time since diagnosis 4.0 ± 5.1 years, range 15 days to 25.8 years) were used for the test-retest reliability analysis (Table 1 and Figure 1). The highest number of patients ($n = 41$, 27.3%) were diagnosed less than 6 months prior to the study and the highest number of patients ($n = 46$, 30.7%) were in the age groups 70–80 years.

TABLE 1 | Demographics characteristics of the study participants (n=150).

n = 150		Median	Range
Age (Years)		68.13	17.9–89.2
Time since Diagnosis (years)		1.9	0.04–25.84
		n	%
Gender	Male	98	65.3
	Female	52	34.7
Ethnic Origin	White	139	92.7
	Asian or Asian British	9	6.0
	Black British	2	1.3
Inpatient/Outpatient	Inpatient	9	6.0
	Outpatient	141	94.0
Disease Type*	ALL	9	6.0
	AML	19	12.7
	CLL	14	9.3
	CML	11	7.3
	MM	29	19.3
	INHL	11	7.3
	ANHL	17	11.3
	HL	11	7.3
	MDS	13	8.7
	MPN	16	10.7
Stage of Disease	Stable	58	38.7
	Remission	51	34
	Progressing	41	27.3
Comorbidities	Comorbidities, cases	45	30.0
	Other Cancer, cases	10	6.7
	No other condition	95	63.3

*ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; INHL, indolent non-Hodgkin lymphoma; ANHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

Internal Consistency

The Cronbach's alpha estimates of the HM-PRO for assessments 1 and 2 (at t1 and t2) were above 0.9 for Part A, and above 0.8 for Part B, showing strong instrument stability. For individual domains of Part A, the lowest alpha value was observed for the social well-being domain for assessment 1 ($\alpha = 0.70$) and assessment 2 ($\alpha = 0.68$). Alpha value was greater than 0.8 (i.e., both assessments) for Physical Behavior, Emotional Behavior, and for Eating and drinking habits. Optimal homogeneity is reflected in moderate inter-item correlation and moderate-to-strong corrected item-total correlations (Streiner and Norman, 2003); hence, this was also examined. The corrected item-total correlation (CITC) of Part A items ranged from 0.42 to 0.75 for assessment 1 and 0.40 to 0.80 for assessment 2, reflecting strong internal consistency. For assessment 1, the lowest correlation was seen for Item “I am worried about dying” and the highest correlation was seen for the item “My eating habits have changed”. For Assessment 2 “I am worried about my appearance” (CITC = 0.40) was the lowest and “I have difficulty leaving the house” (CITC = 0.80) was the highest for Part A. The corrected item-total correlation for Part B ranged from 0.25 to 0.64 for assessment 1 and 0.24 to 0.65 for assessment 2, reflecting mostly moderate internal consistency. The lowest score was observed for item “I have hair loss” (CITC = 0.25) for assessment 1 and “I have night sweats” for assessment 2 (CITC = 0.24). This indicated that the HM-PRO is well-balanced in both Part A and Part B, as no item carried too much weight.

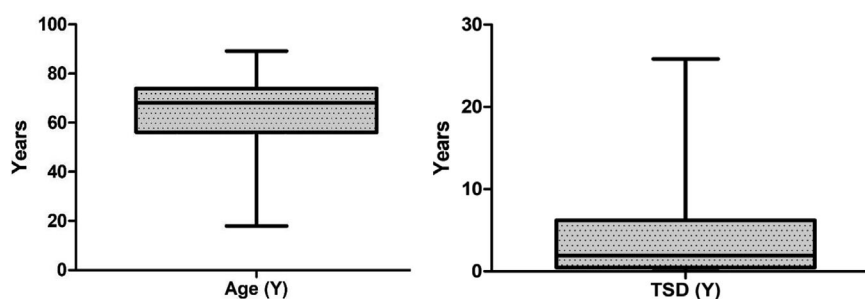


FIGURE 1 | Box plot showing median values and interquartile range (IQR) for age and time since diagnosis (TSD).

Test-Retest Reliability

The reproducibility of the HM-PRO score in repeated administration was tested. Patients completed the HM-PRO on two different occasions, at baseline (assessment 1) and a follow-up assessment after 7 days (assessment 2). The level of agreement was very strong for overall Part A: ICC = 0.93 (95% CI = 0.90–0.95), and Part B: ICC = 0.91 (0.88–0.93) (Table 2). The ICC for four domains of Part A ranged from 0.85 to 0.91, with social well-being scoring the lowest (ICC = 0.85, 95% CI = 0.79–0.89) and physical behavior showing the highest agreement (ICC = 0.91, 95% CI = 0.88–0.94). The correlation between the mean score of test and re-test was calculated by Spearman's correlation

coefficient (r_s) (Table 4). The r_s ranged from 0.74 to 0.87, with Part A ($r_s = 0.87$) and Part B ($r_s = 0.84$) showing strong correlation. With respect to individual domains, physical behavior showed the highest correlation ($r_s = 0.83$), followed by emotional behavior ($r_s = 0.82$), eating and drinking ($r_s = 0.75$), but the lowest correlation for social well-being ($r_s = 0.74$).

With respect to agreement between individual items, ICC for all Part A items were greater than 0.7 and ranged from 0.73 to 0.94 (Table 3), with “My sleeping pattern has changed” scoring the lowest (ICC = 0.73, 95% CI = 0.62–0.80) and “I have difficulty with work (or studies)” showing the highest agreement (ICC = 0.94, 95% CI = 0.91–0.96). Further, the ICC for all the items in

TABLE 2 | Test-retest reliability of the HM-PRO (n = 150).

Domain/Scale (no. of items)	Assessment 1Mean (SD)	Range	Assessment 2Mean (SD)	Range	Mean Diff	r_s	ICC (95% CI)	Alpha (α)
PB (7)	4.8 (3.6)	2–8	4.5 (3.7)	1–8	0.31	0.83	0.91 (0.88–0.94)	0.91
SW (3)	1.5 (1.6)	0–2	1.4 (1.6)	0–2	0.11	0.74	0.85 (0.79–0.89)	0.85
EB (11)	7.9 (4.5)	4–10	7.5 (4.8)	3.8– 10.2	0.34	0.82	0.907 (0.87–0.93)	0.91
ED (2)	1.4 (1.4)	0–2	1.3 (1.3)	0–2	0.12	0.75	0.862 (0.81–0.90)	0.86
Part A (23)	15.4 (9.1)	8–22	14.6 (9.6)	6–21	0.81	0.87	0.926 (0.90–0.95)	0.93
Part B (17)	7.7 (5.2)	4–10	7.3 (5.1)	3–10	0.35	0.84	0.91 (0.88–0.93)	0.91

PB, physical behavior; SW, social well-being; EB, emotional behavior; ED, eating and drinking; r_s , Spearman's correlation coefficient; ICC, intra-class correlation coefficient.

TABLE 3 | Intra-class Correlation Coefficient (ICC) for individual items of Part A and Part B of the HM-PRO (n = 150).

Part A Items	ICC	95% CI		Sig	Part B Items	ICC	95% CI		Sig
		Lower	Upper				Lower	Upper	
PB1Walking	0.91	0.88	0.94	0.001	SS1Fever	0.62	0.48	0.73	0.001
PB2Selfcare	0.84	0.77	0.88	0.001	SS2Stomachache	0.69	0.57	0.77	0.001
PB3Phyactsports	0.83	0.76	0.88	0.001	SS3Energylevel	0.80	0.73	0.86	0.001
PB4Travelling	0.85	0.79	0.90	0.001	SS4Hairloss	0.75	0.65	0.81	0.001
PB5Leavingthehouse	0.81	0.73	0.86	0.001	SS5Tired	0.83	0.77	0.88	0.001
PB6Workorstudies	0.94	0.91	0.96	0.001	SS6Backpain	0.78	0.69	0.84	0.001
PB7Holidays	0.87	0.82	0.91	0.001	SS7Senseoftaste	0.80	0.72	0.85	0.001
SW1Socializing	0.81	0.73	0.86	0.001	SS8Breathing	0.80	0.73	0.86	0.001
SW2Personalrelationships	0.76	0.66	0.83	0.001	SS10Headaches	0.66	0.53	0.75	0.001
SW3Sexlife	0.91	0.85	0.94	0.001	SS11Constipation	0.79	0.71	0.85	0.001
EB1Burdentoothers	0.78	0.69	0.84	0.001	SS12Lumps	0.71	0.60	0.79	0.001
EB2Peoplejudgingme	0.77	0.68	0.84	0.001	SS13Bodypain	0.80	0.73	0.86	0.001
EB3Appearance	0.89	0.86	0.93	0.001	SS14Infections	0.69	0.57	0.77	0.001
EB4Distressed	0.79	0.71	0.85	0.001	SS15Nightsweats	0.81	0.74	0.87	0.001
EB5Anxious	0.76	0.67	0.83	0.001	SS16Diarrhoea	0.76	0.66	0.82	0.001
EB6Dying	0.85	0.79	0.90	0.001	SS17Nausea	0.83	0.76	0.88	0.001
EB7Confidence	0.77	0.68	0.84	0.001	SS18Chestpain	0.71	0.59	0.79	0.001
EB8Futurehealth	0.86	0.81	0.90	0.001					
EB9Sleepingpattern	0.73	0.62	0.80	0.001					
EB10Concentrating	0.79	0.72	0.85	0.001					
EB11Treatment	0.75	0.66	0.82	0.001					
ED1Appetite	0.87	0.82	0.91	0.001					
ED2Eatinghabits	0.80	0.72	0.85	0.001					

PB, physical behavior; SW, social well-being; EB, emotional behavior; ED, eating and drinking; SS, signs and symptoms.

Part B ranged from 0.62–0.83. A total of four items had ICC lower than 0.7: “I have/had fever” (ICC = 0.62, 95% CI = 0.48–0.73); “I have headaches” (ICC = 0.66, 95% CI = 0.53–0.75); “I have stomach ache” (ICC = 0.69, 95% CI = 0.57–0.77); and “I have infections (e.g., chest, lung, urinary, etc.)” (ICC = 0.69, 95% CI = 0.57–0.77). The item with the highest agreement in Part B was “I feel tired” (ICC = 0.83, 95% CI = 0.77–0.88).

Furthermore, since HM-PRO is developed to be used across different hematological malignancies and stages of disease, it is therefore important to test the reliability of the instrument across these patient groups. The patient data were grouped as per the disease diagnosis and stage of disease, and ICC was calculated for the two assessments 1 and 2 (t1 and t2) to test the agreement. With respect to the stage of disease, the ICC was greater than 0.7 for all the four domains and overall score of Part A and Part B (Table 4) confirming the reliability of the HM-PRO across the three stages of disease. The highest agreement was observed for physical behavior domain for “stable” (ICC = 0.92, 0.86–0.95) and “remission” (ICC = 0.91, 0.83–0.95) stage of disease, whereas emotional behavior (ICC = 0.93, 0.87–0.96) had the highest ICC for “progressing” stage of disease. For the overall scores of Parts A and B, ICC was greater than 0.8 showing strong agreement between the two assessments across three stages of disease (Table 4).

With respect to the reliability testing across disease diagnosis, the ICC was greater than 0.80 for the overall score of Parts A and

B, for all the 10 diagnoses, confirming strong reliability. Further, ICC was greater than 0.70 for all for domains across 10 diagnoses, but 0.53 for “eating and drinking” domain, demonstrating that the HM-PRO possesses acceptable reliability in each one of the 10 hematological malignancy (Table 5).

Individual Item Correlation Between the Two Assessments

Following confirmation of the internal consistency and test-retest reliability, Spearman’s rank correlation coefficients were calculated for individual items in Part A and Part B, between the assessments 1 and 2 (t1 and t2). With respect to Part A, the correlation coefficient (r_s) ranged from 0.58 to 0.86, showing a moderate to a strong relationship. The lowest r_s value was observed for the item “My eating habits have changed” (r_s = 0.58). During treatment, patients experienced frequent changes due to chemotherapy, especially in the “sense of taste”. Because of this the lower correlation can be justified for “eating and drinking” habits in the recall period “today”. With respect to individual items in Part B, the correlation coefficient ranged from 0.49 to 0.72. The lower range is expected because of two reasons: first, the signs and symptoms change very frequently; second, the recall period of Part B is the last 3 days, and patients completed the second assessment after 7 days. In general, all the items in Part A and Part B showed a moderate to a strong correlation,

TABLE 4 | Intra-class correlation coefficients of HM-PRO for the three-states of disease.

Domain/Scale	Stable		Remission		Progressing	
	ICC	95% CI	ICC	95% CI	ICC	95% CI
Physical Behavior	0.92	(0.86–0.95)	0.91	(0.83–0.95)	0.89	(0.80–0.94)
Social Well-being	0.75	(0.83–0.94)	0.90	(0.83–0.94)	0.88	(0.78–0.94)
Emotional Behavior	0.89	(0.82–0.94)	0.90	(0.83–0.94)	0.93	(0.87–0.96)
Eating and Drinking	0.91	(0.84–0.94)	0.74	(0.54–0.85)	0.88	(0.77–0.93)
Part A	0.92	(0.86–0.95)	0.92	(0.87–0.96)	0.93	(0.88–0.97)
Part B	0.89	(0.82–0.94)	0.91	(0.84–0.95)	0.92	(0.85–0.96)

ICC, intra-class correlation coefficient.

TABLE 5 | Intra-class correlation coefficient of HM-PRO across different hematological malignancies.

Disease Diagnosis	Part A Domains				Scales	
	Physical Behavior	Social Well-being	Emotional Behavior	Eating and Drinking	Part A	Part B
ALL	0.96	0.80	0.89	0.53	0.94	0.87
MPN	0.88	0.85	0.92	0.87	0.95	0.91
AML	0.77	0.85	0.85	0.81	0.81	0.84
ANHL	0.94	0.98	0.97	0.45	0.97	0.92
CLL	0.99	0.87	0.95	0.82	0.97	0.94
CML	0.74	0.83	0.83	0.93	0.82	0.91
HL	0.89	0.79	0.87	0.81	0.86	0.94
INHL	0.93	0.89	0.92	0.95	0.92	0.93
MDS	0.94	0.86	0.83	0.95	0.91	0.70
MM	0.94	0.71	0.86	0.93	0.93	0.95

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukaemia; CML, chronic myeloid leukemia; MM, multiple myeloma; INHL, indolent non-Hodgkin lymphoma; ANHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

demonstrating further confirmation of the reliability of HM-PRO.

DISCUSSION

There are several health-related QoL instruments which are currently used in hematology (Goswami et al., 2019a). In choosing an instrument to meet the underlying goals of assessing patient-reported outcomes, it is imperative to ascertain that such instrument is valid and reliable. The HM-PRO has been developed as a composite measure combining HRQoL and Symptoms scale for use in both clinical practice and research (Goswami et al., 2016). Therefore, possessing a good reliability not only signifies the internal validity but also ensures that the scores obtained in a setting is representative and stable over time, without which the results and the conclusions may mislead treatment decisions, particularly in a daily clinical practice setting. Evaluating the performance of an intervention may be under or overestimated with an unreliable instrument. This study focused on evaluating the reliability of the newly developed HM-PRO for its two Parts (A and B), as well as the four individual domains of Part A.

One of the main objectives of using PROs in clinical practice setting is to promote patient-centered care [210]. PROs can be used on a “group-level” or on “individual-level”. On the group-level, PROs can be used for treatment decision-making and screening of patients conditions, and on the individual-level they can be used to improve clinician-patient communication or detecting problems and improve patient outcomes or patient management [251, 252, 437–440]. The results suggest that both the scales and the individual domains of HM-PRO are homogenous and a strong level of agreement between test and retest scores. Hence, HM-PRO can be confidently used at both the group as well as individual level.

The concept of HRQoL is very subjective. Every patient has different perspective toward their own HRQoL. What is important to patients in terms of HRQoL issues may differ from individual to individual. Although medicines taken during the treatment might have the same mechanism of action, they may affect each patient differently. Some have high tolerance to pain whereas others may find it extremely difficult to cope with the slightest pain. With a strong evidence of reliability of HM-PRO, it can be used as a patient management tool for monitoring a patient’s condition over time on an individual basis.

The HM-PRO has been developed using both classical test theory as well as modern and sophisticated technique, i.e., item response theory, in particular Rasch modelling. A recent article published on Rasch measurement theory approach reflects how a PRO can be used to identify aspects of HRQoL which are important to patients and the aspects which they can benefit from the new treatment (Browne and Cano, 2019). However, a PRO to be used in important decision making has to be reliable and must have followed robust development methodology. The HM-PRO has the potential to be used as an aid in treatment

decisions during routine clinical practice following further research to demonstrate such a clinical utility.

One of the main barriers to implementation of the PROs in routine clinical practice is the selection of a HRQoL instrument and interpretation of its scores. As identified by a systematic review, there are several HRQoL instruments which are currently used in hematology (Osborne et al., 2012). Some are disease specific instruments which have been recently developed for example MyPOS (Osborne et al., 2015) for multiple myeloma patients and AML-QoL (Buckley et al., 2020) for patients with acute myeloid leukemia, and there are other instruments which have been developed for general oncology with additional disease specific modules. Such a plethora of instruments discourages their use in the clinical practice mainly due to difficulty in selection and lack of understanding on how to calculate the scores and their interpretation. Hence, the HM-PRO as a generic tool being applicable to all hematological malignancies with good discriminant validity can help to overcome one of the major barriers for the use of PROs in routine clinical practice. It can be used across different hematological malignancies, while being sensitive to individual diagnosis as well. Furthermore, availability of a single user-friendly PRO would be far more welcoming by the clinician to use in their daily clinical practice to aid treatment decision making than a dozen from which to choose for each patient presenting a different hematological malignancy.

CONCLUSION

The findings from this study clearly indicate that the HM-PRO possesses very good reliability rendering it an instrument with potential of being able to play an important clinical role; but that future research is needed to demonstrate the clinical utility of using the HM-PRO in routine practice to help clinicians make treatment decisions. The extensive reliability testing described in this study supports the generic nature of the HM-PRO for use in hematological malignancies in both routine clinical practice, as well as in research and its ability to be used as a management tool for monitoring a patient’s condition over a period of time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NRES South West Bristol, UK (ref 14/SW/0033). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PG collected the data, developed the analysis policy, liaised with hospitals for patient recruitment, analyzed the data, interpreted results, and wrote the first draft of the manuscript. RE contributed to data collection as a patient research partner and reviewed the draft manuscript. SS generated the original idea, developed the study protocol, supervised the study, liaised with study centers as part of patient recruitment, developed the analysis policy, interpreted results, and reviewed the draft manuscript. EO and TI contributed to the design of the study, interpreted results, and reviewed the draft manuscript. JK, AF, DJ, MK, SA-I, MO, MA-O, GC, SM, CL, and MA-O contributed to patient recruitment from their respective center and reviewed the draft manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

- Browne, J. P., and Cano, S. J. (2019). A Rasch Measurement Theory Approach to Improve the Interpretation of Patient-reported Outcomes. *Med. Care* 57 Suppl 5 Suppl 1, S18–s23. doi: 10.1097/MLR.0000000000001096
- Buckley, S. A., Halpern, A. B., Othus, M., Jimenez-Sahagun, D., Walter, R. B., and Lee, S. J. (2020). Development and validation of the AML-QOL: a quality of life instrument for patients with acute myeloid leukemia. *Leukemia Lymphoma* 61, 1158–1167. doi: 10.1080/10428194.2019.1709838
- Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika* 16, 297–334. doi: 10.1007/BF02310555
- Devellis, R. F. (2016). *Scale Development: Theory and Applications* (Chapel Hill, USA: Sage Publishing).
- Dobroszi, S., and Panepinto, J. (2015). Patient-reported outcomes in clinical practice. *Hematol. Am. Soc. Hematol. Educ. Program* 2015, 501–506. doi: 10.1182/asheducation-2015.1.501
- Frost, M. H., Reeve, B. B., Liepa, A. M., Stauffer, J. W., and Hays, R. D. (2007). What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health* 10 Suppl 2, S94–s105. doi: 10.1111/j.1524-4733.2007.00272.x
- Goswami, P., Salek, S., Fielding, A. K., Kell, J., Al-Ismael, S., Oliva, E., et al. (2016). Development of a Novel Patient-Reported Outcome Measure in Haematological Malignancy for Use in Routine Clinical Practice: Item Generation. *Blood* 128, 5985. doi: 10.1182/blood.V128.22.5985.5985
- Goswami, P., Salek, S., Ionova, T., Oliva, E. N., Fielding, A. K., Karakantza, M., et al. (2017). HM-PRO: A Novel Patient-Reported Outcome Measure in Hematological Malignancy for Use in Clinical Practice. *Blood* 130, 2176. doi: 10.1182/BLOOD.V130.SUPPL_1.2176.2176
- Goswami, P., Oliva, E. N., Ionova, T., and Salek, S. (2018a). Responsiveness and the Minimal Clinically Important Difference for HM-PRO in Patients with Hematological Malignancies. *Blood* 132, 2294. doi: 10.1182/blood-2018-99-117094
- Goswami, P., Oliva, E. N., Ionova, T., and Salek, S. (2018b). Translating the Science of Patient Reported Outcomes into Practice: Meaningfulness of HM-PRO Scores in Patients with Hematological Malignancies. *Blood* 132, 4860. doi: 10.1182/blood-2018-99-117180
- Goswami, P., Khatib, Y., and Salek, S. (2019a). Haematological malignancy: Are we measuring what is important to patients? A systematic review of quality-of-life instruments. *Eur. J. Haematol.* 102, 279–311. doi: 10.1111/ejh.13203
- Goswami, P., Oliva, E. N., Ionova, T., Else, R., Kell, J., Fielding, A. K., et al. (2019b). Paper and electronic versions of HM-PRO, a novel patient-reported outcome measure for hematology: an equivalence study. *J. Comp. Eff. Res.* 8, 523–533. doi: 10.2217/ce-2018-0108
- Goswami, P., Ionova, T., Oliva, E. N., Else, R., Kell, J., Fielding, A. K., et al. (2020a). Haematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO): Construct Validity Study. *Front. Pharmacol.* 11, 1308. doi: 10.3389/fphar.2020.00209

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- Goswami, P., Oliva, E. N., Ionova, T., Else, R., Kell, J., Fielding, A. K., et al. (2020b). Quality of Life Issues and Symptoms Reported by Patients Living with Haematological Malignancy: A Qualitative Study. *Ther. Adv. Haematol.* doi: 10.1177/2040620720955002
- Goswami, P., Oliva, E. N., Ionova, T., Else, R., Kell, J., Fielding, A. K., et al. (2020c). Development of a Novel Hematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO): Content Validity. *Front. Pharmacol.* 11, 209. doi: 10.3389/fphar.2020.00209
- Hmrn (2004). *Classification [Online]*. Available at: <https://www.hmrn.org/about/classification> (Accessed 23 Feb 2017).
- Hmrn (2014). *Incidence and Survival [Online]*. Available at: <https://www.hmrn.org/statistics/quick> (Accessed 23 Feb 2017).
- Holzner, B., Kemmler, G., Kopp, M., Nguyen-Van-Tam, D., Sperner-Unterwieser, B., and Greil, R. (2004). Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur. J. Haematol.* 72, 381–389. doi: 10.1111/j.1600-0609.2004.00233.x
- John, O. P., and Soto, C. J. (2007). *The importance of being valid: Reliability and the process of construct validation* (New York, NY, US: Guilford Press).
- Johnsen, A. T., Tholstrup, D., Petersen, M. A., Pedersen, L., and Groenvold, M. (2009). Health related quality of life in a nationally representative sample of haematological patients. *Eur. J. Haematol.* 83, 139–148. doi: 10.1111/j.1600-0609.2009.01250.x
- McCrae, R. R., Kurtz, J. E., Yamagata, S., and Terracciano, A. (2011). Internal Consistency, Retest Reliability, and their Implications For Personality Scale Validity. *Pers. Soc. Psychol. Rev. Off. J. Soc. Pers. Soc. Psychol. Inc.* 15, 28–50. doi: 10.1177/1088868310366253
- McDowell, I., and Newell, C. (1996). *Measuring health : a guide to rating scales and questionnaires* (New York: Oxford University Press).
- Mcgraw, K., and Wong, S. P. (1996). Forming Inferences About Some Intraclass Correlation Coefficients. *Psychol. Methods* 1, 30–46. doi: 10.1037/1082-989X.1.1.30
- Mols, F., Aaronson, N. K., Vingerhoets, A. J., Coebergh, J. W., Vreugdenhil, G., Lybeert, M. L., et al. (2007). Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. *Cancer* 109, 1659–1667. doi: 10.1002/cncr.22581
- Osborne, T. R., Ramsenthaler, C., Siegert, R. J., Edmonds, P. M., Schey, S. A., and Higginson, I. J. (2012). What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur. J. Haematol.* 89, 437–457. doi: 10.1111/ejh.12012
- Osborne, T. R., Ramsenthaler, C., Schey, S. A., Siegert, R. J., Edmonds, P. M., and Higginson, I. J. (2015). Improving the assessment of quality of life in the clinical care of myeloma patients: the development and validation of the Myeloma Patient Outcome Scale (MyPOS). *BMC Cancer* 15, 280. doi: 10.1186/s12885-015-1261-6
- Persson, L., Larsson, G., Ohlsson, O., and Hallberg, I. R. (2001). Acute leukaemia or highly malignant lymphoma patients' quality of life over two years: a pilot study. *Eur. J. Cancer Care (Engl.)* 10, 36–47. doi: 10.1046/j.1365-2354.2001.00236.x

- Salek, M. (1992). Health-related quality of life assessment: A review. *J. Drug Dev.* 5, 137–153.
- Santos, F. R., Kozasa, E. H., Chauffaille Mde, L., Colleoni, G. W., and Leite, J. R. (2006). Psychosocial adaptation and quality of life among Brazilian patients with different hematological malignancies. *J. Psychosom. Res.* 60, 505–511. doi: 10.1016/j.jpsychores.2005.08.017
- Shanafelt, T. D., Bowen, D., Venkat, C., Slager, S. L., Zent, C. S., Kay, N. E., et al. (2007). Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br. J. Haematol.* 139, 255–264. doi: 10.1111/j.1365-2141.2007.06791.x
- Strasser-Weippl, K., and Ludwig, H. (2008). Psychosocial QOL is an independent predictor of overall survival in newly diagnosed patients with multiple myeloma. *Eur. J. Haematol.* 81, 374–379. doi: 10.1111/j.1600-0609.2008.01126.x
- Streiner, D. L., and Norman, G. R. (2003). *Health Measurement Scales a practical guide to their development and use* (Oxford, UK: Oxford University press).
- Studenic, P., Stamm, T., Smolen, J. S., and Aletaha, D. (2016). Reliability of patient-reported outcomes in rheumatoid arthritis patients: an observational prospective study. *Rheumatology* 55, 41–48. doi: 10.1093/rheumatology/kev282
- Tavakol, M., and Dennick, R. (2011). Making sense of Cronbach's alpha. *Int. J. Med. Educ.* 2, 53–55. doi: 10.5116/ijme.4dfb.8dfd
- USFDA (2009). Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual. Life Outcomes* 4, 79.
- Who (2017). *Cancer: Diagnosis and Treatment [Online]* (World Health Organization). Available at: <http://www.who.int/cancer/treatment/en/> (Accessed 25 Feb 2017).
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Severe Potential Drug-Drug Interactions and the Increased Length of Stay of Children in Intensive Care Unit

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Children are exposed to drug-drug interactions (DDI) risks due to their organism's complexity and the need for several medicines prescriptions in pediatric intensive care units (PICU). This study aimed to assess the prevalence of potential DDIs in a Brazilian PICU. We carried out a cross-sectional study at a pediatric teaching hospital from Rio de Janeiro (Brazil) over one year. Potential DDIs (pDDIs) between prescribed medicines for hospitalized children in PICU ($n = 143$) were analyzed according to severity using Micromedex[®]. Sex, age group, number of drugs prescribed, vasoactive amines use (a proxy of clinical complexity), and the PICU length of stay were summarized using descriptive statistics. Association between the PICU length stay, and variables sex, age, clinical condition complexity, number of drugs prescribed, and severity of pDDI were examined by univariate and multiple linear regression. Seventy percent of patients aged three days to 14 years old were exposed at least one potential DDIs during PICU stay. Two hundred eighty-four different types of pDDIs were identified, occurring 1,123 times. Nervous system drugs were implicated in 55% of the interactions, and fentanyl (10%) was most involving in pDDIs. Most pDDIs were classified as higher severity (56.2%), with reasonable documentation (64.6%) and unspecified onset time (63.8%). Worse clinical condition, ten or more drugs prescribed, and most severe pDDIs were associated with a longer PICU length of stay. Multiple linear regression analysis showed an increase of 9.83 days (95% confidence interval: 3.61–16.05; $p = 0.002$) in the PICU length of stay in children with major or contraindicated pDDIs. The results of this research may support the monitoring and prevention of pDDIs related to adverse events in children in intensive care and the design and conduction of new studies.

Keywords: child, drug interactions, intensive care units, pediatric, drug utilization review, hospital stay

INTRODUCTION

Adverse drug events (ADE) are among the leading causes of increased morbidity, mortality, and health costs (Dai et al., 2016). Children admitted to critical care units are more exposed to pharmacotherapy damage risk due to several phases and changes in their development, different response mechanisms to harms, and multiple medicines prescription (Silva et al., 2013). The hepatic and urinary systems' maturation is slow, which means less expression or even lack of cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isoenzymes), decreased renal blood flow, glomerular filtration, and tubular function, chiefly until the age of three-years-old (Fernandez et al., 2011). These variations may affect the absorption, distribution, metabolism, and elimination of drugs in children, increasing the risk of toxicity (Fernandez et al., 2011).

The combination of several drugs and the occurrence of drug interactions in pediatric intensive care units (PICU) is frequently unavoidable and needed during the patient stabilization process, diagnosis, and specific treatment but increases the risk of toxicity and can reduce therapeutic's efficacy (Brunton et al., 2010; Silva, 2012; Dai et al., 2016). Drug-drug interaction (DDI) is defined as a clinical event in which one drug's effect is significantly modified by the presence of another previously or concurrently administered drug. Potential DDI (pDDI) refers to the possibility, in theory, of one drug physiologically altering the pharmacological effects of another drug, concomitantly prescribed (Brunton et al., 2010).

DDIs may benefit clinical management when one drug is used to optimize another drug's action, as ascorbic acid and non-heme iron in concomitant use, for example, (Brunton et al., 2010; Queiroz et al., 2014). However, undesirable DDIs are related to ADE and increased length of hospital stay (Khan, 2013; Alvim et al., 2015; Fitzmaurice et al., 2019).

Knowledge about pDDIs in child health care may contribute to monitoring and minimizing ADE and treatment failures. The literature is scarce on pediatric pharmacoepidemiological studies, especially in developing countries (Osokugu et al., 2016), which motivated the investigation of the prevalence of pDDI in a PICU in a Brazilian teaching hospital.

METHODS

Design and Setting

A cross-sectional study was conducted, and data were collected over one year (May 2014 and April 2015) at a pediatric teaching hospital located in Rio de Janeiro (Brazil) and integrated into the public health system. In addition to outpatient care in general pediatrics, the hospital studied had a pediatric emergency service, oncohematology, and surgical hospitalization for medium and high-complexity care. PICU's installed capacity was ten hospital beds, of which six were pediatric beds and four neonatal surgical beds, and one isolation room.

Eligibility Criteria

All patients aged 0–17 years old admitted to the PICU who stayed for more than 24 h and were administered at least two medicines

during hospitalization were included. No exclusion criteria were applied.

Variables Collected and Other Measures

Data was collected from 1) medical records: sex, age on the first day of hospitalization, the length of PICU stays in days, cause of admission, and severity of illness; 2) daily records of the prescriptions using the electronic hospital management system: name, dose and route of administration; and 3) pharmacotherapeutic plans prepared by the clinical pharmacist: pDDI reported and any information possibly incomplete in data sources mentioned above.

Children were classified by age group as neonates (0–28 days old); infants (29 days–11 months old); toddlers (1 year–2 years and 11 months old); preschoolers (3–5 years and 11 months old); middle childhood (6–11 years and 11 months old) and teenagers (12–16 years old) (Osokugu et al., 2016). Readmissions of the same patient were considered as new cases.

Patient's diagnoses (main hospitalization cause) were classified according to the International Classification of Diseases (ICD10). None score that predicted morbidity or mortality of children was used in the investigated PICU. The prescription at least one vasoactive amine among those commonly used in PICU (epinephrine, norepinephrine, dobutamine, and nitroprusside by parenteral route) was the variable considered as a *proxy* for patient's clinical condition. These drugs were used to restore tissue perfusion in hemodynamically unstable patients by the drastic and widespread reduction of effective oxygen and other nutrient delivery to tissues, leading to cell damage and multiple organ failure (Guimarães et al., 2008; Paediatric Intensive Care Pharmacist's Special Interest Group Neonatal and Paediatric Pharmacists Group, 2011). The need of vasoactive amines was described as a clinical signal of seriousness and worse prognostic in this study (Roque et al., 2016; Pollack et al., 2018).

All prescribed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization. The number of concomitant drugs prescribed was stratified in three groups 1): two to four drugs; 2) five to nine drugs (polypharmacy) and 3) ten or more drugs (excessive polypharmacy) (Dai et al., 2016). Drugs prescribed *Pro re nata* (if needed) were excluded. Topical medications, electrolyte solutions, parenteral and enteral nutrition also were not considered in the analysis.

Each potential DDIs identified were characterized using the *Thomson Micromedex*® software; since it is a database that gathers a larger number of drug monographs, it is available at the studied hospital and is easily accessible online. They were classified according to the level of scientific evidence documentation (excellent, good, reasonable) about pDDI, severity (minor, moderate, major, and contraindicated), and the onset of action (fast, slow, unknown). Minor pDDI may generate limited clinical outcomes, including an increase in the frequency or seriousness of adverse drug reactions and therapeutics changes. Moderate pDDI may result in aggravation of the children's condition and require an adjustment in therapy. Major pDDI may be life-threatening and need medical intervention to minimize or

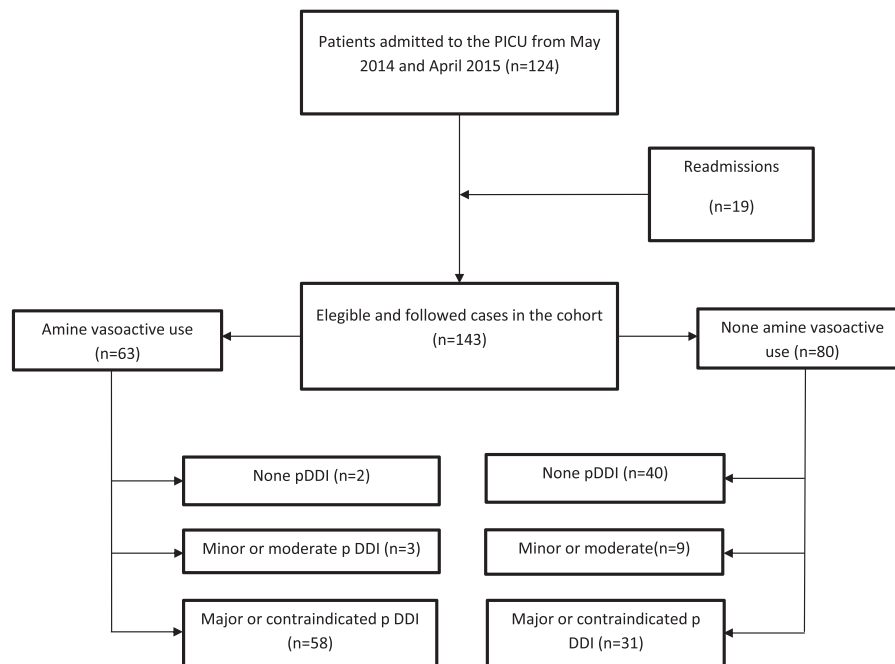


FIGURE 1 | Flow chart of followed cases in the cohort study (May 2014–April 2015).

prevent serious adverse drug reactions (Micromedex Healthcare Series, 2019).

Statistical Analysis

We carried out a descriptive analysis of cases including sex, age group, clinical condition (vasoactive amines use), number of drugs prescribed (two to four; five to nine; ten or more), and PICU length of stay (mean as a cut-off point) by the occurrence of pDDI severity (minor and moderate; major and contraindicated) or not.

Association between the PICU length of stay and sex, age group, clinical condition, number of drugs prescribed, and severity of pDDI were verified by linear regression.

Multivariate linear regression, adjusted by sex, age group and clinical condition was performed to assess whether the length of stay in a PICU was influenced by severity of pDDI. All the analyses were performed using Stata (v.14.2), with a calculation of 95% confidence intervals (95%CI). Statistically significant was considered if $p < 0.005$.

Ethical Issues

This observational study was approved by the Instituto de Puericultura e Pediatria Martagão Gesteira Research Ethics Committee (REC) (CAAE 52065415.5.0000.5264/Number of reference: 1,451,562).

Retrospective secondary data was collected without any interaction between researchers and children or parents. Personal information of the participants was kept blinded to investigators. Waiver of parental permission (Written informed consent from the participant's legal guardian) was requested and authorized by REC.

RESULTS

Characterization of the Patients and the Pharmacotherapeutic Profile

There were 124 children admitted (for more than 24 h) to the PICU during the investigation period, and they were included. Nineteen were readmitted and included twice in the study, totaling 143 cases analyzed (**Figure 1**). Their age ranged from three days of life to 14 years old (median = 11 months; mean = 2.6 years; standard deviation ± 3.9 years) (**Table 1**). The distribution of male and female patients was balanced (**Table 1**). No statistically significant difference was found between the sex and the age of the patients.

Most children had respiratory (29.4%), infectious and parasitic (25.9%), or digestive system (9.8%) diseases as the principal diagnosis. During the course of 63 hospitalizations (44%), the use of vasoactive amines was required, indicating more complex clinical cases. The PICU length of stay ranged from one to 113 days, with a mean length of 11.3 days (standard deviation ± 15.5). In 43 cases (35%), the length of stay was longer than the mean.

During the period, 1,916 drug prescriptions (with 149 different active ingredients) for 143 children were analyzed (mean = 13.4 ± 8.3).

The number of medicines prescribed per patient ranged from two to 46 medications (median = 12). Most of the patients (60%) used more than ten different medications. Antibacterial for systemic use (19.31%) and analgesic drugs (8.56%) were the most prescribed anatomical subgroups. **Table 2** shows the medicines more frequently observed in prescriptions.

Potential Drug-Drug Interactions Frequency

284 different pDDIs prescribed 1,123 occasions were identified for 101 (70.6%) children. Prescriptions of 42 (30.4%) children did

TABLE 1 | Children's profile distribution by the most severe pDDI observed (Teaching Hospital PICU, Rio de Janeiro, Brazil).

Characterization	pDDI observed			Total	
	None	Minor or moderate	Major or contraindicated	N	%
Sex					
Male	23	4	46	73	51
Female	19	8	43	70	49
Clinical condition (vasoactive amines use)					
Yes	2	3	58	63	44
No	40	9	31	80	56
Age group (mean = 2.6 ± 3.9)					
Baby (0–11 months)	26	5	42	73	51
Toddler (12–23 months)	3	4	4	11	8
Early childhood (2–5 years)	6	1	23	30	21
Middle childhood (6–11 years)	5	1	16	22	15
Early adolescence (12–17 years)	2	1	4	7	5
Total number of drugs prescribed (mean = 13.4 ± 8.3)					
2–4	15	0	1	16	11
5–9	24	7	10	41	29
10 or more	3	5	78	86	60
PICU length of stay (mean = 11.3 ± 15.5)					
Until 11 days	41	9	50	100	70
12 or more days	1	3	39	43	30
Total	42	12	89	143	100

pDDI, potential drug-drug interaction; PICU, pediatric intensive care unit.

not have drugs that interacted with each other throughout the treatment at PICU. The mean of pDDIs observed in prescriptions by total hospitalizations in the period was 7.85 (±0.08).

Fourteen pDDIs were classified as contraindicated, 631 had higher severity, 425, moderate severity, and 53, lower severity. Most of the pDDIs had a reasonable level of evidence (64.6%) and the unspecified onset of action (63.8%).

Drugs more involving in pDDI were classified in groups N (Nervous system, 55%), J (Anti-infectives for systemic use, 16%), and A (Alimentary tract and metabolism, 8%) according to ATC code. The most prevalent drugs were phenytoin (5.6%), fentanyl (4.6%), methadone (4.6%), phenobarbital (3.9%), morphine (3.7%), fluconazole (3.3%), cyclosporine (3.2%), clarithromycin (3%), midazolam (2.8%) and furosemide (2.5%). **Figure 2** presented the clinical effects and recommended management of most frequent pDDI pairs observed in this study.

TABLE 2 | Distribution of the most frequently drugs prescribed (Teaching Hospital PICU, Rio de Janeiro, Brazil).

Drugs	ATC Classification	Total	
		N	%
Metamizole	N02BB02	130	91
Ranitidine	A02BA02	112	78
Fentanyl	N02AB03	71	50
Midazolam	N05CD08	70	49
Dexamethasone	H02AB02	67	47
Vancomycin	J01XA01	67	47
Cefepime	J01DE01	54	38
Salbutamol	R03CC02	53	37
Methylprednisolone	H02AB04	50	35
Dobutamine	C01CA07	47	33

ATC, Anatomical Therapeutic Chemical.

Association between PICU length of stay and patient clinical condition (vasoactive amines use during PICU hospitalization), number of drugs prescribed (more than ten), and severity of pDDI (major and contraindicated) were statistically significant ($p < 0.005$) in linear regression analysis (**Table 3**). Multivariate analysis showed an increase in the length of stay of 9.83 days (95% CI = 3.61–16.05; $p = 0.002$) for children with major or contraindicated pDDI (**Table 4**).

DISCUSSION

This study pointed out relevant data about the occurrence of pDDIs in hospitalized children. Seventy percent of patients aged three days to 14 years old were exposed to at least one pDDI during PICU stay. There were 284 different types of potential drug interactions prescribed 1,123 occasions. Severe pDDIs (major and contraindicated) showed associated with the PICU length of stay increase.

Profile of children in intensive care unit included in this study (mean age, subtle male predominance, respiratory diseases as the principal cause of hospitalization) confirmed the findings of other national and international researches (Corullón, 2007; Vonbach et al., 2008; Ferreira et al., 2012; Lanetzki et al., 2012; Alves et al., 2014; Medina-Barajas et al., 2020). However, the mean length of hospital stays of children in the ICU (11.3 days) was longer than that observed in other Brazilian hospitals, which ranged from 5.5 to 10.6 days (Corullón, 2007; Molina et al., 2008; Lima and Cassiani, 2009; Ferreira et al., 2012; Alves et al., 2014). The length of stay in intensive care can differ due to clinical and social factors. However, institutional factors (practice patterns of physicians, clinical protocols, the proportion of nurses by patients, availability of intermediary care, for example) are the likely

pDDI	N	Level of evidence	Possible clinical effects	Management*
Contraindicated				
Fluconazole + Ondansetron	6	Reasonable	↑ risk of QT prolongation	Monitor the patient with electrocardiogram.
Fluconazole + Methadone	5	Excellent	↑ methadone exposure and risk of QT prolongation	Follow the signs of CNS or respiratory depression and reduce the methadone dose if necessary.
Amitriptyline + Linezolid	1	Good	↑ risk of serotonin syndrome	Monitor the patient for signs and symptoms of serotonin syndrome, and consider discontinuing one or both drugs if these symptoms occur.
Fluconazole + Propafenone	1	Reasonable	↑ propafenone exposure and QT prolongation	Contraindicated use due to increased exposure of CYP3A4 substrate and increased risk of QT prolongation.
Sildenafil + Sodium Nitroprusside	1	Reasonable	Potential of hypotensive effect	Monitor the patient for safe reintroduction of sildenafil.
Major				
Fentanyl + Midazolam	65	Reasonable	↑ risk of CNS depression	Monitor the patient and, if necessary, adjust the dose of one or both drugs.
Fentanyl + Ketamine	30	Reasonable	↑ risk of CNS depression	Monitor the patient and, if necessary, adjust the dose of one or both drugs.
Fentanyl + Phenobarbital	18	Reasonable	Fentanyl plasma concentration variation	Monitor for signs of opioid withdrawal and consider dose adjustments.
Lorazepam + Methadone	18	Reasonable	↑ risk of CNS depression	Start methadone dose of 2.5 mg every 12 hours, and consider reducing the CNS depressant dose. Monitor the patient.
Fentanyl + Methadone	17	Reasonable	↑ risk of fatal serotonin syndrome and CNS depression	Reduce the dose of one or both drugs and monitor sedation, hypotension, and respiratory depression especially at the beginning of fentanyl therapy.
Moderate				
Midazolam + Ranitidine	55	Reasonable	↑ midazolam bioavailability	Monitor the patient
Midazolam + Omeprazole	22	Reasonable	↑ risk of CNS depression, ataxia and lethargy.	Monitor the patient and, if necessary, adjust the dose of midazolam or exchange the benzodiazepine.
Minor				
Phenytoin + Ranitidine	14	Good	↑ phenytoin plasma concentration	Monitor the patient and consider the therapeutic phenytoin drug monitorization.
Phenobarbital + Phenytoin	6	Good	Phenytoin plasma concentration variation	Monitor the patient and consider the therapeutic phenytoin drug monitorization.

Legend: pDDI: potential drug-drug interaction; CNS central nervous system. Source: Micromedex®

FIGURE 2 | Description of the five most frequently contraindicated and major pDDIs (Teaching Hospital PICU, Rio de Janeiro, Brazil–May/2014–April/2015, n = 1,123). *Source as: Micromedex Healthcare Series 2019.

TABLE 3 | Association between the PICU length of stay and sex, age group, clinical condition, number of drugs prescribed, and pDDI observed (n = 143, Teaching Hospital PICU, Rio de Janeiro, Brazil).

Variables	Increase of PICU length stay (days) (CI 95%)	p value
Sex		
Male	Ref	0.814
Female	0.62 (−0.77; 4.54)	
Age (months)		
0–23	Ref	0.610
≥24	1.35 (−3.88; 6.58)	
Clinical condition (vasoactive amines use)		
No	Ref	0.009
Yes	6.79 (1.73; 11.86)	
Number of drugs prescribed		
2–9	Ref	<0.001
10 or more	11.71 (6.83; 16.60)	
pDDI observed		
None, minor or moderate	Ref	<0.001
Major or contraindicated	10.61 (5.60; 15.62)	

pDDI, potential drug-drug interaction; PICU, pediatric intensive care unit. Linear regression. CI, confidence interval; Ref, reference group.

primary cause of much of the variability in PICU length of stay and that need to be better investigated in other studies (Pollack et al., 2018). In Latin America, a pDDI investigation in a PICU from a Mexican tertiary hospital for two months, but they did not assess the length hospital stay (Medina-Barajas et al., 2020).

Antibacterials and analgesic drugs ATC subgroups were the most prevalent in this research, which corresponded to data found by Ferreira et al. (2012) in a PICU in Minas Gerais (Brazil). The median of drugs prescribed 12) in the intensive care unit was also close to that observed in other studies (Carvalho et al., 2003; Ferreira et al., 2012).

High frequency of metamizole prescribing reflects common practice in Brazilian hospitals. About 90% of the inpatients had a painkiller prescribed during their hospitalization. A similar percentage (88%) was observed at a pediatric hospital from Brasília (Meiners and Bergsten-Mendes, 2001). Prescription of ranitidine or omeprazole is related to the stress ulcer prophylaxis protocol adopted by the PICU. In a prospective, cross-sectional, observational study in five PICUs in Porto Alegre, ranitidine was also the most commonly used drug for this prophylaxis (Araujo et al., 2010).

TABLE 4 | Multivariate analysis for PICU length stay ($n = 143$; Teaching Hospital PICU, Rio de Janeiro, Brazil).

Variables	Increase of PICU length stay (days) (CI 95%)	p value
Sex		
Male	Ref	0.955
Female	-0.14 (-5.18; 4.89)	
Age (months)		
0–23	Ref	0.870
≥24	0.42 (-5.53; 4.69)	
Clinical condition (vasoactive amines use)		
No	Ref	0.621
Yes	1.52 (-4.56; 7.60) $p = 0.621$	
pDDI observed		
None, minor or moderate	Ref	0.002
Major or contraindicated	9.83 (3.61; 16.05)	

pDDI, potential drug-drug interaction; PICU, pediatric intensive care unit. Multiple linear regression. CI, confidence interval; Ref, reference group.

National and international studies on adult critical care units indicated a variation of 44.3%–87.9% in the frequency of pDDIs observed (Hammes et al., 2008; Spriet et al., 2009; Reis and Cassiani, 2011). In pediatrics, analysis of prescriptions in the wards of a Brazilian teaching hospital (excluding the PICU, oncology, and emergency) identified seven pDDIs per patient at average, which was slightly lower than the value found in the exclusive PICU analysis conducted in this study (7.85 ± 0.08) (Martinbiancho et al., 2007). The incidence observed in this study (70%) was similar to findings in PICU of United States children hospitals (75%) and another Brazilian PICU (72%) (Lima and Cassiani, 2009; Dai et al., 2016). Other studies found lower frequencies in Indian (63%), Pakistani (59.4%), Mexican (42%), Chilean (41%) PICUs (Santibáñez et al., 2014; Ismail et al., 2017; Rao et al., 2019; Medina-Barajas et al., 2020). An investigation at a Brazilian neonatal intensive care unit found a pDDI prevalence equal to 51% (Queiroz et al., 2014).

The prevalence of pDDIs with major (56.2%) and moderate (37.8%) severity observed was higher than that obtained in cohort with 498,956 American inpatients under 21 years old from pediatric beds (41% and 28%, respectively) (Feinstein et al., 2015). Some frequent pDDIs pairs observed in this study also were described in Chilean PICU (midazolam and omeprazole), in the American cohort (midazolam and ranitidine, fluconazole and ondansetron). The pair midazolam and fentanyl were reported in both studies (Santibáñez et al., 2014; Feinstein et al., 2015).

Of the 1,123 pDDIs found, the drugs belonging to the nervous system's anatomical group accounted for 55%. Among these, fentanyl was the most frequent medicine prescribed (10%), followed by midazolam (10%). Among the 284 different pDDIs, phenytoin was the drug relatively more present (5%) in pairs. Phenytoin-related DDIs are mainly related to competition for plasma protein binding since phenytoin binding occurs in a proportion of 90%. Drugs with high plasma protein binding displace phenytoin from its site of action, transiently increasing the free drug fraction. In addition, phenytoin is also an inducer of microsomal enzymes,

increasing the activity of these enzymes leading to lower serum levels of other drugs (Micromedex Healthcare Series, 2019).

Studies on pDDIs, with different methodologies and scenarios, also show that the combination of midazolam and fentanyl corresponded to the most frequent pDDI (Lima and Cassiani, 2009; Carvalho et al., 2013). However, in intensive care, this pDDI has less clinical relevance due to continuous multiparametric and multimodal monitorization of the patients, including possible signs of abstinence from weaning.

Although a small number of contraindicated pDDIs have been found (1.2%), the high risk of severe harm to patients should be considered (Feinstein et al., 2015). Fluconazole was the most involved drug in this type of DDI. The potential interaction of this antifungal with ondansetron, methadone, or propafenone may result in cardiac abnormalities due to QT interval prolongation. Continuous electrocardiographic monitoring is recommended. Intensive care unit patients with QT interval prolongation have a longer length of hospital stay and higher mortality compared to ICU patients with normal QT (Beitland et al., 2014). Interactions involving fluconazole have also been highlighted in the literature because of the risk of inhibition of CYP3A, CYP1A2, CYP2C8/9, and CYP2C19 isoenzymes, which are responsible for the biotransformation of other drugs (Fonseca and Secoli, 2008; Alvim et al., 2015).

Regarding the other contraindicated pDDIs, the combination of linezolid and amitriptyline may cause a serotonergic additive effect. This interaction may result in hyperthermia, hyperreflexia, myoclonus, changes in mental state (Lawrence, 2006). The pDDI between sildenafil and sodium nitroprusside is contraindicated due to the risk of severe hypotension (Micromedex Healthcare Series, 2019).

Excessive polypharmacy (more than ten drugs) is commonly required in patients critically ill, and it is a risk factor for adverse drug reactions and medication errors in children (Smith et al., 2012). According to a study that included 54,549 admissions to 42 pediatric hospitals from the United States, a typical inpatient is exposed to 20 drugs over the PICU (median of three days of length stay) (Dai et al., 2016).

The relationship between the number of drugs prescribed and pDDI occurrence, observed in this study, is known, and both are related to a longer length of stay of adults (Moura et al., 2009; Moura et al., 2011; Reis and Cassiani, 2011; Rodrigues et al., 2017) and children (Santibáñez et al., 2014; Ismael et al., 2017; Carrillo-Alarcon et al., 2018; Rao et al., 2019; Medina-Barajas et al., 2020) in intensive care units.

However, our findings pointed out the association of pDDI more severe (major and contraindicated) with the increase of PICU length of stay. Severe pDDIs may have greater clinical relevance, and the pDDIs severity differences are rarely investigated in studies, notably those involving pediatric patients. It is the main contribution of this investigation.

The identification of pDDI, especially those that offer more significant risk to the patient, was one of the strategic actions of clinical pharmacists in the investigated PICU. However, there was physician resistance to adjust the prescription. The observation of increased length of hospital stay for patients with major and contraindicated pDDI may contribute to a change in the team's practices. We believe these results could be generalized to similar settings.

This research has limitations related to real-world evidence studies (Camm and Fox, 2018) and the fact that the patient's clinical condition is based on a *proxy* variable of case complexity. The occurrence of pDDI laboratory and clinical manifestations also cannot be verified. However, the findings presented may support new observational studies in pediatric patients that relate mainly to the pDDI mechanism to the patients' clinical evolution.

There is also a need to identify, and deprescribe (when possible) medicines that have potential contraindicated or more severe pDDIs in critically ill pediatric patients until new evidence is found to substantiate the risk analysis and the possible benefit of keeping the association of certain medications.

It is suggested 1) to discuss the available pharmacotherapeutic alternatives and the possibility to replace the drug by another of the same pharmacological group for the previous risk and benefit assessment by the healthcare team; 2) to monitor the serum level of drugs that may change in the presence of interactions; and 3) to investigate the correlation between some clinical manifestations and the presence of potential DIs, especially those related to the risk of drug ineffectiveness and QT interval prolongation, given the possible consequences of these events.

CONCLUSION

This study identified 284 different potential pDDIs in prescriptions of 70.6% of children from a Brazilian teaching PICU involving mainly drugs for the nervous system and anti-infectives for systemic use. More than 60% of pDDIs were classified as contraindicated or with major severity.

Multiple linear regression analyses suggested the association of more severe pDDIs with an increase of PICU length of stay (almost ten days).

REFERENCES

- Alves, M. V. M. F. F., Bissiguini, P. O., Nitsche, M. J. T., Olbrich, S. R. L. R., Luppi, C. H. B., and Toso, L. A. R. (2014). Perfil dos pacientes internados em uma unidade de terapia intensiva pediátrica de um hospital escola do interior de São Paulo. *Ciência, Cuid. Saúde* 13, 294–301. doi:10.4025/ciencucuidsaude.v13i2.21912
- Alvim, M. M., Silva, L. A., Leite, I. C. G., and Silvério, M. S. (2015). Eventos adversos por interações medicamentosas potenciais em unidade de terapia intensiva de um hospital de ensino. *Revista Brasileira de Terapia Intensiva* 27, 353–359. doi:10.5935/0103-507X.20150060
- Araujo, T. E., Vieira, S. M. G., and Carvalho, P. R. A. (2010). Stress ulcer prophylaxis in pediatric intensive care units. *J. Pediatr., Rio de Janeiro* 86, 525–530. doi:10.1590/s0021-75572010000600014
- Beitland, S., Platou, E. S., and Sunde, K. (2014). Drug-induced long QT syndrome and fatal arrhythmias in the intensive care unit. *Acta Anaesthesiol. Scand.* 58, 266–272. doi:10.1111/aas.12257
- Brunton, L., Chabner, B. A., and Knollmann, B. (2010). Goodman, and Gilman's. *The Pharmacological basis of therapeutics*. 12th Edn. (New York: McGraw-Hill), 1808.
- Camm, A. J., and Fox, K. A. A. (2018). Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. *Open Heart* 5, e000788. doi:10.1136/openhrt-2018-000788
- Carrillo-Alarcon, L. C., Norato-Canales, L., Chavez-Gallegos, D., Vizuet-Martinez, A., Moedano-Alvarez, E., Vargas-Carrillo, J. P., et al. (2018). Characterization of polypharmacy and drug interactions in pediatric patients in a hospital in Pachuca Mexico. *World J. Pharm. Pharmaceut. Sci.* 7 (8), 128–138. doi:10.20959/wjpps20188-12050
- Carvalho, P. R. A., Carvalho, C. G., Alievi, P. T., Martinbiancho, J., and Trotta, E. A. (2003). Identificação de medicamentos "não apropriados para crianças" em prescrições de unidade de tratamento intensivo pediátrica. *J. Pediatr.* 79, 397–402. doi:10.1590/S0021-75572003000500006
- Carvalho, R. E. F. L., Reis, A. M. M., Faria, L. M. P., Zago, K. S. A., and Cassiani, S. H. B. (2013). Prevalência de interações medicamentosas em unidades de terapia intensiva no Brasil. *Acta Paul. Enferm.* 26 (2), 150–157. doi:10.1590/S0103-21002013000200008
- Corollón, J. L. (2007). *Perfil epidemiológico de uma UTI pediátrica no sul do Brasil*. Bissertação/tese de mestrado. Porto Alegre (Brazil): Faculdade de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, 100.
- Dai, D., Feinstein, J. A., Morrison, W., Zuppa, A. F., and Feudtner, C. (2016). Epidemiology of polypharmacy and potential drug-drug interactions among pediatric patients in intensive care units of U.S. children's hospitals. *Pediatr. Crit. Care Med.* 17, 218–228. doi:10.1097/PCC.0000000000000684
- Feinstein, J., Dai, D., Zhong, W., Freedman, J., and Feudtner, C. (2015). Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. *Pediatrics* 135, e99. doi:10.1542/peds.2014-2015
- Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., and Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics* 3, 53–72. doi:10.3390/pharmaceutics3010053

It is believed that the results of this research may further the monitoring and prevention of potential drug-drug interactions related to adverse events in children in intensive care and support the design and conduction of new studies assessing the clinical consequences of drug-drug interactions in pediatric patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Instituto de Puericultura e Pediatria Martagão Gesteira Research Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ECL and LCL conceived and designed the study. BDC and NCFB contributed to the acquisition and the interpretation of data for the work. MTS contributed to the statistical analysis. ECL, BDC, NCFB, AGP, RBS, MTS, and LCL discussed the results. ECL drafted the manuscript. All authors critically revised the work and approved the final manuscript.

- Ferreira, L. A., Ibiapina, C. C., Machado, M. G. P., and Fagundes, E. D. T. (2012). A alta prevalência de prescrições de medicamentos off-label e não licenciados em uma unidade de terapia intensiva pediátrica brasileira. *Revista Associação Médica Brasileira* 58, 82–87. doi:10.1590/s0104-42302012000100019
- Fitzmaurice, M. G., Wong, A., Akeberg, H., Avramovska, S., Smithburger, P. L., Buckley, M. S., et al. (2019). Evaluation of potential drug–drug interactions in adults in the intensive care unit: a systematic review and meta-analysis. *Drug Saf.* 42 (9), 1035–1044. doi:10.1007/s40264-019-00829-y
- Fonseca, R. B., and Secoli, S. R. (2008). Medicamentos utilizados em transplante de medula óssea: um estudo sobre combinações dos antimicrobianos potencialmente interativos. *Revista da Escola de Enfermagem da USP, São Paulo*. 42, 703–711. doi:10.1590/s0080-62342008000400013
- Guimarães, H. P., Falcão, L. F. R., and Orlando, J. M. C. (2008). *Guia Prático de UTTI*. Rio de Janeiro, Brazil: Atheneu, 1904.
- Hammes, J. A., Pfuetzenreiter, F., Silveira, F., Koenig, A., and Westphal, G. A. (2008). Potential drug interactions prevalence in intensive care units. *Revista Brasileira de Terapia Intensiva* 20, 349–354. doi:10.1590/S0103-507X2008000400006
- Ismail, M., Aziz, S., Noor, S., Haider, I., Shams, F., Haq, I., et al. (2017). Potential drug-drug interactions in pediatric patients admitted to intensive care unit of Khyber Teaching Hospital, Peshawar, Pakistan: a cross-sectional study. *J. Crit. Care* 40, 243–250. doi:10.1016/j.jcrr.2017.04.028
- Khan, L. M. (2013). Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay—a systematic review. *Eur. J. Clin. Pharmacol.* 69, 1985–1996. doi:10.1007/s00228-013-1563-z
- Lanetzi, C. S., Oliveira, C. A. C., Bass, L. M., Abramovici, S., and Troster, E. J. (2012). O perfil epidemiológico do centro de terapia intensiva pediátrico do hospital Israelita Albert Einstein. *Einstein* 10, 16–21. doi:10.1590/S1679-45082012000100005
- Lawrence, K. R., Adra, M., and Gillman, P. K. (2006). Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin. Infect. Dis.* 42, 1578–1583. doi:10.2307/4484794
- Lima, R. E. F., and Cassiani, S. H. D. B. (2009). Potential drug interactions in intensive care patients at a teaching hospital. *Rev. Latino-Am. Enferm.* 17, 222–227. doi:10.1590/s0104-11692009000200013
- Martinbiancho, J., Zuckermann, J., Santos, L., and Silva, M. M. (2007). Profile of drugs interactions in hospitalized children. *Pharm. Pract.* 5(4), 157–161. doi:10.4321/s1886-36552007000400003
- Medina-Barajas, F., Vásquez-Mendez, E., Perez-Guerrero, E. E., Sánchez-López, V. A., Hernández-Cañaveral, I. I., Real-Ornelas, G. A., et al. (2020). Pilot study: evaluation of potential drug–drug interactions in hospitalized pediatric patients. *Pediatr. Neonatol.* 61 (3), 279–289. doi:10.1016/j.pedneo.2019.11.006
- Meiners, M. M. M. A., and Bergsten-Mendes, G. (2001). Prescrição de medicamentos para crianças hospitalizadas: como avaliar a qualidade?. *Revista da Associação Médica Brasileira, São Paulo*. 47, 332–337. doi:10.1590/s0104-42302001000400036
- Micromedex Healthcare Series (2019). Greenwood village (Colorado): Thomson healthcare. Available online at: <https://www.micromedexsolutions.com/micromedex2/librarian/> (Accessed May 2019).
- Molina, R. C. M., Marcon, S. S., Uchimura, T. T., and Lopes, E. P. (2008). Caracterização das internações em uma unidade de terapia intensiva pediátrica, em um hospital-escola na região sul do Brasil. *Ciência, Cuid. Saúde* 7 (Suppl. m. 1), 112–120. doi:10.4025/cienccuidsaude.v7i0.6581
- Moura, C., Acúrcio, F., and Belo, N. (2009). Drug-drug interactions associated with the length of stay and cost of hospitalization. *J. Pharm. Pharmaceut. Sci.* 12 (3), 266–272. doi:10.18433/j35c7z
- Moura, C., Prado, N., and Acúrcio, F. (2011). Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. *Clin. Drug Invest.* 31 (5), 309–316. doi:10.1007/BF03256929
- Osokogu, O. U., Dukanovic, J., Ferrajolo, C., Dodd, C., Pacurariu, A. C., Bramer, W. M., et al. (2016). Pharmacoepidemiological safety studies in children: a systematic review. *Pharmacoepidemiol. Drug Saf.* 25, 861–870. doi:10.1002/pds.4041
- Paediatric Intensive Care Pharmacist's Special Interest Group Neonatal and Paediatric Pharmacists Group (2011). FC PICU Guidelines. Clinical pharmacy for paediatric critical care. (Brentford: NPPG), 12–27.
- Pollack, M. M., Holubkov, R., Reeder, R., Dean, J. M., Meert, K. L., and Berg, R. A. (2018). Pediatric intensive care unit (PICU) length of stay: factors associated with bed utilization and development of a benchmarking model. *Pediatr. Crit. Care Med.* 19 (3), 196–203. doi:10.1097/PCC.0000000000001425
- Queiroz, K. C. B., Nascimento, M. F. S., Fernandes, V., and Miotto, F. A. (2014). Drug interactions on the neonatal prescription at ICU-HGU. *UNOPAR Cient Ciênc Biol Saúde* 16 (3), 203–207. doi:10.17921/2447-8938.2014v16n3p25p
- Rao, C., Shenoy, V., and Udaykumar, P. (2019). Potential drug–drug interactions in the pediatric intensive care unit of a tertiary care hospital. *J. Pharmacol. Pharmacother.* 10, 63–68. doi:10.4103/jpp.JPP_27_19
- Reis, A. M. M., and Cassiani, S. H. D. B. (2011). Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. *Clinics* 66, 9–15. doi:10.1590/S1807-59322011000100003
- Rodrigues, A. T., Stahlschmidt, R., Granja, S., Pilger, D., Falcão, A. L. E., and Mazzola, P. G. (2017). Prevalence of potential drug-drug interactions in the intensive care unit of Brazilian teaching hospital. *Braz J Pharm Sci* 53 (1), e16109. doi:10.1590/s2175-97902017000116109
- Roque, K. E., Tonini, T., and Melo, E. C. P. (2016). Adverse events in the intensive care unit: impact on mortality and length of stay in a prospective study. *Cad. Saúde Pública*. 32 (10), e00081815. doi:10.1590/0102-311X00081815
- Santibáñez, C., Roque, J., Morales, G., and Corrales, R., (2014). Characteristics of drug interactions in a pediatric intensive care unit. *Rev. Chil. Pediatr.* 85 , 2014 (5), 546–553. doi:10.4067/S0370-41062014000500004
- Silva, D. C. B., Araujo, O. R., Arduini, R. G., Alonso, C. F. R., Shibata, A. R. O., and Troster, E. J. (2013). Adverse drug events in a pediatric intensive care unit: a prospective cohort. *BMJ Open* 3 , 2013 (2), e001868. doi:10.1136/bmjopen-2012-001868
- Silva, D. C. B. (2012). Eventos adversos medicamentosos em unidade de terapia intensiva pediátrica. Dissertação/tese de doutorado. São Paulo (Brazil): Faculdade de Medicina da Universidade de São Paulo.
- Smyth, R. M. D., Gargon, E., Kirkham, J., Cresswell, L., Golder, S., Smyth, R., et al. (2012). Adverse drug reactions in children—a systematic review. *PLoS One* 7 (3), e24061. doi:10.1371/journal.pone.0024061
- Spriet, I., Meersseman, W., de Hoon, J., von Winckelmann, S., Wilmer, A., and Willems, L. (2009). Mini-series: II. clinical aspects. Clinically relevant CYP450-mediated drug interactions in the ICU. *Intensive Care Med.* 35, 603–612. doi:10.1007/s00134-008-1383-2
- Vonbach, P., Dubied, A., Krahenbuhl, S., and Beer, J. H. (2008). Evaluation of frequently used drug interaction screening programs. *Pharm. World Sci.* 30, 367–374. doi:10.1007/s11096-008-9191-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Frequency and Severity of Adverse Drug Reactions to Medications Prescribed for Alzheimer's Disease in a Brazilian City: Cross-Sectional Study

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Background: There is lack of national studies that assess the risks associated with the drugs provided under the Brazilian public health system for treating Alzheimer's disease. Then, this study determined the prevalence and severity of self-reported adverse drug reactions (ADRs) prescribed to patients with Alzheimer's disease in the Brazilian public health system.

Methods: A cross-sectional study was carried out based on public data from the MEDEX system (information on dispensing data, known as exceptional dispensing medications) and interviews with patients and/or caregivers who get access to Alzheimer's drugs at a public pharmacy in a large Brazilian city, between July and September 2017, inquiring about ADRs and serious adverse events (SAEs).

Results: The subjects were asked about ADRs and SAEs related to the use of donepezil, galantamine, rivastigmine and memantine. Out of 285 patients enrolled on the database, 250 participated in the study (87.7%). Among the participants, approximately 63.0% were female, 70.3% aged ≥ 75 years and 70.3% had comorbidities. Overall, 209 patients (83.6%) reported at least one ADR (total 1,149 ADRs) and rivastigmine was associated with the largest number of ADRs per patient (7.9 ADRs/patient). The predominant adverse effects were psychiatric disorders with common frequency (57.1%) and mild severity (89.0%). Six patients (2.4%) had SAEs that required hospitalization. The use of antipsychotics was the variable associated with ADR (OR = 4.95; 95% CI: 1.45–16.93; $p = 0.011$).

Conclusion: There was a large number of reported ADRs and most of them were of common frequency and mild severity, being mainly related to psychiatric disorders. Considering the fragility of these patients, it is important to improve safety-related care in the use of drugs for treating this disease.

Keywords: Alzheimer's disease, safety, adverse reaction, pharmacoepidemiology, older adults

INTRODUCTION

Dementia is characterized by a cognitive decline that significantly impacts a person's ability to perform activities of daily living. Alzheimer's disease, the most common form of dementia, has become a major health problem worldwide, as the number of older adults continues to rise (Winblad et al., 2016). The number of older adults suffering from Alzheimer's disease totals 35.6 million globally and, by 2,050, this figure is set to increase to 115.4 million (Prince et al., 2013).

Brazil's population is around 210,158,000, consisting of approximately 20 million (9.5%) older adults aged 65 and above. Over the next few decades, the proportion of older adults will double and account for 21.9% of the total population (Instituto Brasileiro de Geografia e Estatística IBGE, 2019). However, determining dementia prevalence in the Brazilian population is difficult due to the regional nature of the studies available, which may not be representative of the country as a whole (Fagundes et al., 2011).

A systematic review of studies published up until 2010, found a prevalence of Alzheimer's disease among Brazilian older adults of 11.1%. According to the authors, this figure is above the average found for other countries, but similar to rates reported in Latin America and the Caribbean (Fagundes et al., 2011).

The Specialized Component of Pharmaceutical Services is an important Brazilian strategy aimed at ensuring access to drugs provided by the Unified Health System (Sistema Único de Saúde). This strategy is characterized by providing better care to patients at ambulatory levels and its guidelines are defined by the Brazilian Ministry of Health (Brasil, 2017). It is important to mention that Brazilian guidelines are according to the international recommendation (National Institute for Health and Clinical Excellence - NICE, 2018; BMJ Best Practice, 2019).

Since 2002, drug therapies for the treatment of Alzheimer's disease have been funded by the national public health system. These medicines include anticholinergic drug (donepezil, galantamin and rivastigmine) as first drugs of choice for treatment whereas the N-methyl-D-aspartate receptor antagonist (memantine) was included in the list of medicines provided in 2017 (Brasil, 2017). Such drugs contribute to an improvement in the clinical conditions of patients with Alzheimer's disease with modest efficacy, but safety data that can differ. A systematic review showed an enhancement of cognitive effects for all drugs and behavioural benefits for donepezil 10 mg and galantamine 24 mg. There was a larger number of dropouts and adverse events occurring with the cholinesterase inhibitors when compared to memantine (Tan et al., 2014).

Cognitive deficit, low adherence to drug therapy and increased sensitivity to anticholinergic drugs are risk factors for adverse reactions in patients with dementia (Laroche et al., 2013). In addition, older age is frequently accompanied by polypharmacy, comorbidity and frailty (Davies and O'Mahony, 2015). Managing this scenario has proven challenging for health care systems and health policymakers (Laroche et al., 2013).

The increasing attention to drug safety and the lack of national studies to assess the risks associated with the drugs provided

under the public health system for treating Alzheimer's disease prompted this study. Patients' reports on adverse drug reactions (ADRs) may be an important source of information for their safety and that may be unavailable from other sources (Wetzels et al., 2008; Zhu et al., 2011).

This cross-sectional study determined the prevalence and the severity of self-reported ADRs caused by the use of these medications by patients enrolled in the public health system, in a large Brazilian city.

METHODS

Study Design

This cross-sectional study investigating ADRs to medications prescribed for the treatment of Alzheimer's disease, self-reported by patients enrolled in the Brazilian public health system, the Unified Health System (Sistema Único de Saúde - SUS), was conducted in Sorocaba city, São Paulo state, Brazil. The Brazilian public health system comprises a number of health actions and services delivered by federal, state and municipal public organizations and institutions (Brasil, 2000).

Data were obtained from the MEDEX system and from interviews carried out with patients and/or caregivers.

Eligibility Criteria of Study Population

Patients were considered eligible if diagnosed with International Classification of Diseases code (ICD 10): F00 (dementia in Alzheimer's disease), F00.0 (dementia in early-onset Alzheimer's disease), F00.1 (dementia in late-onset Alzheimer's disease), F00.2 (dementia in Alzheimer's disease, atypical or mixed form), F00.9 (dementia, unspecified in Alzheimer's disease) and G30 (Alzheimer's disease), G30.0 (early-onset Alzheimer's disease), G30.1 (late-onset Alzheimer's disease), G30.8 (other forms of Alzheimer's disease), G30.9 (Alzheimer's disease, unspecified). They were previously registered on the MEDEX system for drug dispensing and taking at least one of the following drugs: donepezil, galantamine, rivastigmine and memantine.

The interviewed subjects were the patients and/or their caregiver (aged 18 or above, considered to be involved in the daily care of the patient, regardless of being a relative or not). When the patient and caregiver were present, both were interviewed. Patients with insufficient registered data were excluded from the study.

Study Site

Sorocaba is a major city within a metropolitan area located 92 km southeast of São Paulo city, capital of the São Paulo state, Brazil. The area of the city consists of 450,382 km² and its population is approximately 671,186 (2018 estimate) (Instituto Brasileiro de Geografia e Estatística - IBGE, 2018).

The interviews were performed at the specialty drugs pharmacy. There are 40 such pharmacies in the state of São Paulo. The unit located in Sorocaba serves the patients of Sorocaba and also 48 other municipalities under the DRS-XVI (Regional Health Department - XVI). It is one of 17 departments

comprising the administrative division of the Health Department for São Paulo State. It is part of Sorocaba city and it is in charge of coordinating the activities of the Department at a regional level and interfacing with municipalities and non-governmental organizations.

Data Collection

In order to identify eligible patients, the researchers obtained data from the MEDEX system, for the period between December 2016 and April 2017. The gathered information included database registration date, health unit of origin, ICD-10 for Alzheimer's disease and the provided drug. The enrolment status of patients on the MEDEX system is considered active while there is monthly dispensing of drugs.

The interviews with patients/caregivers were carried out at the time of patients were visiting the pharmacy to collect their medications. A pharmacy employee would notify the research team that a patient was waiting to collect their medications and the researchers would then introduce themselves. Patients that met the inclusion criteria were then invited to participate in the study. All patients/caregivers consented. All interviews took place between July and September 2017.

The questionnaire used for gathering data was developed by experts and considered the recommendation consistent across guidelines (Brasil, 2017; National Institute for Health and Clinical Excellence - NICE, 2018). There was also a pilot study testing. The researchers were trained on the proper use of scientific terminology, time spent, and the way of conducting the interviews.

The author asked patients and/or caregivers to get sociodemographic data (gender, age and assisted by caregiver or not) and the period concerning the use of the drug. The information was cross-checked with the MEDEX system. Clinical information (previous diagnosis, previous treatments, comorbidities, type of medical care, other concomitant medicines and polypharmacy) was collected too. There is no international consensus on the definition of polypharmacy. The most commonly used definition stipulates the number of concurrent drugs and the definition adopted was concerning the use of five or more medications (Laroche et al., 2013).

We also booked a second interview when the information was insufficient or when answers were not consistent. This interview was through telephone calls to the patients' caregivers or other family members who knew about the patient's drug treatment.

Adverse Drug Reactions Reporting

ADR or adverse effect is any response to a medicine or medicinal product that is "noxious and unintended," and which normally occurs in doses used in humans for the prophylaxis, diagnosis, or therapy of the disease or for the modification of physiological function (VigiAccess®, 2018).

Serious Adverse Event (SAE) is a medical occurrence that at any dose may result in death, require patient hospitalization or extension of hospitalization period. Also, it may create persistent or significant disability/incapacity, or a congenital anomaly/birth defect (VigiAccess®, 2018).

The authors collected information regarding to the self-reported of ADRs or SAEs similar to Tadesse et al. (2014). In addition, a questionnaire contained the adapted Naranjo algorithm (Pathirana et al., 2009; Lopes et al., 2014) was applied in order to establish causality for the adverse effect. The probable and definitive events were used to determine type, severity and frequency.

The characterization of ADRs was done based on the physiological system, according to the classification used by VigiBase (VigiAccess®, 2018). The treatment for Alzheimer's disease can entail use of one medication or in association with memantine (the association commercially available in Brazil is only donepezil with memantine). Therefore, ADRs associated with drug combinations were also defined as "ADR reported by patient and/or caregiver, but not described in medication package insert."

ADRs severity was categorized as: mild (not requiring specific treatment or antidotes or discontinuation of treatment); moderate (requiring change in drug therapy, and although discontinuation of treatment is unnecessary, hospitalization might be prolonged, requiring specific treatment); severe (potentially lethal, requiring suspension of the drug and specific treatment of the ADR and certainly prolonging hospitalization); and lethal (contributing directly or indirectly to patient death) (Pearson et al., 1994).

The frequency of ADRs was categorized as: very common $\geq 1/10$ ($\geq 10\%$), common $\geq 1/100$ and $< 1/10$ (≥ 1 and $< 10\%$), uncommon $\geq 1/1000$ and $< 1/100$ (≥ 0.1 and $< 1\%$), rare $\geq 1/10,000$ and $< 1/1,000$ ($\geq 0.01\%$ and $< 0.1\%$), very rare $< 1/10,000$ ($< 0.01\%$) and unknown (described in package insert as ADR observed at post-commercialization stage but not during drug trials; these ADRs were not classified by frequency) (Meyboom and Egberts, 1999).

Reports of possible ADRs not described in the package insert were defined as "ADR reported by patient and/or caregiver, but not described in medication package insert."

Statistical Analyses

Categorical variables were expressed as absolute and relative frequencies. Proportions were compared using the Chi-square test or Fisher's exact test. Differences were considered significant when $p < 0.05$.

To identify the characteristics of the population associated with the occurrence of ADR, we used the binary and multivariable logistic regression analysis. After the binary logistic regression analysis, the variables with $p < 0.20$ were included in the multivariable analysis.

The statistical analysis was carried out using Stata, version 12.0 and software Bioestat® (version 5.3 Mamiraua Institute) software's. Values of $p < 0.05$ were deemed statistically significant.

Ethical Issues

This study was approved by the Research Ethics Committee of the University of Sorocaba (protocol number: 1860724). All subjects enrolled in the study were informed of the aims of the studies and signed a free and detailed consent form.

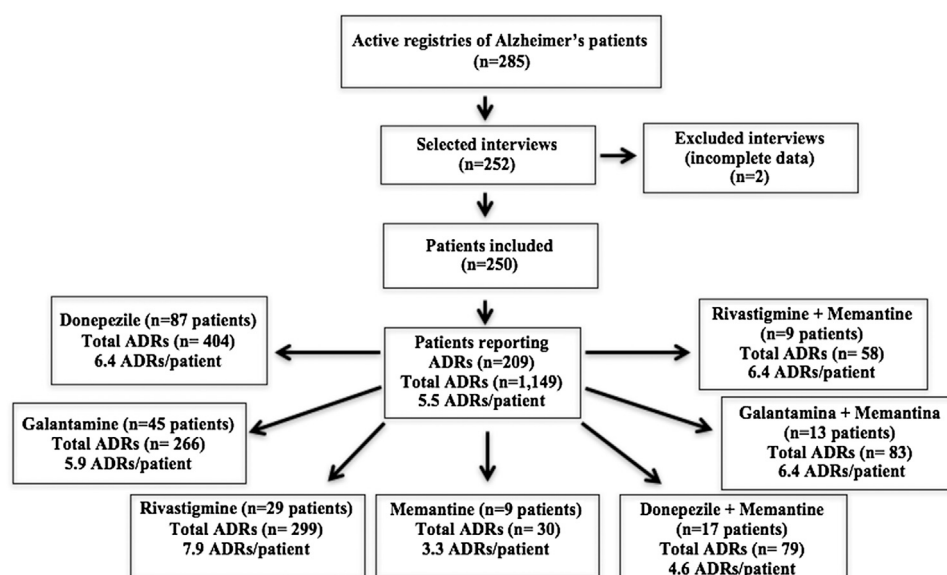


FIGURE 1 | Flowchart depicting study process.

RESULTS

Among all 285 patients enrolled at the public pharmacy for treatment of Alzheimer's disease, 252 (88.4%) were interviewed. Two interviews were subsequently excluded for not containing the necessary information for the study, generating a final sample of 250 patients (87.7%). Out of the total sample, 209 patients (83.6%) reported at least one possible ADR. Rivastigmine was associated with the largest number of ADRs per patient (7.9 ADRs/patient) followed by galantamine (5.9 ADRs/patient). Most patients (81.3%) used only a single medicine for treatment of Alzheimer's disease and, on average, had more than one adverse effect related to the drugs (Figure 1).

The majority of patients were female (63.1%), aged ≥ 75 years (70.3%) and had been diagnosed with Alzheimer for 2–5 years (57.4%). The patients were being treated mainly with donepezil (46.1%). The drug combination was less frequent with donepezil + memantine which was used by only 8.1% of the patients. The treatment period varied between 1 and 10 years. Approximately 55.0% of the patients were assisted by a caregiver, usually a relative. A total of 70.3% of the patients suffered from comorbidities, the most cited being systemic arterial hypertension, diabetes mellitus, hypercholesterolemia and hypothyroidism (data not shown). Polypharmacy was reported in 32.5% of the assessed cases and most participants (65.5%) used the private health sector for medical visits. All 209 patients used a total of 906 drugs (average of 4.5 drug/person), with most ADRs being related to donepezil and galantamine (Table 1).

The most widely used drugs were to treat diseases of the cardiovascular system (33.0%) and central nervous system (25.0%) being mainly: selective serotonin reuptake inhibitors (ATC: N06AB); Beta blocking agents, non-selective (ATC: C07AA); angiotensin II receptor blockers (ATC: C09CA) and diazepam, oxazepam, thiazepam and oxepin (ATC: N05AH) (data not show).

According to causality score, the events related to the Alzheimer drugs classified as probable or definitive were shown in Tables 2–4.

Table 2 describes possible ADRs according to physiological systems and frequency. Effects were reported predominantly for donepezil and galantamine and mainly related to psychiatric disorders, being 25.5% for donepezil and 25.5% for galantamine. The most commonly reported effects for donepezil were agitation, vertigo, insomnia and headaches (considered common or very common). The most commonly reported effects for galantamine were somnolence, depression, malaise (considered common) and hallucinations (rare). Confusion, anxiety, agitation and headaches were the effects most commonly reported for rivastigmine and also considered common.

Among all 1,149 ADRs reported, most were classified as “common” (46.3%), 5.3% were of unknown frequency and approximately 24% of ADRs were not described in the medication package insert (there were patient/caregiver reports of the effect, but this was not described in the medication package insert). No uncommon ADRs were reported for donepezil, but for galantamine, rivastigmine and memantine, 7.1% of ADRs were classified as “uncommon.” Galantamine presented the most “very rare” ADRs, although the total number of these reactions was very small (Table 3).

TABLE 1 | Sociodemographic and clinical characteristics of Alzheimer's disease patients reporting ADRs due to drug therapy (n = 209)

Variables	Donepezil 87 (41.6%) n (%)	Galantamine 45 (21.5%) n (%)	Rivastigmine 29 (13.8%) n (%)	Memantine 9 (4.3%) n (%)	Donepezil and memantine 17 (8.1%) n (%)	Galantamine and memantine 13 (6.2%) n (%)	Rivastigmine and Memantine 9 (4.3%) n (%)	Total 209 (100%) n (%)	p-value
Sex (n)									
Female	60 (69.0)	21 (47.0)	18 (62.0)	6 (67.0)	11 (65.0)	7 (54.0)	9 (100)	132 (63.1)	0.0002 ^a
Male	27 (31.0)	24 (53.3)	11 (38.0)	3 (34.0)	6 (35.3)	6 (46.1)	0	77 (36.8)	—
Age (years)									
≤64	8 (9.2)	0	1 (3.4)	0	1 (5.9)	1 (7.7)	0	11 (5.3)	—
≥65–74	19 (22.0)	11 (24.4)	11 (38.0)	2 (22.2)	5 (29.4)	2 (15.4)	0	50 (24.0)	0.0002 ^a
≥75	60 (69.0)	34 (75.5)	17 (58.6)	7 (77.7)	11 (5.9)	10 (77.0)	9 (100.0)	148 (71.0)	—
Not stated	0	0	0	0	0	0	0	0	—
Time of diagnosis of disease (years)									
0–2	8 (9.2)	2 (4.4)	4 (14.0)	1 (11.1)	1 (5.9)	0	0	16 (7.6)	<0.0001 ^a
>2–5	55 (63.2)	27 (60.0)	10 (34.6)	3 (33.3)	9 (52.9)	10 (77.0)	4 (44.4)	118 (56.4)	
>5–10	20 (23.0)	13 (29.0)	10 (34.4)	3 (34.0)	6 (35.3)	3 (23.0)	5 (55.5)	60 (28.7)	
>10	3 (3.4)	1 (2.2)	3 (10.3)	0	1 (5.9)	0	0	8 (3.8)	
Not stated	1 (1.1)	2 (4.4)	2 (6.9)	2 (22.2)	0	0	0	7 (3.3)	
Time of use of drug (years)									
0–1	12 (13.8)	5 (11.1)	4 (13.8)	2 (22.2)	1 (5.9)	0	1 (11.1)	25 (12.0)	<0.0001 ^a
>1–2	21 (24.1)	11 (24.4)	4 (13.8)	2 (22.2)	5 (29.4)	4 (30.7)	0	47 (22.5)	
>2–3	20 (23.0)	2 (4.4)	2 (6.9)	1 (11.1)	2 (11.7)	2 (15.4)	2 (22.2)	31 (15.0)	
>3–5	13 (15.0)	13 (29.0)	4 (13.8)	2 (22.2)	4 (23.5)	3 (23.0)	1 (11.1)	40 (19.1)	
>5–10	14 (16.0)	10 (22.2)	9 (31.0)	2 (22.2)	3 (17.6)	2 (15.4)	4 (44.4)	44 (21.0)	
>10 or more	3 (3.4)	3 (6.6)	4 (13.8)	0	1 (5.9)	0	0	11 (5.3)	
Not stated	4 (4.1)	1 (2.2)	2 (6.9)	0	1 (5.9)	2 (15.4)	1 (11.1)	11 (5.3)	
Caregiver (n)									
None	14 (16.1)	3 (6.6)	5 (17.2)	0	0	0	0	22 (10.5)	<0.0001 ^a
1	55 (63.2)	22 (49.0)	15 (52.0)	1 (11.1)	11 (65.0)	9 (69.2)	3 (33.3)	116 (55.5)	
2–4	13 (16.0)	16 (35.6)	6 (20.8)	2 (22.2)	4 (23.5)	2 (15.4)	5 (55.5)	49 (23.4)	
>4	3 (3.4)	1 (2.2)	0	4 (44.4)	1 (5.9)	2 (15.4)	0	11 (5.3)	
Not stated	2 (2.2)	3 (6.6)	3 (10.3)	2 (22.2)	1 (5.9)	0	1 (11.1)	11 (5.3)	
Medical care									
Public	55 (63.2)	14 (31.1)	8 (27.6)	1 (11.1)	3 (17.6)	2 (15.4)	1 (11.1)	57 (27.3)	<0.0001 ^a
Private	4 (4.6)	28 (62.2)	18 (62.0)	6 (66.7)	13 (76.5)	11 (84.6)	6 (66.7)	137 (65.5)	
Not stated	—	3 (6.7)	3 (10.3)	2 (22.2)	1 (5.9)	0	2 (22.2)	15 (7.2)	
Comorbidities									
Yes	68 (78.2)	31 (69.0)	21 (72.4)	5 (55.5)	9 (53.0)	8 (61.5)	5 (55.5)	147 (70.3)	<0.0001 ^a
No	11 (12.6)	11 (24.4)	2 (6.9)	0	3 (17.6)	1 (7.7)	0	17 (8.1)	
Not stated	—	—	6 (20.6)	4 (44.4)	5 (29.4)	4 (30.7)	4 (44.4)	45 (2.5)	
Comorbidities (n)	138	66	52	18	21	14	12	321	
Polypharmacy#									
Yes	15 (17.2)	13 (29.0)	11 (38.0)	8 (89.0)	9 (53.0)	6 (46.1)	6 (67.0)	68 (32.5)	<0.0001 ^a
No	54 (62.0)	27 (60.0)	17 (58.6)	1 (11.1)	8 (47.0)	7 (54.0)	3 (33.3)	117 (56.0)	
Not stated	18 (20.7)	5 (11.1)	1 (3.4)	0	0	0	0	24 (11.5)	
Medications (n)	224	194	142	70	101	65	68	874	

n, number. # Polypharmacy, use of five or more medications.

^aStatistically significant difference on Chi-square test, $p < 0.05$.

Table 4 describes the reported ADRs, adequate measures to handle them and their classification according to severity. The caregiver is the individual that most frequently recognized certain symptoms as ADRs (56.0%). Most ADRs were considered of mild severity (89.0%). Six patients (2.4%) reported SAEs leading to hospitalization (galantamine $n = 5$ and donepezil $n = 1$), which involved nausea, vomiting, abdominal discomfort, diarrhea, dehydration and syncope.

In **Table 5**, we showed the crude and adjusted analyses, which aimed at identifying patients' characteristics regardless of the association with ADR. After the adjusted analyses, the use of

antipsychotics was the variable associated with ADR (Odds Ratio = 4.95; 95% CI: 1.45–16.93; $p = 0.011$).

DISCUSSION

Summary of Evidence and Comparison to the Findings of Previous Studies

The study comprises a sample of patients with Alzheimer's disease who were users of the Brazilian public health system in the city of Sorocaba, State of São Paulo. The assessed

TABLE 2 | Prevalence of self-reported adverse effects to medications used for treatment of Alzheimer's disease according to physiological system and frequency (n = 1,149)

Physiological systems	Donepezil	Galantamine	Rivastigmine	Memantine	Donepezil + memantine	Galantamine + memantine	Rivastigmine + memantine	Total
Central nervous system disorders	103 (25.5)	68 (25.5)	58 (25.3)	6 (20.7)	19 (24.0)	27 (32.5)	13 (22.4)	294
Dizziness	40 (10.0) ^b	0	14 (6.1) ^a	0	4 (5.0) ^a	2 (2.4) ^g	2 (3.4) ^g	62
Syncope	10 (2.5) ^b	3 (1.1) ^b	2 (0.9) ^c	0	1 (1.3) ^g	0	0	16
Convulsion	3 (0.7) ^f	2 (0.7) ^e	2 (0.9) ^d	1 (3.4) ^e	3 (3.8) ^g	0	0	11
Headache	31 (7.7) ^a	10 (3.7) ^b	16 (7.0) ^b	1 (3.4) ^b	4 (5.0) ^g	1 (1.2) ^g	4 (6.9) ^g	67
Tremor	0	9 (3.4) ^b	12 (5.2) ^b	0	0	2 (2.4) ^g	3 (5.2) ^g	26
Somnolence	2 (0.5) ^g	36 (13.5) ^b	9 (0.9) ^b	0	2 (2.5) ^g	13 (15.7) ^g	3 (5.2) ^g	65
Lethargy	0	4 (1.5) ^b	0	0	0	3 (3.6) ^g	0	7
Balance disorders	17 (4.2) ^b	4 (1.5) ^b	3 (1.3) ^c	4 (13.8) ^g	5 (6.3) ^g	6 (7.2) ^g	1 (1.7) ^g	40
General disorders	19 (4.7)	27 (10.1)	24 (10.5)	6 (20.7)	4 (5.0)	11 (13.2)	3 (5.2)	94
Asthenia	0	1 (0.4) ^b	0 (0)	0	0	1 (1.2) ^g	0	2
Fatigue (tiredness)	19 (4.7) ^b	9 (3.4) ^b	20 (8.7) ^b	2 (6.9) ^c	3 (3.8) ^g	5 (6.0) ^g	2 (3.4) ^g	60
Malaise	0	16 (6.0) ^b	2 (0.9) ^b	0	0	4 (4.8) ^g	0	22
Ataxia	0	1 (0.4) ^g	2 (0.9) ^b	4 (13.8) ^c	1 (1.3) ^g	1 (1.2) ^g	1 (1.7) ^g	10
Gastrointestinal disorders	52 (12.9)	49 (18.4)	24 (10.5)	2 (6.9)	10 (12.6)	8 (9.6)	6 (10.3)	151
Nausea	12 (2.9) ^a	13 (4.9) ^a	9 (0.9) ^a	0	3 (3.8) ^g	2 (2.4) ^g	3 (5.2) ^g	42
Vomiting	8 (2.0) ^b	12 (4.5) ^a	4 (1.7) ^a	0	1 (1.3) ^g	0	0	25
Abdominal discomfort	3 (0.7) ^b	11 (4.1) ^b	5 (2.2) ^b	2 (6.9) ^g	3 (3.8) ^g	3 (3.6) ^g	1 (1.7) ^g	28
Diarrhea	28 (7.0) ^a	8 (3.0) ^b	6 (2.6) ^a	0	3 (3.8) ^a	2 (2.4) ^g	2 (3.4) ^g	49
Dyspepsia	1 (0.2) ^g	5 (1.9) ^c	0	0	0	1 (1.2) ^g	0	7
Psychiatric disorders	152 (37.6)	37 (14.0)	93 (40.6)	14 (48.3)	34 (43.0)	19 (22.9)	30 (51.7)	379
Hallucinations	22 (5.4) ^f	19 (7.1) ^e	6 (2.6) ^f	6 (20.7) ^c	5 (6.3) ^g	11 (13.2) ^g	4 (6.9) ^g	73
Agitation	34 (8.4) ^f	1 (0.4) ^g	18 (7.8) ^b	0	10 (12.6) ^a	0	6 (10.3) ^g	69
Aggression	20 (5.0) ^g	0	1 (0.4) ^f	0	8 (10.1) ^g	0	0	29
Anxiety	0	0	20 (8.7) ^b	0	0	0	5 (8.6) ^g	25
Depression	1 (0.2) ^g	17 (6.4) ^b	8 (3.5) ^c	0	0	6 (7.2) ^g	3 (5.2) ^g	35
Insomnia	39 (9.6) ^b	0	10 (4.4) ^c	0	4 (5.0) ^g	1 (1.2) ^g	2 (3.4) ^g	56
Mental confusion	10 (2.5) ^g	0	21 (9.2) ^b	8 (27.6) ^c	2 (2.5) ^a	1 (1.2) ^g	8 (13.8) ^g	50
Sleep disorders	26 (6.4) ^b	0	9 (4.0) ^g	0	5 (6.3) ^g	0	2 (3.4) ^g	42
Heart diseases	2 (0.5)	4 (1.5)	0	0	1 (1.3)	1 (1.2)	0	6
Bradycardia	2 (0.5) ^g	1 (0.4) ^b	0	0	1 (1.3) ^g	1 (1.2) ^g	0	5
Palpitation	0	3 (1.1) ^c	0	0	0	0	0	3
Metabolism and nutrition disorders	4 (1.0)	37 (14.0)	10 (4.3)	0	1 (1.3)	11 (13.2)	1 (1.7)	64
Decreased appetite	0	16 (6.0) ^b	6 (2.6) ^a	0	0	2 (2.4) ^g	0	24
Dehydration	0	7 (2.6) ^c	1 (0.4) ^f	0	0	3 (3.6) ^g	1 (1.7) ^g	12
Weight loss	1 (0.2) ^g	14 (5.2) ^b	3 (1.3) ^b	0	0	4 (4.8) ^g	0	22
Anorexia	3 (0.7) ^b	0	0	0	1 (1.3) ^g	2 (2.4) ^g	0	6
Skin and subcutaneous tissue disorders	1 (0.2)	1	3 (1.3)	0	0	0	2 (3.4)	7
Hyperhidrosis	1 (0.2) ^g	1 (0.4) ^c	0	0	0	0	1 (1.7) ^g	3
Pruritus (itching)	0	0	3 (1.3) ^d	0	0	0	1 (1.7) ^g	4
Vascular disorders	0	1 (0.4)	0	1 (3.4)	1 (1.3)	0	1 (1.7)	4
Hypertension	0	0	0	1 (3.4) ^b	1 (1.3) ^g	0	1 (1.7) ^g	3
Hypotension	0	1 (0.4) ^c	0	0	0	0	0	1
Musculoskeletal disorders	44 (10.9)	22 (8.3)	16 (7.0)	0	4 (5.0)	4 (4.8)	0	90
Muscle spasms	24 (6.0) ^b	5 (1.9) ^b	0	0	3 (3.8) ^g	0	0	32
Myalgia	18 (4.5) ^b	4 (1.5) ^g	7 (3.0) ^b	0	0	0	0	29
Muscle weakness	1 (0.2) ^g	13 (4.9) ^c	9 (4.0) ^b	0	0	4 (4.8) ^g	0	27
Rhabdomyolysis	1 (0.2) ^g	0	0	0	1 (1.3) ^g	0	0	2
Respiratory diseases	10 (2.5%)	2 (0.7)	0	0	1 (1.3)	0	1 (1.7)	14
Dyspnea	0	1 (0.4) ^g	0	0	0	0	1 (1.7) ^g	2
Hiccups	0	1 (0.4) ^g	0	0	0	0	0	1
Common cold	10 (2.5) ^b	0	0	0	1 (1.3) ^a	0	0	11
Infections and infestations	15 (3.7)	0	0	1 (3.4)	4 (5.0)	0	0	20
Urinary tract infection	14 (3.5) ^g	0	0	1 (3.4) ^g	4 (5.0) ^a	0	0	19
Nasopharyngitis	1 (0.2) ^g	0	0	0	0	0	0	1
Hepatobiliary disorders	0	11 (4.1)	1 (0.4)	0	0	2 (2.4)	1 (1.7)	15
Hepatitis	0	2 (0.7) ^e	1 (0.4) ^g	0	0	0	1 (1.7) ^g	4
Blurred vision	0	9 (3.4) ^c	0	0	0	2 (2.4) ^g	0	11

(Continued on following page)

TABLE 2 | (Continued) Prevalence of self-reported adverse effects to medications used for treatment of Alzheimer's disease according to physiological system and frequency (n = 1,149)

Physiological systems	Donepezil	Galantamine	Rivastigmine	Memantine	Donepezil + memantine	Galantamine + memantine	Rivastigmine + memantine	Total
Ear and inner ear disorders	2 (0.5)	7 (2.6)	0	0	0	0	0	9
Vertigo	2 (0.5) ^a	6 (2.2) ^b	0	0	0	0	0	8
Dizziness	0	1 (0.4) ^c	0	0	0	0	0	1
Total ADRs	404 (100.0)	266 (100.0)	229 (100.0)	30 (100.0)	79 (100.0)	83 (100.0)	58 (100.0)	1,149

ADR, adverse drug reaction.

^aVery common (10% frequency).

^bCommon (1–10% frequency).

^cUncommon (0.1–1% frequency).

^dRare (0.01–0.1% frequency).

^eVery rare (frequency <0.01%).

^fUnknown (described on medication package insert as adverse effect seen only at post-commercialization stages, not classified for frequency).

^gADR reported by patient and/or caregiver, but not described in medication package insert.

Physiological system has been classified according to Vigibase.

TABLE 3 | Prevalence of self-reported adverse effects to medications commonly used for treating Alzheimer disease according to frequency (n = 1,149).

ADR frequency	Donepezil n (%)	Galantamine n (%)	Rivastigmine n (%)	Memantine n (%)	Donepezil and memantine n (%)	Galantamine and memantine n (%)	Rivastigmine and memantine n (%)	Total n (%)
Very common ^a	71 (17.6)	25 (9.4)	39 (17.0)	0	24 (30.4)	0	0	159 (13.8)
Common ^b	217 (54.0)	170 (64.0)	144 (62.9)	2 (6.7)	0	0	0	533 (46.3)
Uncommon ^c	0	39 (14.7)	23 (10.0)	20 (66.7)	0	0	0	82 (7.1)
Rare ^d	0	0	5 (2.2)	0	0	0	0	5 (0.4)
Very rare ^e	0	24 (9.0)	6 (2.6)	1 (3.3)	0	0	0	31 (2.7)
Unknown ^f	59 (14.6)	0	2 (0.8)	0	0	0	0	61 (5.3)
Not described in medication package insert ^g	57 (14.1)	8 (3.0)	10 (4.4)	7 (23.3)	55 (69.6)	83 (100.0)	58 (100.0)	278 (24.2)
Total	404 (100.0)	266 (100.0)	229 (100.0)	30 (100.0)	79 (100.0)	83 (100.0)	58 (100.0)	1149 (100.0)

ADR, adverse drug reaction.

^aVery common (10% frequency).

^bCommon (1–10% frequency).

^cUncommon (0.1–1% frequency).

^dRare (0.01–0.1% frequency).

^eVery rare (<0.01%).

^fUnknown (described in medication package insert as adverse effect seen only at post-commercialization stages, not classified for frequency).

^gADR reported by patient or caregiver, but not described in medication package insert.

population was predominantly female, aged 75 or older, suffered from other comorbidities and required at least one caregiver (usually a family member). Also, the patients were unable to take medications without assistance and used the private health sector for most visits.

National scientific literature has also shown that females are more likely to develop Alzheimer's disease than males (Fagundes et al., 2011; Barros De Matos and Decesaro, 2012). A study showed that postmenopausal females, between 40 and 60 years old, when compared to premenopausal females, had lower levels of glucose in the brain and also exhibited higher levels of mitochondrial dysfunction. This phenomenon might cause diminished energy processing and reduced memory, which can be linked to dementia (Fagundes et al., 2011).

Almost 70% of patients suffered from at least one other disease; this might be due to the advanced age of the assessed subjects. Among the reported comorbidities, systemic arterial

hypertension, diabetes, hypothyroidism and hypercholesterolemia were the most frequent ones. According to the scientific literature, hypertension, dyslipidemias, hyperinsulinemias, type 2 diabetes, obesity, atherosclerosis and arrhythmias are associated with increased risk for cognitive deficit, dementia and Alzheimer's disease (Kalaria et al., 2008). A study involving 130 older Brazilian adults with this disease discovered that 75% of these individuals also suffered from another disease, with the main prevalence of hypertension (53.3%) and diabetes mellitus (21.7%) (Barros De Matos and Decesaro, 2012).

Although patients collected their medications from the public health system, most of them used the private sector for medical appointments and exams. This may be due to the high cost of these medications (Brasil, 2013) and to the fact that the private health sector is a faster option for medical treatment, more readily providing the exams required to meet the criteria determined by the national health services.

TABLE 4 | Clinical aspects of Alzheimer's disease patients and self-reported ADRs (n = 209).

Variables	Donepezil (n = 87) n (%)	Galantamine (n = 45) n (%)	Rivastigmine (n = 29) n (%)	Memantine (n = 9) n (%)	Donepezil and memantine (n = 17) n (%)	Galantamine and memantine (n = 13) n (%)	Rivastigmine and memantine (n = 9) n (%)	Total n (%)	p-value
Individual identifying adverse effect									
Patient	7 (8.0)	2 (4.4)	4 (13.7)	0	0	0	1 (11.1)	14 (6.7)	tbl4fnlowast < 0.0001 ^a
Caregiver	74 (85.0)	40 (88.9)	24 (82.7)	4 (44.4)	16 (94.1)	12 (92.3)	7 (77.7)	177 (86.0)	
Health professional	6 (6.8)	3 (6.6)	1 (3.4)	5 (55.5)	1 (5.9)	1 (7.7)	1 (11.1)	18 (8.8)	
Adverse effect severity									
Mild	79 (91.0)	36 (80.0)	25 (86.2)	9 (100.0)	16 (94.1)	12 (92.3)	9 (100.0)	186 (89.0)	tbl4fnlowast < 0.0001 ^a
Moderate	7 (8.0)	4 (8.9)	4 (13.7)	0	1 (5.9)	1 (7.7)	0	17 (8.1)	
Severe	1 (1.1)	5 (11.1)	0	0	0	0	0	6 (2.9)	
Adverse effect									
Discontinuation or switch of medication	9 (10.3)	4 (8.9)	4 (13.7)	0	1 (5.9)	1 (7.7)	0	19 (9.1)	tbl4fnlowast < 0.0001 ^a
Hospitalization	1 (1.1)	5 (11.1)	0	0	0	0	0	6 (2.9)	
No change	77 (88.5)	36 (80.0)	25 (86.2)	9 (100.0)	16 (94.1)	12 (92.3)	9 (100.0)	184 (88.0)	

^aStatistically significant difference on Chi-square test, p < 0.05.

The most used medications were donepezil and galantamine. Most of the patients (83.5%) reported at least one ADR which involved mainly donepezil and galantamine although the largest number of ADRs per patient referred to rivastigmine (7.9 ADRs per patient) and galantamine (5.9 ADRs per patient). There was a small number of prescriptions for memantine due to the fact that this drug was only available through the public health system in the year of 2017, which coincided with the year of the data collection.

In general, mild severity and common frequency were the adverse effects. The reported effects were mostly associated with psychiatric disorders, insomnia, agitation, and sleep disorders being the most commonly reported effect. Although hallucination was considered a rare effect, it was reported by patients that used galantamine. Among the treatments for the most common diseases in the patients who were studied, adjusted analyses showed that the use of antipsychotics was the variable associated with ADR.

The use of galantamine, rivastigmine and memantine was associated with rare or very rare ADRs, accounting for 3.8% of all samples and mainly due to galantamine. Approximately 2.5% of SAEs resulted in hospitalization due to the use of galantamine (n = 5 patients) and donepezil (n = 1 patient), leading to gastrointestinal complications which involved nausea, vomiting, abdominal discomfort, diarrhoea, dehydration and syncope.

The findings of this study corroborate data from the Vigibase database, an international drug monitoring program created by the World Health Organization, showing a larger number of suspected ADRs caused by donepezil and rivastigmine (Vigibase®, 2018). The main ADR reports described for donepezil (agitation, vertigo, insomnia and headache), galantamine (somnia, depression and malaise), and rivastigmine (mental confusion, hallucination, ataxia and impaired balance) are also among the most commonly reported reactions in the Vigibase database (Vigibase®, 2018).

Effects were predominantly reported for donepezil and galantamine and mainly related to psychiatric disorders, being 25.5% for donepezil and 25.5% for galantamine. The most commonly reported effects for donepezil were agitation, vertigo, insomnia and headaches (with common or very common frequency). The most commonly reported effects for galantamine were somnolence, depression, malaise (considered common) and hallucinations (rare). Confusion, anxiety, agitation and headaches were the effects most commonly reported for rivastigmine and also considered of common frequency. The main ADR reports described for donepezil, galantamine and rivastigmine were also the most commonly reported reactions in the Vigibase database (Vigibase®, 2018).

An observational study collected information from a French database of spontaneous notification of adverse events related to the use of anticholinergic drug. Although the population in this study does not represent the population with Alzheimer's disease, it is noteworthy that around 31% (n = 118) of the observed drug interactions were responsible for ADRs that involved mainly the cardiovascular system (bradycardia, atrioventricular block and hypotension) and central nervous system (mainly causing mental confusion) (Tavassoli et al., 2007). Future studies may consider collecting information regarding the role of drug interactions in causing ADRs in the population with Alzheimer's disease or other dementias.

TABLE 5 | Crude and adjusted analyses of adverse drug reactions (ADR) according to demographic and health variables and polypharmacy in patients with Alzheimer's disease (n = 244)

Variables	ADR (%)	Crude analyses OR (95%CI)	p value ^a	Adjusted analyses OR (95%CI)	p value ^b
Sex	—	—	0.522	—	—
Male	87.1	1.00	—	—	—
Female	84.0	0.78 (0.36; 1.67)	—	—	—
Age (years)	—	—	0.124	—	0.127
≤59	100.0	1.00	—	1.00	—
60–74	90.2	1.80 (0.71; 4.59)	—	1.80 (0.71; 4.59)	—
≥75	83.5	0.83 (0.34; 2.04)	—	0.83 (0.34; 2.04)	—
Diabetes mellitus	—	—	0.789	—	—
No	82.9	1.00	—	—	—
Yes	84.4	1.12 (0.50; 2.48)	—	—	—
Hypertension	—	—	0.458	—	—
No	85.4	1.00	—	—	—
Yes	81.6	0.76 (0.36; 1.58)	—	—	—
Dyslipidemia	—	—	0.110	—	0.107
No	85.8	1.00	—	1.00	—
Yes	76.4	0.53 (0.25; 1.15)	—	0.52 (0.24; 1.15)	—
Depression	—	—	0.852	—	—
No	82.9	1.00	—	—	—
Yes	83.9	1.07 (0.52; 2.23)	—	—	—
Hypothyroidism	—	—	0.197	—	0.452
No	85.0	1.00	—	1.00	—
Yes	76.7	0.58 (0.25; 1.33)	—	0.71 (0.29; 1.73)	—
Osteoporosis	—	—	0.304	—	—
No	84.1	1.00	—	—	—
Yes	75.0	0.56 (0.19; 1.67)	—	—	—
Time of treatment (years)	—	—	0.848	—	—
0 to 1	79.3	1.00	—	—	—
> 1 to 3	89.7	2.26 (0.73; 7.02)	—	—	—
> 3 or more	82.3	1.26 (0.45; 3.52)	—	—	—
Drugs for AD	—	—	0.623	—	—
Memantine	75.0	1.00	—	—	—
Donepezil	85.4	1.96 (0.47; 8.06)	—	—	—
Galantamine	84.9	1.88 (0.41; 8.47)	—	—	—
Rivastigmine	87.9	2.42 (0.45; 12.88)	—	—	—
Donepezil + memantine	84.2	1.78 (0.29; 10.72)	—	—	—
Galantamine + memantine	85.7	2.00 (0.27; 14.59)	—	—	—
Rivastigmine + memantine	100.0	1.00 (0.51; 3.46)	—	—	—
Donepezil + rivastigmine	50.0	0.33 (0.02; 7.14)	—	—	—
Use of antipsychotics	—	—	0.011	—	0.011
No	79.0	1.00	—	1.00	—
Yes	94.8	4.88 (1.43; 16.65)	—	4.95 (1.45; 16.93)	—
Polypharmacy	—	—	0.327 ^a	—	—
No	81.6	1.00	—	—	—
Yes	87.0	1.50 (0.66; 3.42)	—	—	—

^aLogistic binary regression.^bMultivariate logistic regression

AD, Alzheimer's disease; OR, odds ratio.

Another study analyzed, for a period of 16 years (1998–2013), the ADRs registered in VigiBase (referring to 58 countries and five continents) related to the use of anticholinesterase drugs for the treatment of Alzheimer's disease. Rivastigmine and donepezil were involved in most reports and occurred mainly due to neuropsychiatric disorders, which is similar to the findings of our study. However, they noticed that serious ADRs were more often reported than nonserious, which differs from our findings (Kröger et al., 2015).

A survey analyzed two national pharmacovigilance databases (Food and Drug Administration Adverse Event Reporting System - FAERS and the Canada Vigilance Adverse Reaction Database -

CVARD) concerning the adverse effects of cholinesterase inhibitors in dementia, between 2004 and 2012. There is higher frequency of reports of death and serious adverse events for rivastigmine when compared to other drugs (FAERS, odds ratio = 3.42 and CVARD, odds ratio = 3.67 databases) (Ali et al., 2015).

Our results differed from the findings of Kröger et al. (2015) and Ali et al. (2015) since the ADRs in our study were mainly of mild severity. It is important to mention that there is a limited number of studies related to the topic in the literature, and the studies that were found refer to spontaneous notification of ADRs, which differ from the present study that performed the active search for them.

Strengths and Limitations of This Study

In the present study, patients could have difficulties remembering the name of diseases, medications currently being used, and other information. Thus, some relevant data may have been missed, as they had not been registered in the MEDEX system. In order to minimize the effects of this limitation, missing information was substituted with data found in medical prescriptions and gathered through new interviews. Other limitation of the MEDEX system is lack of classification concerning the stages or types of dementia (early or late stages and atypical or mixed form, among others).

It is important to emphasize that the findings of this study are limited to individuals with Alzheimer's disease whose medications were provided by the public health system, and did not include patients who paid for their treatment. Although the data cannot be generalized due to the fact that they are restricted to the population of a city and of a health public sector, lack of information regarding this population reinforces the need of this study.

The fact that the subjects self-reported the ADRs might represent a limitation, as other diseases that affect the older adults can often cause similar symptoms to those self-reported, which may have led to overestimation of ADR prevalence. On the other hand, when the patient and caregiver report the adverse effect and/or when the report is done during the use of the drug, there is an increase in the confidence of these findings and a decrease in the recall bias. In addition, the use of modified Naranjo algorithm, to standardize the causality estimate, conferred greater confidence in the report.

There is insufficient available data in the scientific literature regarding the prevalence of ADRs in patients undergoing treatment for Alzheimer's disease, which makes the preliminary data, described in this study, useful in helping the public health service to better manage this problem.

In the assessed period, the sample comprised 88% of the whole population suffering from Alzheimer's disease with an active status, allowing the patients to obtain medicines from the Specialty Drug Pharmacy of the city of Sorocaba. Also, the instrument used for data gathering was carefully developed, and a pilot study test was also carried out. The researchers involved in the study had been previously trained to better use terminology and conduct interviews.

Implications for Clinical Practice and for Research

Although the cholinergic effects of these drugs may contribute to the incidence of neuropsychiatric events, it is important to note that patients suffering from Alzheimer's disease are likely to experience neuropsychiatric symptoms as part of the disease process and psychotropic use may further increase this likelihood (Gustafsson et al., 2013). In fact, in the present study, the use of antipsychotics increased the risk of ADR in these patients.

It is noteworthy that results from clinical exams for identifying ADRs are usually unspecific, and more than one organ is often involved, which makes it difficult to precisely identify ADRs. There is also a chance of a possible iatrogenic cascade, which can increase treatment costs, when signs and symptoms caused by ADRs are treated as a new disease (Fonteles et al., 2009). In older adult patients, this situation is even more critical due to other comorbidities associated with aging (Varallo et al., 2010).

Despite the large number of ADRs reported, the majority of them were classified as mild severity and resolved without the need for intervention of health professionals or hospitalization, or constituting an emergency. There was a total of six reported ADRs that were considered severe requiring hospitalization, largely due to the use of galantamine.

Given that projections indicate an increase in Alzheimer's disease cases, the demand for these medications is set to rise in the upcoming years. Clinical protocols could better address the follow-up of patients undergoing drug therapy for Alzheimer's disease. Such procedures could allow early identification of therapeutic failure and facilitate handling of ADRs. The findings of this study can help guide public health administrators, drug prescribers, caregivers and patients through safety aspects and improve care regarding the drug treatment of patients with Alzheimer's disease.

In light of insufficient data on this issue in the scientific literature, more primary studies on drug treatment of Alzheimer's disease in the Brazilian population should be encouraged.

CONCLUSION

The results revealed a large number of ADRs used in the treatment of Alzheimer's disease, which were generally classified as being of common frequency and mild severity. Donepezil had the largest number of reported ADRs. The most prevalent adverse effects were psychiatric disorders.

In this way, before starting a treatment for neuropsychiatric symptom, it is essential to verify if it is not a result of the use of these drugs. Improving safety-related care in the use of drugs for treating Alzheimer's disease is extremely important when taking into account fragility, the use of a larger number of drugs, and comorbidities in patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of the University of Sorocaba (protocol number: 1860724). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TF is the principal investigator, participated in all stages of the study and writhed the manuscript. CB is the project manager and co-investigator, was involved in study selection and data analysis, and contributed to the writing and revision of the manuscript. LL is co-investigator, contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

REFERENCES

- Ali, T. B., Schleret, T. R., Reilly, B. M., Chen, W. Y., and Abagyan, R. (2015). Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS One* 10 (12), e0144337. doi:10.1371/journal.pone.0144337
- Barros De Matos, P. C. and Decesaro, M. C. d. N. (2012). Características de idosos acometidos pela doença de Alzheimer e seus familiares cuidadores principais. *Rev. Eletrônica Enferm.* 14 (4), 857–865.
- BMJ Best Practice (2019). Alzheimer's dementia. The right clinical information, right where it's needed. Available at: <https://bestpractice.bmj.com/topics/pt-br/317> (Accessed July 16 2019).
- Brasil (2000). Ministério da Saúde. Secretaria Executiva. Sistema Único de Saúde (SUS): princípios e conquistas. Brasília: Ministério da Saúde. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/sus_principios.pdf (Accessed August 2019).
- Brasil (2013). Ministério da Saúde. Portaria nº 1554, de 30 de julho de 2013. Dispõe sobre as regras de financiamento e execução do Componente Especializado da Assistência Farmacêutica no âmbito do Sistema Único de Saúde (SUS). Diário Oficial da União, nº 146 31 julho 2013, Seção I, página 69. Alterada pela Portaria GM/MS no 1996 11 setembro 2013, publicada no Diário Oficial da União nº 177 12 setembro 2013, Seção I, página 37. Available at: <http://portal.arquivos.saude.gov.br/images/pdf/2014/abril/02/pt-gm-ms-1554-2013-alterada-1996-2013.pdf> (Accessed July 16 2019).
- Brasil (2017). Ministério da Saúde. Portaria conjunta nº 13, de 28 de novembro de 2017 aprova o protocolo clínico e diretrizes terapêuticas da doença de Alzheimer. Available at: http://conitec.gov.br/images/Relatorios/2017/Recomendacao/Portaria_Conjunta_13_PCDT_Alzheimer_28_11_2017.pdf (Accessed July 16 2019).
- Davies, E. A. and O'Mahony, M. S. (2015). Adverse drug reactions in special populations - the elderly. *Br. J. Clin. Pharmacol.* 80 (4), 796–807. doi:10.1111/bcp.12596
- Fagundes, S. D., Silva, M. T., Thees, M. F. R. S., and Pereira, M. G. (2011). Prevalence of dementia among older adults Brazilians: a systematic review. *Sao Paulo Med. J.* 129 (1), 46–50. doi:10.1590/S1516-31802011000100009
- Foteles, M. M. de F., Francelino, E. V., Santos, L. K. X., Silva, K. M., Siqueira, R., Viana, G. S. D. B., et al. (2009). Reações adversas causadas por fármacos que atuam no sistema nervoso: análise de registros de um centro de farmacovigilância do Brasil. *Arch. Clin. Psychiatr.* 36 (4), 137–144.
- Gustafsson, M., Sandman, P. O., Karlsson, S., Gustafson, Y., and Lövhem, H. (2013). Association between behavioral and psychological symptoms and psychotropic drug use among old people with cognitive impairment living in geriatric care settings. *Int. Psychogeriatr.* 25 (9), 1415–1423. doi:10.1017/S1041610213000859
- Instituto Brasileiro de Geografia e Estatística - IBGE (2018). Cidades, Brasil, São Paulo, Sorocaba. Available at: <https://cidades.ibge.gov.br/brasil/sp/sorocaba/panorama> (Accessed July 01 2019).
- Instituto Brasileiro de Geografia e Estatística (IBGE) (2019). Projeção da população do Brasil e das Unidades da Federação. Available at: <https://www.ibge.gov.br/apps/populacao/projecao/> (Accessed July 09 2019).
- Kalaria, R. N., Maestre, G. E., Arizaga, R., Friedland, R. P., Galasko, D., Hall, K., et al. (2008). Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* 7 (9), 812–826. doi:10.1016/S1474-4422(08)70169-8
- Kröger, E., Moulis, M., Wilchesky, M., Berkers, M., Carmichael, P. H., Van Marum, R., et al. (2015). Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from Vigibase. *Ann. Pharmacother.* 49 (11), 1197–1206. doi:10.1177/1060028015602274
- Laroche, M. L., Perault-Pochat, M. C., Ingrand, I., Merle, L., Kreft-Jais, C., Castot-Villepelet, A., et al. (2013). Adverse drug reactions in patients with Alzheimer's disease and related dementia in France: a national multicentre cross-sectional study. *Pharmacoevidemiol. Drug Saf.* 22 (9), 952–960. doi:10.1002/pds.3471
- Lopes, L. C., Silveira, M. S., de Camargo, M. C., de Camargo, I. A., Luz, T. C., Osorio-de-Castro, C. G., et al. (2014). Patient reports of the frequency and severity of adverse reactions associated with biological agents prescribed for psoriasis in Brazil. *Expet Opin. Drug Saf.* 13 (9), 1155–1163. doi:10.1517/14740338.2014.942219
- Meyboom, R. H. and Egberts, A. C. (1999). Comparing therapeutic benefit and risk. *Therapie* 54, 29–34.
- National Institute for Health and Clinical Excellence - NICE (2018). Guidelines. Dementia: assessment, management and support for people living with dementia and their carers. Available at: <https://www.guidelines.co.uk/mental-health/nice-dementia-guideline/454244.article> (Accessed July 16 2019).
- Pathirana, D., Ormerod, A. D., Saiag, P., Smith, C., Spuls, P. I., Nast, A., et al. (2009). European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J. Eur. Acad. Dermatol. Venereol.* 23 (Suppl. 2), 1–70. doi:10.1111/j.1468-3083.2009.03389.x
- Pearson, T. F., Pittman, D. G., Longley, J. M., Grapes, Z. T., Vigliotti, D. J., and Mullis, S. R. (1994). Factors associated with preventable adverse drug reactions. *Am. J. Hosp. Pharm.* 51 (18), 2268–2272.
- Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., and Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 9 (1), 63. e2. doi:10.1016/j.jalz.2012.11.00710
- Tadesse, W. T., Mekonnen, A. B., Tesfaye, W. H., and Tadesse, Y. T. (2014). Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. *BMC Pharmacol. Toxicol.* 15 (15), 32. doi:10.1186/2050-6511-15-32
- Tan, C. C., Yu, J. T., Wang, H. F., Tan, M. S., Meng, X. F., Wang, C., et al. (2014). Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J. Alzheimers Dis.* 41 (2), 615–631. doi:10.3233/JAD-132690
- Tavassoli, N., Sommet, A., Lapeyre-Mestre, M., Bagheri, H., and Monstrauc, J. L. (2007). Drug interactions with cholinesterase inhibitors. *Drug Saf.* 30 (11), 1063–1071. doi:10.2165/00002018-200730110-00005
- Varallo, F. R., Mastroianni, P. C., and Planeta, C. S. (2010). Internações hospitalares por Reações Adversas a Medicamentos (RAM) em um hospital de ensino. Available at: http://www2.fcfa.unesp.br/Home/Posgraduacao/CienciasFarmaceuticas/fabiana_rossi_varallo_ME.pdf (Accessed September 11, 2019).
- VigiAccess® (2018). The World health Organization's (the "WHO") global database for ADRs, maintained by the Uppsala monitoring centre (the "UMC"). Available at: <http://www.vigiaccess.org/> (Accessed September 3 2018).
- Wetzels, R., Wolters, R., van Weel, C., and Wensing, M. (2008). Mix of methods is needed to identify adverse events in general practice: a prospective observational study. *BMC Fam. Pract.* 9 (1), 35. doi:10.1186/1471-2296-9-35
- Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., et al. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol.* 15 (5), 455–532. doi:10.1016/S1474-4422(16)00062-4
- Zhu, J., Stuver, S. O., Epstein, A. M., Schneider, E. C., Weissman, J. S., and Weingart, S. N. (2011). Can we rely on patients' reports of adverse events? *Med. Care* 49 (10), 948–955. doi:10.1097/MLR.0b013e31822047a8

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Even High-Quality CPGs Seldom Include Implementation Strategies

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Background: Implementation is a key step in ensuring that high-quality clinical practice guideline (CPG) recommendations are followed and have a positive impact. This step must be planned during CPG development. This study aims to inform professionals tasked with developing and implementing CPGs regarding implementation strategies and tools reported in high-quality CPGs for chronic non-communicable diseases (NCDs).

Methods: NCD guidelines were selected based on Appraisal of Guideline Research and Evaluation (AGREE) II assessment. CPGs with a score of $\geq 60\%$ in AGREE II domains 3 (rigor of development), 5 (applicability), and 6 (editorial independence), were considered high quality. The content related to implementation was extracted from CPG full texts and complementary materials. Implementation strategies and tools were assessed and classified using Mazza taxonomy.

Results: Twenty high-quality CPGs were selected, most of which were developed by government institutions (16; 80%) with public funding (16; 80%); almost half (9; 45%) addressed the treatment of cardiovascular diseases. The countries with the most high-quality CPGs were the UK (6; 30%) and Colombia (5; 25%). These countries also had the highest average number of strategies, Colombia with 28 (SD = 1) distributed in all levels, and the UK with 15 (SD = 7), concentrating on professional and organizational levels. Although the content of the Colombian CPGs was similar regardless the disease, the CPGs from the UK were specific and contained data-based feedback reports and information on CPG compliance. Implementation strategies most frequently identified were at the professional level, such as distributing reference material (18; 80%) and educating groups of healthcare professionals (18; 80%). At the organizational level, the most frequent strategies involve changes in structure (15; 75%) and service delivery method (13; 65%).

Conclusion: Countries with established CPG programs, such as the UK and Colombia, where identified as having the highest number of high-quality CPGs, although CPG implementation content had significant differences. Among high-quality CPGs, the most common implementation strategies were at the professional and organizational levels. There is still room for improvement regarding the implementation strategies report, even among high-quality CPGs, especially concerning monitoring of implementation outcomes and selection of strategies based on relevant implementation barriers.

Keywords: clinical practice guideline, agree II, appraisal (evaluation), applicability, non communicable chronic diseases, implementation tools, implementation strategies

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INTRODUCTION

Clinical practice guidelines (CPGs) have been developed by several institutions aiming at reducing the variability in the health care procedures, as well as producing trustworthiness guidelines (Greenfield et al., 2011). Developing a high-quality CPG requires a great deal of financial and human resources and time. There is a need to involve a multidisciplinary group, including patient and methodologists, as stakeholders (Fervers et al., 2011; Burgers et al., 2012; Qaseem et al., 2012; Kristiansen et al., 2014). Implementation is a key step and must be planned during the CPG development, as suggested in the checklist proposed by Schünemann et al. (Schünemann et al., 2014). The effort and resources involved in developing a CPG of high methodological quality can be wasted if not properly implemented (Greenfield et al., 2011).

CPG quality has progressed, as shown by at least two meta-reviews (Alonso-Coello et al., 2010; Armstrong et al., 2017). Both included primary studies where CPG quality was assessed using the Appraisal of Guideline Research and Evaluation (AGREE) instrument in its first and/or second version (Alonso-Coello et al., 2010; Armstrong et al., 2017). The AGREE instrument is considered the best validated instrument for CPG quality assessment (Siering et al., 2013) and comprises the following domains: 1) scope and purpose; 2) stakeholder's involvement; 3) rigor of development; 4) clarity of presentation; 5) applicability, and 6) editorial independence. Although CPG quality has improved in many domains, such as rigor of development, clarity, scope, and even stakeholder involvement, applicability scores remain the lowest. Another systematic review of this domain showed that scores did not improve between 2008 and 2013, remaining below other AGREE domains and only reaching a mean of 43.6%, at a scale of 0–100%, with 100% being the best (Brouwers et al., 2010; Brouwers et al., 2013; Gagliardi and Brouwers, 2015).

Although assessment of the AGREE II applicability domain helps identify implementation gaps, other aspects must be considered. In 2002, the Cochrane Effective Practice and Organization of Care (EPOC) group published a checklist to guide systematic reviews on implementation, as well as a taxonomy to guide the extraction of relevant information from implementation studies (Cochrane Effective Practice and Organisation of Care (EPOC), 2011). Based on the EPOC checklist, Mazza et al. developed a revised taxonomy with four levels (professional, financial, organizational, and regulatory) and 49 implementation strategies (Mazza et al., 2013).

Gagliardi et al. (Gagliardi et al., 2016), has previously used Mazza taxonomy on randomized and non-randomized studies to assess implementation strategies that described methods used to implement new guidelines or promote compliance with guidelines on specific conditions (arthritis, colorectal cancer, diabetes, and heart failure). This study aimed to describe the strategies used and identify trends in overtime and clinical topic use, which may suggest implementation strategies that suit different barriers and circumstances. The study has shown that the most common strategies are at the professional level as education on guideline intent and benefits, reminders to

professional groups about guideline intent, and provision of print material, such as summaries, algorithms, or referral forms.

Studies on the management of individual conditions evaluated the impact of specific implementation strategies (Forsetlund et al., 2009; Ardit et al., 2012; Giguère et al., 2012), but to the best of our knowledge, no study has evaluated the report of implementation strategies and tools in high-quality CPGs. Assessing implementation content in high-quality CPGs can contribute to disseminate good practices and opportunities for improvement in this area. Thus, the primary objective of this study was to inform professionals tasked with developing and implementing CPGs regarding the most frequent implementation strategies and tools reported in high-quality CPGs in chronic non-communicable diseases (NCDs) by using Mazza taxonomy (Mazza et al., 2013).

METHODS

Selection and Description of CPGs

The CPGs were selected from a previous study from our research group, hereinafter referred to as the CHRONIDE study, where 421 CPGs on the pharmacological treatment of NCDs (cardiovascular disease, lung disease, diabetes, osteoporosis, depression, osteoarthritis dementia, gastroesophageal reflux disease, and benign prostatic hyperplasia), published in English, Spanish, or Portuguese, were assessed using the AGREE II instrument (Molino et al., 2019). The focus on NCD with pharmacological treatment was decided because of the burden of these conditions in the healthcare system and the variety of treatment options. The implementation of evidence-based CPG in NCD can improve health outcomes.

To guarantee consistency on the use of AGREE II, all documents were reviewed by three independent appraisers. They were trained following the AGREE II online training tool and pilot appraisal of two international guidelines to confirm reviewers' understanding. The final rate for each item in the AGREE II domains (total of 23 items) was decided by consensus. Differences of ≥ 2 , in the 7-point scale, where 1 and 7 indicate "strongly disagree" and "strongly agree," respectively, were considered discrepant. The final score for each domain was calculated according to the instrument manual.

The AGREE II manual does not define a specific cut off or the domains considered in classifying CPGs as high quality. Thus, in this study, CPGs with scores of $\geq 60\%$ in domains 3 (rigor of development), 5 (applicability), and 6 (editorial independence), were considered high quality. These domains were chosen based on other studies that considered these as the most relevant domains for assessing CPG quality (Hoffmann-Eßer et al., 2017; Hoffmann-Eßer et al., 2018). By choosing the cut off of 60% in the selected three domains, we believe that the sample is composed of CPGs with more comprehensive report of implementation strategies and, at the same time, with an adequate description of development methods and disclaimer.

Two researchers extracted the following CPG data: year of publication, country, disease, and type of institution that developed the guideline (government, professional society, or

TABLE 1 | Representation of Mazza's taxonomy.

Level		Strategies
Professional		Distribute guideline materials (via hard-copy, audio-visual and/or electronic means)
		Educate groups of health care professionals about the intent and benefit of complying with a guideline
		Present guideline materials at meetings (including conferences, lectures, workshops or traineeships)
		Educate individual health care professionals about the intent and benefit of complying with a guideline
		Identify barriers to guideline implementation (including any activity aimed at identifying reasons why compliance with a guideline might not be achieved, to assist in planning strategies)
		Feedback data and information about patients to individual health care professionals or groups to improve compliance (including clinical outcome data and information, and patient self-assessments)
		Advertise guideline materials (including advertising via any medium, targeted advertising, personal interviews, group discussions aimed at raising awareness)
		Provide feedback based on data and information on CPG compliance to health professionals or groups of health professionals
		Provide feedback with patient information to healthcare professionals or groups of healthcare professionals to improve compliance
		Provide reminders to individual health care professionals or groups about the intent and benefit of complying with a guideline (via any means)
		Provide alerts to individual health care professionals or groups when clinical practice deviates from a guideline (via any means)
		Recruit an opinion leader who recommends the implementation of a guideline (health care professionals must recognize the authority of the opinion leader in regard to the guideline)
		Achieve consensus among health care professionals that the guideline is appropriate for implementation (there must be data that measures consensus)
		Feedback information from health care professionals to individuals or groups to improve compliance (including personal testimony about the experience of implementing a guideline)
Other		
Level		Strategies
Financial	Healthcare professionals	Incentive applicable to a health care professional (a health care professional may receive a direct or indirect financial reward or benefit for complying with a guideline)
		Incentive applicable available to the institution (the institution or a group of health care professionals may receive a direct or indirect financial reward or benefit for complying with a guideline)
		Change in reimbursement (including any addition, subtraction or substitution of a reimbursable product or service that increases the likelihood of improved implementation)
		Incentive applicable to a patient (a patient may receive a direct or indirect financial reward or benefit if provided with care that complies with a guideline)
	Patients	Other
Level		Strategies
Organizational	Healthcare professionals	Creation of an implementation team (including creation of a multidisciplinary team of health professionals who work together on implementation)
		Reallocated roles to assist implementation (including any redistribution of roles among health professionals to facilitate implementation)
		Additional human resources provided for implementation (including increase in the number of staff and change in the type and qualifications of staff to facilitate implementation)
		Communication between distant health professionals (including establishment of any type of telecommunication link for implementation)
	Patients	Consumer feedback, suggestions and complaints (including any new process that uses information from patients to improve implementation)
		Consumer participation in governance (including any change in governance that enables patients to recommend the implementation of a guideline)
		Other
	Structural	Change in organizational structure (including any service reorganization designed to improve implementation)
		Change to the setting or site of service delivery (including any translocation of a service designed to improve implementation)
		Change in the integration of services (including change in how services are linked and integrated to improve implementation)
		Change in the method of service delivery (including any change to how a service is delivered; e.g. replacement of a traditional pharmacy with a mail order pharmacy)
		Change in the physical structure, facilities or equipment of a service (including any change to the infrastructure of a service designed to improve implementation)
		Change in quality assurance, quality improvement and/or performance measurement systems (including any quality system designed to improve implementation)
		Change in information and communication technology supporting a service (including any IT application designed and commissioned to improve implementation; e.g., computerized records, patient tracking systems, electronic referral systems, picture archiving and communication system, telehealth system, on-line text messaging)
		Change in risk management provisions (including any change in insurance cover for loss or damage to facilities, injury to staff, adverse patient outcomes and malpractice that encourages implementation)
		Other

(Continued on following page)

TABLE 1 | (Continued) Representation of Mazza's taxonomy.

Level	Strategies
Regulatory	Change in licensing, credentialing or accreditation of the health service and its elements (including any change that is relevant to the status, legality or reputation of the health service and its employees that increases the likelihood of implementation success) Change in the ownership or affiliation (include any change which increases the likelihood of implementation success) Change in legislation or regulation (include any change which enforces or mandates implementation) Other

university). The institution is classified as government if the CPG was developed or implemented by a government agency.

Assessment of Implementation Strategies

To assess implementation strategies, all contents on the implementation session and tools were extracted from complete CPGs and supplementary documents and stored in an Excel® spreadsheet. Only one researcher extracted these data (LVP). This was applied to identify and categorize strategies and tools based on Mazza taxonomy (Mazza et al., 2013). The taxonomy is composed of 49 strategies divided in four levels: professional, finance, organizational, and regulatory levels with 15, 12, 18, and four strategies, respectively (Table 1).

Similarities were identified in high-quality CPGs developed in the same country; therefore, these were presented in clusters by country to summarize the findings. Codes were developed to identify CPGs based on the country of development and health condition addressed.

RESULTS

Selection and Description of CPGs

Of 421 CPGs, 20 had scores of $\geq 60\%$ in domains 3, 5, and 6 (Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA), 2012; National Vascular Disease Prevention Alliance, 2012; Goblirsch et al., 2013; Ministerio de Salud, 2013; Ministerio de Salud y Protección Social-Colciencias, 2013a; Ministerio de Salud y Protección Social-Colciencias, 2013b; National Institute for Health and Care Excellence, 2014a; National Institute for Health and Care Excellence, 2014b; Ministerio de Salud y Protección Social-Colciencias, 2014a; Ministerio de Salud y Protección Social-Colciencias, 2014b; Ministerio de Salud y Protección Social-Colciencias, 2014a; Ministerio de Salud y Protección Social-Colciencias, 2014b; Guideline Adaptation Committee, 2016; Ministerio de Salud y Protección Social, Departamento Administrativo de Ciencia, Tecnología e Innovación - Colciencias, 2016; National Institute for Health and Care Excellence, 2016; Scottish Intercollegiate Guidelines Network (SIGN), 2016a; Scottish Intercollegiate Guidelines Network (SIGN), 2016b; Malaysian Ministry of Health, 2017a; Malaysian Ministry of Health, 2017b; National Institute for Health and Care Excellence, 2019a; National Institute for Health and Care Excellence, 2019b; National Institute for Health and Care Excellence, 2019c). These CPGs were

developed in the UK ($n = 6$), Colombia ($n = 5$), Australia ($n = 2$), Scotland ($n = 2$), Malaysia ($n = 2$), Chile ($n = 1$), Spain ($n = 1$), and USA ($n = 1$). They were mostly developed by governmental institutions (15; 75%) and predominantly (11; 55%) addressed the treatment of cardiovascular diseases, as described in Table 2.

Implementation Strategies

The largest number of strategies in a single CPG was 29 from 49 strategies described in the Mazza taxonomy (Mazza et al., 2013), as shown in Figure 1. The mean of strategies per CPG was 16.8 ± 8.5 , with more strategies at the professional level. Only CPGs from Colombia and one from Australia (AUScdv) mentioned strategies at all four levels of the Mazza taxonomy.

The vast majority of implementation strategies in the CPGs from Colombia were identical, indicating that the same outline had been applied to describe the implementation strategies independent of the specific health condition addressed in each CPG.

The implementation strategies and tools in six CPGs from the UK were specific to each disease. All UK CPGs contain implementation priorities and tools to measure implementation results. The National Institute of Clinical Excellence (NICE) impact reports are comprehensive tools wherein indicators mentioned in the CPG are measured, and improvement opportunities are discussed.

The content and tools related to professional-level strategies were standard, for example health professional education strategies and short guideline versions aimed at physicians. Even in CPGs that include implementation barriers identification as strategy, the relationship between strategies and such barriers was not clearly stated. Although 10 of these 20 CPGs mention the establishment of implementation teams, it was unclear which professionals should take part in these teams or what training is needed.

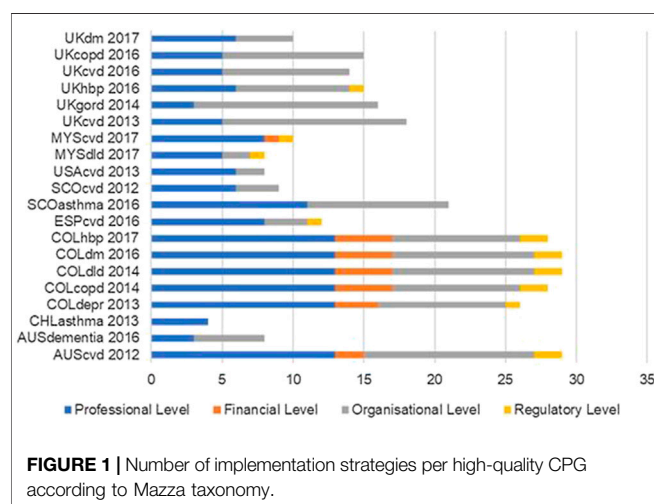
Implementation Strategies and Tools Highlights

All CPGs from Colombia (Qaseem et al., 2012), one from Scotland (SCOasthma), and one from Australia (AUScdv) included most of the 15 possible professional-level strategies. The most frequent strategies related to the distribution of guideline materials and healthcare professional education is shown in Table 3.

TABLE 2 | Description of 20 high-quality clinical practice guidelines (CPGs).

CPG Code	Country	Disease	Year	Institution	Type of institution
AUScvd (National Vascular Disease Prevention Alliance, 2012)	Australia	Cardiovascular	2012	NVDPA	Government
AUSdementia (Guideline Adaptation Committee, 2016)	Australia	Dementia	2016	NHMRC	Government
CHLasthma (Ministerio de Salud, 2013)	Chile	Asthma	2013	SSP	Government
COLdepr (Ministerio de Salud y Protección Social-Colciencias, 2013a)	Colombia	Depression	2013	IETS	Government
COLcopd (Ministerio de Salud y Protección Social-Colciencias, 2014a)	Colombia	Chronic obstructive pulmonary disease	2014	PUJ	University
COLldd (Ministerio de Salud y Protección Social-Colciencias, 2014b)	Colombia	Dyslipidemia	2014	IETS	Government
COLdm (Ministerio de Salud y Protección Social, Departamento Administrativo de Ciencia, Tecnología e Innovación-Colciencias, 2016)	Colombia	Diabetes mellitus	2016	PUJ	University
COLhbp (Ministerio de Salud y Protección Social-Colciencias, 2013b)	Colombia	High blood pressure	2013	IETS	Government
SP0 (Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA), 2012)	Spain	Atrial fibrillation	2012	AETSA	Government
SCOasthma (Scottish Intercollegiate Guidelines Network (SIGN), 2016a)	Scotland	Asthma	2016	SIGN	Government
SCOchf (Scottish Intercollegiate Guidelines Network (SIGN), 2016b)	Scotland	Chronic heart failure	2016	SIGN	Government
USAcvd (Goblirsch et al., 2013)	United States	Stable coronary artery disease	2013	ICSI	Professional society
MYSdd (Malaysian Ministry of Health, 2017b)	Malaysia	Dyslipidemia	2017	NHAM	Professional society
MYScvd (Malaysian Ministry of Health, 2017a)	Malaysia	Cardiovascular	2017	NHAM	Professional society
UKaf (National Institute for Health and Care Excellence, 2014a)	United Kingdom	Atrial fibrillation	2013	NICE	Government
UKgord (National Institute for Health and Care Excellence, 2014b)	United Kingdom	Gastroesophageal reflux	2014	NICE	Government
UKhbp (National Institute for Health and Care Excellence, 2019a)	United Kingdom	High blood pressure	2016	NICE	Government
UKcvd (National Institute for Health and Care Excellence, 2016)	United Kingdom	Stable angina: Management	2016	NICE	Government
UKcopd (National Institute for Health and Care Excellence, 2019b)	United Kingdom	Chronic obstructive pulmonary disease	2016	NICE	Government
UKdm (National Institute for Health and Care Excellence, 2019c)	United Kingdom	Diabetes mellitus	2017	NICE	Government

NVDPA, National Vascular disease Prevention Alliance; NHMRC, National Health and Medical Research Council; SSP, Subsecretaría de Salud Pública; IETS, Instituto de Evaluación Tecnológica en Salud; PUJ, Pontificia Universidad Javeriana; SIGN, Scottish Intercollegiate Guidelines Network; AETSA, Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; ICSI, Institute for Clinical Systems Improvement; NHAM, National Heart Association of Malaysia; NICE, National Institute for Health and Care Excellence.


FIGURE 1 | Number of implementation strategies per high-quality CPG according to Mazza taxonomy.

In general, strategies that covered financial aspects were minimally explored even in high-quality CPGs, and in 13 (65%) CPGs no financial-level strategy had been described.

At the organizational level, CPGs from Colombia, UK, and Australia had the most strategies identified, especially in the structural category. Only one CPG, the SCOaf2012, mentioned distance communication between health professionals and patients as a means of enhancing implementation. None of the

CPGs analyzed provided any guidance on how to measure the satisfaction and commitment of professionals with the implementation of the document.

Four of the five CPGs from Colombia (COLcopd, COLldd, COLdm, and COLhbp) contained two strategies at the regulatory level, and one (COLdepr) contained one strategy. Changes in licensing, credentialing, or accreditation of healthcare services were the most frequent strategy, being identified in eight (40%) CPGs, including the five CPGs from Colombia. No implementation tool had been identified at the regulatory level (Table 4).

DISCUSSION

Most of the high-quality CPGs were developed in countries with existing CPG development programs, such as the UK and Colombia, consistent with previous studies (Burgers et al., 2003; Molino et al., 2019). Our results showed that CPGs from Colombia contained the most implementation strategies, including strategies at all levels. Although the Colombian CPG development program stood out in producing high-quality CPGs and implementation strategies, it should be highlighted that the content devoted to implementation was similar regardless of disease. By contrast, the strategies and tools were specific to each disease in CPGs developed in the UK, and implementation

TABLE 3 | Strategies highlights per level.

Level	Professional	Financial	Organizacional	Regulatory
Strategies	Distribute guideline materials (18, 90%) - educate groups of health care professionals about the intent and benefit of complying with a guideline (18, 90%)	The CPGs from Colombia are the ones with more strategies related: 4 CPGs (COLcopd, COLdld, COLdm, COLhbp) contain 4 strategies and 1 (COLdepr) contain 3 strategies - the following strategies were not identified in any of the 20 CPGs: Grant or allowance provided to a health care professional, grant or allowance provided to the institution, penalty applicable to a health care professional, penalty applicable to the institution	Only one CPG, the SCOaf2012, mentions distance communication between health professionals and patients aiming at enhancing implementation-none of the 20 CPGs provides any guidance on health worker satisfaction for increasing commitment and satisfaction with the implementation of the CPG <i>Structural Category</i> -change in organizational structure (15; 75%)- change in the method of service delivery (13; 65%)-change in service integration (13; 65%). Health professional category <i>Health professional category</i> -creation of an implementation team (10; 50%) <i>Patient category</i> -consumer feedback (11; 55%)	4 of the 5 CPG from Colombia (COLcopd, COLdld, COLdm, COLhbp) contain 2 strategies at this level and 1 (COLdepr) contain 1 strategy - change in licensing, credentialing or accreditation of the health service and its elements, was a strategy more frequent, identified in 8 (40%) CPGs, including the 5 CPG from Colombia

TABLE 4 | Tools highlights per level.

Level	Professional	Financial	Organizacional	Regulatory
Tools	Clinical algorithms-summarized versions of CPGs for physicians - materials for classes and presentations of CPGs	None implementation tool was identified	The largest number of tools at organizational level was found in CPGs from United Kingdom. Patient's category-version of the CPGs written in lay language for patients and caregivers Structural category-spreadsheets with implementation tracking indicators,- implementation plans - spreadsheets for initial assessment of clinical parameters	None implementation tool was identified

was expected to be more effective. A Cochrane systematic review concluded that tailored implementation strategies were more effective than general ones (Baker et al., 2015). Therefore, analysis of the number of implementation strategies is not sufficient to fully understand CPG implementation. The qualitative assessment of the strategies is relevant to understand how CPG developers and relevant institutions plan implementation. Although the number of strategies varies across high-quality CPGs, strategies at the professional level are predominant, whereas financial and regulatory level strategies are reported less frequently.

In the CHRONIDE study, Europe had the second highest number of CPGs (124; 30%) (Molino et al., 2019), and in the current study, Europe had contributed with half of the high-quality CPGs (10; 50%). It is worth noting that only CPGs available in English, Spanish, or Portuguese were included in our sample, which may have led to the exclusion of CPGs from other WHO countries, such as Germany and France, potentially limiting the generalization of findings (Panteli et al., 2019). There were 6 (30%) out of the 20 high-quality CPG that had been developed by NICE, which is based in the UK.

Since 2009, NICE was responsible for developing and maintaining quality indicators within the Quality Outcomes Framework. Concerning implementation tools, CPGs from the

UK are highly regarded for tools, such as the NICEimpact for cardiovascular disease prevention and NICEimpact for diabetes, with data based on feedback reports and information on CPG compliance (National Institute for Health and Care Excellence, 2018). These reports aim to evaluate the acceptance of CPG recommendations developed by the NICE and measure their impact on health outcomes. Thus, NICE develops and evaluates CPG results as part of a structured program, which may have contributed to CPGs from the UK being considered high quality (National Institute For Health And Care Excellence, 2020).

Although Latin America was the fourth region with the most CPGs (54; 13%) in the CHRONIDE study (Molino et al., 2019), it had the highest proportion of high-quality CPGs (6; 11%). However, it should be noted that the results can be largely attributed to Colombia (5; 25%). Most Colombian CPGs were developed by the Institute of Health Technology Assessment and Technology (IETS), established in 2012 by the Colombian Administrative Department of Science, Technology, and Innovation (COLCIENCIAS). In addition to developing CPGs, IETS is also responsible for developing implementation strategies and tools, which may contribute to their quality (IETS, 2020). The fact that the Colombian's CPG contained the largest number of implementation strategies does not necessarily mean that the Colombian health system has the best health outcomes. The

Colombian Health-Related Sustainable Development Goals (SDGs) Index was 58.8 and 65.8 in 2011 and 2017, respectively, and despite this improvement, it is still behind countries, such as the UK, with an index of 77.0 and 80.4 in 2011 and 2017, respectively. This index evaluates how far countries are from the United Nations SDGs created to encourage improvements in health, equity, and well-being by 2030 (Institute for Health Metrics and Evaluation, 2020).

As expected, although the United States and Canada were responsible for the largest number of CPG evaluated in the CHRONIDE study (129; 31%) (Molino et al., 2019), only one of these was considered high quality in the present study. These results might be due to the structure of their healthcare systems. Despite the USA Institute of Medicine developing the Clinical Guidelines We Can Trust report in 2011 (Greenfield et al., 2011) with standards for developing trustworthy guidelines and the existence of other important CPG sources in the country, such as Emergency Care Research Institute repository of CPGs, there is no national CPG development program, such as NICE. In Canada, the Canadian Agency for Drugs and Technologies in Health is responsible for evaluating health technologies and making recommendations; however, the provinces are autonomous, and CPGs are usually developed by medical societies (Molino et al., 2019).

The implementation strategies most frequently found among the high-quality CPGs were at the professional level, consisting mainly of the distribution of reference material, individual and group education of healthcare professionals, and presentation of CPG material at meetings. This is consistent with reports in previous studies (Pantoja et al., 2017; Tomasone et al., 2020). Clinical algorithms, CPG versions directed at physicians, and material for classes, and presentations on CPGs were commonly found at the professional level. Such tools mainly aim to disseminate CPGs to healthcare professionals, and although they can be seen as a basic and essential strategy, studies show these strategies alone are insufficient (Francke et al., 2008), with the impact of educational meetings, for example, considered low (Forsetlund et al., 2009).

Financial and regulatory level strategies were not mentioned in the UK guidelines, possibly due to the healthcare system structure, with funding based on nationwide collection and allocation of resources by the Department of Health and Social Care (Nicoletti and Faria, 2017). Therefore, strategies, such as financial incentives or changes in licensing, accreditation, or credentialing of healthcare services and its elements, are not the responsibility of NICE (National Institute For Health And Care Excellence, 2020). This does not mean that financial incentive strategies do not exist in the UK, but that they were not found in CPGs and supplementary documents provided by NICE. Therefore, to fully understand CPG implementation programs in a specific country, understanding its healthcare system's organization, funding, and social determinants is necessary. This is an important insight for future studies of CPG implementation best practices.

In the structural category of organizational level, strategies related to changes in organizational structure were the most frequent (15; 75%), followed by changes in the method of service delivery (13; 65%), and integration between health

services (13; 65%), especially in CPGs from Australia, Colombia, and the UK. In the health professional's category, strategies, such as the establishment of an implementation team (10; 50%) and relocation of roles (9; 45%) were the most frequent. Although CPGs suggested that implementation teams should be established, they did not define appropriate team composition or training. Studies show that although implementation of science training programs exists, few are intended for the practitioners responsible for planning and carrying out implementation strategies. These studies call such professional implementers, "implementation champions," "knowledge brokers," and "facilitators" (Proctor et al., 2019).

None of high-quality CPGs clearly addressed the relationship between implementation strategies and possible barriers to implementation. This aspect should be further explored by institutions developing CPGs as strategies aimed at overcoming such barriers can increase their effectiveness (Jäger et al., 2016). Most institutions do not routinely monitor the implementation of CPGs. Publications reporting surveillance data, such as the NICEimpact reports, could be helpful. Other types of reports, such as those using structured interviews with healthcare professionals on implementation strategies, may provide important information on preferred and most effective strategies (Adams et al., 2018).

The identification of barriers to guideline implementation is a fundamental step toward the selection of appropriate implementation strategies and is presented in 15 of the 20 CPGs. However, these CPGs did not provide any guidance on how to identify and solve the barriers. Brainstorming is a technique for identifying barriers that has no cost and can be used in chronic diseases (Krause et al., 2014). Including explanations and advice on this strategy in CPGs might help institutions identify relevant barriers and choose the most appropriate implementation strategies for their context. Therefore, the association between implementation strategies and their barriers was unclear in these high-quality CPGs. This is consistent with results found in a scoping review on trends in CPG implementation, wherein the authors show that the process of defining strategies based on relevant barriers did not change over time, despite increased awareness of its relevance to health outcomes, and the publication of several models, theories, taxonomies, and frameworks aimed at improving implementation (Gagliardi and Alhabib, 2015).

Because some studies show that the use of implementation strategies, such as alerts and reminders, can increase adherence to CPG recommendations, the use of these strategies should be encouraged. (Flodgren et al., 2016; Stein et al., 2018). However, such interventions were uncommon in the CPGs analyzed. The most common strategy (13; 65%) was the direct provision of patient data and feedback to healthcare professional. CPGs from Colombia and Australia frequently described the use of alerts and feedback regarding compliance or deviation CPGs. Organizational level tools related to patient category, such as plain-language CPG directed at patients and caregivers, were very frequent.

Decision support tools such as decision aids and option grid were identified in only three CPGs in the UK. The adoption of decision support tools based on good communication, patient autonomy, and active involvement in treatment choice has

been reported in the literature as fundamental for the progression of the healthcare systems toward a value-based outlook (Bae, 2017). Although such tools are well-known, caution should be taken in their development to ensure that they are reliable. It is important to avoid scientific, financial, and ideological interests outweighing the benefits of increased patient participation in decision making by balancing risks and benefits and considering patient values and preferences (Moore et al., 2017).

The CPGs described implementation strategies at different levels of the Mazza taxonomy; however, none used the multifaceted approach, characterized by the simultaneous use of several implementation strategies (Suman et al., 2016). Based on the contents of these CPGs, it is not possible to affirm that countries are following this approach. Although publications, such as the BRIDGE study (Berwanger et al., 2012), show that the multifaceted approach increases CPG adherence, other studies report that multifaceted strategies do not change professional behavior toward CPG adherence (Suman et al., 2016).

The main limitations of this study are the language restriction and the review of published documents only, which may exclude strategies that influence implementation but are used internally by institutions as audit reports for example. Although AGREE II is a highly accepted instrument for assessing the quality of CPG, it has inherent limitations such as some degree of subjectivity, which has been reduced by the participation of three trained appraisers. Regarding the influence of the chosen 60% cut-off, although it is directly related to the number of selected CPG, this cut off has been used in most studies that use AGREE II to identify high-quality CPG. The data extraction and classification of strategies and tools were performed by only one researcher. For more complete view of all implementation strategies, future studies may include the assessment of all institutions' policies and procedures, which would imply active participation of institutions in information collection. Although the number of high-quality CPGs was small, the institutions that developed them are incorporating implementation strategies in their documents, as recommended by some authors (Gagliardi et al., 2015). However guidelines developers and stakeholders can improve the reporting of implementation by considering the following: report tailored strategies, assess barriers, describe specific strategies to overcome those barriers, consider strategies in all four levels of Mazza taxonomy to avoid the tendency of focusing on the professional level, and establish monitoring of adherence of CPG recommendations with assessment of outcomes. The GRADE working group advises that institutions and teams responsible for CPG development must consider the aspects influencing the decision to adopt recommendations in a planned, detailed, and clear way (Alonso-Coello et al., 2016).

CONCLUSION

This was the first assessment of implementation strategies in high-quality CPGs using the Mazza taxonomy. This tool was important in identifying the main strategies included in CPGs. However, the qualitative analysis of CPG and supplementary material was essential to highlight the implementation gaps where institutions should focus for improvement.

Although Colombia CPGs presented a large quantity of strategies, these were not disease specific, whereas implementation strategies and tools were specific for each disease in UK CPGs. These differences can be explained, at least partially, by the maturity of these countries' healthcare systems and CPG development programs. Therefore, implementation studies should include a critical analysis of CPG content, as well as health policies and procedures of institutions and countries in addition to the number of strategies.

The most implementation strategies specified in these CPGs were at the professional and organizational levels, mainly consisting of strategies for disseminating CPGs among healthcare professionals and patients. There is still room for improvement regarding the implementation strategies report, even among high-quality CPGs, especially concerning monitoring of implementation outcomes and selection of strategies based on relevant implementation barriers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study was assessed and approved by the Ethics Committee at São Paulo Medicine University on December 12, 2018.

AUTHOR CONTRIBUTIONS

LV collected, analyzed, and interpreted the data regarding implementation strategies in high-quality CPG. DM and AS participated in data interpretation and contributed in writing the manuscript, and HC substantively revised this work. All authors read and approved the final manuscript.

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REFERENCES

- Adams, S. A., Rohweder, C. L., Leeman, J., Friedman, D. B., Gizlice, Z., Vanderpool, R. C., et al. (2018). Use of evidence-based interventions and implementation strategies to increase colorectal cancer screening in federally qualified health centers. *J. Community Health*. 43 (6), 1044–1052. doi:10.1007/s10900-018-0520-2
- Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) (2012). *Guía para la elección de tratamiento anticoagulante oral en la prevención de las complicaciones tromboembólicas asociadas a la fibrilación auricular no valvular*. Junta de Andalucía.
- Alonso-Coello, P., Irfan, A., Solà, I., Gich, I., Delgado-Noguera, M., Rigau, D., et al. (2010). The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. *Qual. Saf. Health Care*. 19 (6), e58. doi:10.1136/qshc.2010.042077
- Alonso-Coello, P., Oxman, A. D., Moberg, J., Brignardello-Petersen, R., Akl, E. A., Davoli, M., et al. (2016). GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 353, i2089. doi:10.1136/bmj.i2089
- Arditi, C., Rège-Walther, M., Wyatt, J. C., Durieux, P., and Burnand, B. (2012). Computer-generated reminders delivered on paper to healthcare professionals; effects on professional practice and health care outcomes. *Cochrane Database Syst. Rev.* 12 (12), CD001175. doi:10.1002/14651858.CD001175.pub3
- Armstrong, J. J., Goldfarb, A. M., Instrum, R. S., and MacDermid, J. C. (2017). Improvement evident but still necessary in clinical practice guideline quality: a systematic review. *J. Clin. Epidemiol.* 81, 13–21. doi:10.1016/j.jclinepi.2016.08.005
- Bae, J. M. (2017). Shared decision making: relevant concepts and facilitating strategies. *Epidemiol. Health*. 39, e2017048. doi:10.4178/epih.e2017048
- Baker, R., Camosso-Steinovic, J., Gillies, C., Shaw, E. J., Cheater, F., Flottorp, S., et al. (2015). Tailored interventions to address determinants of practice. *Cochrane Database Syst. Rev.* 2015 (4), CD005470. doi:10.1002/14651858.CD005470.pub3
- Berwanger, O., Guimarães, H. P., Laranjeira, L. N., Cavalcanti, A. B., Kodama, A. A., Zazula, A. D., et al. (2012). Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. *J. Am. Med. Assoc.* 307 (19), 2041–2049. doi:10.1001/jama.2012.413
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., et al. (2010). AGREE II: advancing guideline development, reporting, and evaluation in health care. *CMAJ*. 182 (18), E839–E842. doi:10.1016/j.cjmed.2010.08.005
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., et al. (2013). Appraisal of guidelines for research & evaluation II. advancing guideline development, reporting and evaluation in healthcare. *CMAJ*. 182 (12), 63. doi:10.1503/cmaj.090449
- Burgers, J. S., Anzueto, A., Black, P. N., Cruz, A. A., Fervers, B., Graham, I. D., et al. (2012). Adaptation, evaluation, and updating of guidelines: article 14 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. *Proc. Am. Thorac. Soc.* 9 (5), 304–310. doi:10.1513/pats.201208-067ST
- Burgers, J. S., Cluzeau, F. A., Hanna, S. E., Hunt, C., and Grol, R. (2003). Characteristics of high-quality guidelines: evaluation of 86 clinical guidelines developed in ten European countries and Canada. *Int. J. Technol. Assess. Health Care*. 19 (1), 148–157. doi:10.1017/s026646230300014x
- Cochrane Effective Practice and Organisation of Care (EPoC) (2011). *Data collection checklist*. Ottawa, Canada: Institute of Population Health, University of Ottawa.
- Fervers, B., Burgers, J. S., Voellinger, R., Brouwers, M., Browman, G. P., Graham, I. D., et al. (2011). Guideline adaptation: an approach to enhance efficiency in guideline development and improve utilisation. *BMJ Qual. Saf.* 20 (3), 228–236. doi:10.1136/bmjqs.2010.043257
- Flodgren, G., Hall, A. M., Goulding, L., Eccles, M. P., Grimshaw, J. M., Leng, G. C., et al. (2016). Tools developed and disseminated by guideline producers to promote the uptake of their guidelines. *Cochrane Database Syst. Rev.* 2016, CD010669. doi:10.1002/14651858.CD010669.pub2
- Forsetlund, L., Bjørndal, A., Rashidian, A., Jamtvedt, G., O'Brien, M. A., Wolf, F., et al. (2009). Continuing education meetings and workshops: effects on professional practice and health care outcomes. *Cochrane Database Syst. Rev.* 2009, CD003030. doi:10.1002/14651858.CD003030.pub2
- Francke, A. L., Smit, M. C., De Veer, A. J., and Mistiaen, P. (2008). Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med. Inf. Decis. Mak.* 8, 38. doi:10.1186/1472-6947-8-38
- Gagliardi, A. R., and Alhabib, S. Members of Guidelines International Network Implementation Working Group (2015). Trends in guideline implementation: a scoping systematic review. *Implement. Sci.* 10, 54. doi:10.1186/s13012-015-0247-8
- Gagliardi, A. R., and Brouwers, M. C. (2015). Do guidelines offer implementation advice to target users? A systematic review of guideline applicability. *BMJ Open*. 5 (2), e007047. doi:10.1136/bmjopen-2014-007047
- Gagliardi, A. R., Légaré, F., Brouwers, M. C., Webster, F., Badley, E., and Straus, S. (2016). Patient-mediated knowledge translation (PKT) interventions for clinical encounters: a systematic review. *Implement. Sci.* 11 (1), 26. doi:10.1186/s13012-016-0389-3
- Gagliardi, A. R., Marshall, C., Huckson, S., James, R., and Moore, V. (2015). Developing a checklist for guideline implementation planning: review and synthesis of guideline development and implementation advice. *Implement. Sci.* 10 (1), 19. doi:10.1186/s13012-015-0205-5
- Goblirsch, G., Bershow, S., Cummings, K., Hayes, R., Kokoszka, M., Lu, Y., et al. (2013). Stable coronary artery disease. pdated.
- Giguère, A., Légaré, F., Grimshaw, J., Turcotte, S., Fiander, M., Grudniewicz, A., et al. (2012). Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database Syst. Rev.* 10 (10), CD004398. doi:10.1002/14651858.CD004398.pub3
- Greenfield, S., Steinberg, E. P., Auerback, A., Avorn, J. L., Galvin, R. S., Gibbons, R., et al. (2011). *Clinical practice guidelines we can trust*. Washington, DC: National Academies Press.
- Guideline Adaptation Committee (2016). *Clinical practice guidelines and principles of care for people with dementia*. Canberra, Australia: NHMRC Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People.
- Hoffmann-Esser, W., Siering, U., Neugebauer, E. A., Brockhaus, A. C., Lampert, U., and Eikermann, M. (2017). Guideline appraisal with AGREE II: systematic review of the current evidence on how users handle the 2 overall assessments. *PLoS One*. 12 (3), e0174831. doi:10.1371/journal.pone.0174831
- Hoffmann-Eßer, W., Siering, U., Neugebauer, E. A. M., Brockhaus, A. C., McGauran, N., and Eikermann, M. (2018). Guideline appraisal with AGREE II: online survey of the potential influence of AGREE II items on overall assessment of guideline quality and recommendation for use. *BMC Health Serv. Res* 18 (1), 143. doi:10.1186/s12913-018-2954-8
- IETS (2020). Instituto de Evaluación Tecnológica en Salud. Available at: <https://www.iets.org.co/> (Accessed June 15, 2020).
- Institute for Health Metrics and Evaluation (2020). Health-related SDGs. Available at: <http://www.healthdata.org/data-visualization/health-related-sdgs> (Accessed November 8, 2020).
- Jäger, C., Steinhäuser, J., Freund, T., Baker, R., Agarwal, S., Godycki-Cwirko, M., et al. (2016). Process evaluation of five tailored programs to improve the implementation of evidence-based recommendations for chronic conditions in primary care. *Implement. Sci.* 11 (1), 123. doi:10.1186/s13012-016-0473-8
- Krause, J., Van Lieshout, J., Klomp, R., Huntink, E., Aakhus, E., Flottorp, S., et al. (2014). Identifying determinants of care for tailoring implementation in chronic diseases: an evaluation of different methods. *Implement. Sci.* 9 (1), 102. doi:10.1186/s13012-014-0102-3
- Kristiansen, A., Brandt, L., Agoritsas, T., Akl, E. A., Berge, E., Flem Jacobsen, A., et al. (2014). Applying new strategies for the national adaptation, updating, and dissemination of trustworthy guidelines: results from the Norwegian adaptation of the antithrombotic therapy and the prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 146 (3), 735–761. doi:10.1378/chest.13-2993
- Malaysian Ministry of Health (2017a). Primary & secondary prevention of cardiovascular disease. Available at: <https://www.moh.gov.my/moh/resources/Penerbitan/CPG/CARDIOVASCULAR/3.pdf> (Accessed March 14, 2020)

- Malaysian Ministry of Health (2017b). Management of dyslipidaemia guidelines 2017. Available at: [http://www.moh.gov.my/penerbitan/CPG2017/CPG%20Management%20of%20Dyslipidaemia%202017%20\(5th%20Edition\).pdf](http://www.moh.gov.my/penerbitan/CPG2017/CPG%20Management%20of%20Dyslipidaemia%202017%20(5th%20Edition).pdf) (Accessed March 14, 2020).
- Mazza, D., Bairstow, P., Buchan, H., Chakraborty, S. P., Van Hecke, O., Grech, C., et al. (2013). Refining a taxonomy for guideline implementation: results of an exercise in abstract classification. *Implement. Sci.* 8 (32), 32. doi:10.1186/1748-5908-8-32
- Ministerio de Salud (2013). *Guía Clínica Asma Bronchial del Adulto*. Santiago, Chile: Minsal.
- Ministerio de Salud y Protección Social-Colciencias (2013a). *Detección temprana y diagnóstico del episodio depresivo y trastorno depresivo recurrente en adultos. Atención integral de los adultos con diagnóstico de episodio depresivo o trastorno depresivo recurrente*. Bogotá, Colombia: Ministerio de Salud y Protección Social-Colciencias.
- Ministerio de Salud y Protección Social-Colciencias (2013b). *Guía de práctica clínica. Hipertensión arterial primaria (HTA)*. Bogotá, Colombia: Ministerio de Salud y Protección Social-Colciencias.
- Ministerio de Salud y Protección Social-Colciencias (2014a). *Guía de práctica clínica. Basada en la evidencia para la prevención, diagnóstico, tratamiento y seguimiento de la enfermedad pulmonar obstructiva crónica (EPOC) en población adulta*. Bogotá, Colombia: Ministerio de Salud y Protección Social-Colciencias.
- Ministerio de Salud y Protección Social-Colciencias (2014b). *Guía de práctica clínica para la prevención, detección temprana, diagnóstico, tratamiento y seguimiento de las dislipidemias en la población mayor de 18 años*. Bogotá, Colombia: Ministerio de Salud y Protección Social-Colciencias.
- Ministerio de Salud y Protección Social, Departamento Administrativo de Ciencia, Tecnología e Innovación-Colciencias (2016). *Guía de práctica clínica para el diagnóstico, tratamiento y seguimiento de la diabetes mellitus tipo 2 en la población mayor de 18 años*. Bogotá, Colombia: Ministerio de Salud y Protección Social, Departamento Administrativo de Ciencia, Tecnología e Innovación - Colciencias.
- Molino, C. G. R. C., Leite-Santos, N. C., Gabriel, F. C., Wainberg, S. K., Vasconcelos, L. P., Mantovani-Silva, R. A., et al. (2019). Factors associated with high-quality guidelines for the pharmacologic management of chronic diseases in primary care: a systematic review. *JAMA Intern. Med.* 179, 553–560. doi:10.1001/jamainternmed.2018.7529
- Moore, A. E., Straus, S. E., Kasperavicius, D., Bell, N. R., Dickinson, J. A., Grad, R., et al. (2017). Knowledge translation tools in preventive health care. *Can. Fam. Physician.* 63 (11), 853.
- National Institute for Health and Care Excellence (2014a). Atrial fibrillation: management. Available at: <https://www.nice.org.uk/guidance/cg180> (Accessed April 20, 2020).
- National Institute for Health and Care Excellence (2014b). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Available at: <https://www.nice.org.uk/guidance/CG184> (Accessed April 20, 2020).
- National Institute for Health and Care Excellence (2016). Stable angina: management. Available at: <https://www.nice.org.uk/guidance/cg126> (Accessed May 10, 2020).
- National Institute for Health and Care Excellence (2018). NICE impact diabetes. Available at: <https://www.nice.org.uk/Media/Default/About/what-we-do/Intro-practice/measuring-uptake/impact-diabetes.pdf> (Accessed June 12, 2020).
- National Institute for Health and Care Excellence (2019a). Hypertension in adults: diagnosis and management. Available at: <https://www.nice.org.uk/guidance/CG184>; <https://www.nice.org.uk/guidance/cg180> (Accessed April 20, 2020).
- National Institute for Health and Care Excellence (2019b). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Available at: <https://www.nice.org.uk/guidance/ng115> (Accessed June 01, 2020).
- National Institute for Health and Care Excellence (2019c). Type 2 diabetes in adults: management. Available at: <https://www.nice.org.uk/guidance/ng28> (Accessed June 12, 2020).
- National Institute For Health And Care Excellence. Who we are. NICE. Available at: <https://www.nice.org.uk/about/who-we-are> (Accessed June 12, 2020).
- National Vascular Disease Prevention Alliance (2012). *Guidelines for the management of absolute cardiovascular disease risk*. Melbourne, Australia: National Stroke Foundation.
- Nicoletti, M. A., and Faria, T. D. M. (2017). Análise comparativa do sistema de saúde brasileiro e britânico na atenção básica. *Infarma-Cienc. Farm* 29 (4), 316–327. doi:10.14450/2318-9312.v29.e4.a2017
- Panteli, D., Legido-Quigley, H., Reichebner, C., Ollenschläger, G., Schäfer, C., and Busse, R. (2019). *Clinical practice guidelines as a quality strategy*. Copenhagen, Denmark: European Observatory on Health Systems and Policies.
- Pantoja, T., Opiyo, N., Lewin, S., Paulsen, E., Ciapponi, A., Wiysonge, C. S., et al. (2017). Implementation strategies for health systems in low-income countries: an overview of systematic reviews. *Cochrane Database Syst. Rev.* 9 (9), CD011086. doi:10.1002/14651858.CD011086.pub2
- Proctor, E., Ramsey, A. T., Brown, M. T., Malone, S., Hooley, C., and McKay, V. (2019). Training in Implementation Practice Leadership (TRIPLE): evaluation of a novel practice change strategy in behavioral health organizations. *Implement. Sci.* 14 (1), 66. doi:10.1186/s13012-019-0906-2
- Qaseem, A., Forland, F., Macbeth, F., Ollenschläger, G., Phillips, S., and van der Wees, P. (2012). Guidelines International Network: toward international standards for clinical practice guidelines. *Ann. Intern. Med.* 156 (7), 525–531. doi:10.7326/0003-4819-156-7-201204030-00009
- Schünemann, H. J., Wiercioch, W., Etzeandia, I., Falavigna, M., Santesso, N., Mustafa, R., et al. (2014). Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ* 186 (3), E123. doi:10.1503/cmaj.131237
- Scottish Intercollegiate Guidelines Network (SIGN) (2016a). *British guideline on the management of asthma*. London, United Kingdom: British Thoracic Society.
- Scottish Intercollegiate Guidelines Network (SIGN) (2016b). Management of chronic heart failure. Available at: <http://www.sign.ac.uk> (Accessed September 30, 2012).
- Siering, U., Eikermann, M., Hausner, E., Hoffmann-Eßer, W., and Neugebauer, E. A. (2013). Appraisal tools for clinical practice guidelines: a systematic review. *PLoS One.* 8 (12), e82915. doi:10.1371/journal.pone.0082915
- Stein, A. T., Lang, E., and Migowski, A. (2018). Implementing clinical guidelines: a need to follow recommendations based on the best evidence available. *Rev. Bras. Epidemiol.* 22 (21), e180021. doi:10.1590/1980-549720180021
- Suman, A., Dijkers, M. F., Schaafsma, F. G., van Tulder, M. W., and Anema, J. R. (2016). Effectiveness of multifaceted implementation strategies for the implementation of back and neck pain guidelines in health care: a systematic review. *Implement. Sci.* 11 (1), 126. doi:10.1186/s13012-016-0482-7
- Tomasone, J. R., Kauffeldt, K. D., Chaudhary, R., and Brouwers, M. C. (2020). Effectiveness of guideline dissemination and implementation strategies on health care professionals' behaviour and patient outcomes in the cancer care context: a systematic review. *Implement. Sci.* 15 (1), 41. doi:10.1186/s13012-020-0971-6

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GLOSSARY

AETSA: agencia de evaluación de tecnologías sanitarias de andalucía

af: atrial fibrillation

AGREE: appraisal of guideline research and evaluation

AUST: australia

chf: chronic heart failure

CHI: Chile

Col: Colombia

COLCIENCIAS: Colombian administrative department of science, technology and innovation

copd: chronic obstructive pulmonary disease

CPGs: clinical practice guidelines

cvd: cardiovascular disease

depr: depression

DH: department of health

dld: dyslipidemia

dm: diabetes mellitus

EPOC: Effective Practice and Organization of Care

ESP: Spain

gord: gastroesophageal reflux disease

hbp: high blood pressure

ICSI: institute for clinical systems improvement

IETS: institute of health technology assessment and technology

MYS: Malaysia

NCD: non-communicable diseases

NHAM: national heart association of Malaysia

NHMRC: national health and medical research council

NICE: national institute for health and care excellence

NVDPA: national vascular disease prevention alliance

PHC: primary health care

PUJ: pontificia universidad javeriana

SCO: Scotland

SIGN: scottish intercollegiate guidelines network

SSP: subsecretaria de salud pública

StaRI: standards for reporting implementation studies (stari) statement

UK: United Kingdom

USA: United States of America



Cost-Effectiveness of Point-of-Care A1C Tests in a Primary Care Setting

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Objective: We evaluated the cost-effectiveness of the point-of-care A1c (POC-A1c) test device vs. the traditional laboratory dosage in a primary care setting for people living with type 2 diabetes.

Materials and Methods: The Markov model with a 10-year time horizon was based on data from the HealthRise project, in which a group of interventions was implemented to improve diabetes and hypertension control in the primary care network of the urban area of a Brazilian municipality. A POC-A1c device was provided to be used directly in a primary care unit, and for a period of 18 months, 288 patients were included in the point-of-care group, and 1,102 were included in the comparison group. Sensitivity analysis was performed via Monte Carlo simulation and tornado diagram.

Results: The results indicated that the POC-A1c device used in the primary care unit was a cost-effective alternative, which improved access to A1c tests and resulted in an increased rate of early control of blood glucose. In the 10-year period, POC-A1c group presented a mean cost of US\$10,503.48 per patient and an effectiveness of 0.35 vs. US\$9,992.35 and 0.09 for the traditional laboratory test, respectively. The incremental cost was US\$511.13 and the incremental effectiveness was 0.26, resulting in an incremental cost-effectiveness ratio of 1,947.10. In Monte Carlo simulation, costs and effectiveness ranged between \$9,663.20–\$10,683.53 and 0.33–0.37 for POC-A1c test group, and \$9,288.28–\$10,413.99 and 0.08–0.10 for traditional laboratory test group, at 2.5 and 97.5 percentiles. The costs for nephropathy, retinopathy, and cardiovascular disease and the probability of being hospitalized due to diabetes presented the greatest impact on the model's result.

Conclusion: This study showed that using POC-A1c devices in primary care settings is a cost-effective alternative for monitoring glycated hemoglobin A1c as a marker of blood glucose control in people living with type 2 diabetes. According to our model, the use of POC-A1c device in a healthcare unit increased the early control of type 2 diabetes and, consequently, reduced the costs of diabetes-related outcomes, in comparison with a centralized laboratory test.

Keywords: low and middle-income countries, primary health care, point-of-care testing, diabetes mellitus, glycated hemoglobin A, cost-effectiveness

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INTRODUCTION

People living with diabetes mellitus (DM) have an increased risk of disabilities and early death due to macro and microvascular complications resulting from poor glycemic control (Camargos et al., 2018). Achieving glycemic targets in DM is directly associated with the appropriate use of medicines, changes in lifestyle, and the monitoring of blood glucose levels through a glucometer and periodic glycated hemoglobin A1c tests (Karkare et al., 2019). The A1c test allows the healthcare team to determine which individuals need to have their treatment reviewed, with the aim of avoiding both overtreatment and the worsening of their clinical presentation due to the lack of glycemic control (Hirst et al., 2017). Moreover, A1c tests predict which individuals have a higher risk of complications due to their target status (Camargos et al., 2018). However, there are several obstacles that prevent people living with DM from having A1c tests regularly. For example, people with low-income and rural populations face this difficulty (Zheng et al., 2018).

In 2019, 463 million people aged 20 to 79 were living with type 2 diabetes around the world, and almost 80% belonged to low- and middle-income countries (LMIC). The predicted mortality rate was 11% (International Diabetes Federation, 2019). Besides the alarming mortality numbers, DM also represents an important source of healthcare-related expenditure. A person living with DM represents yearly average direct costs estimated at US\$11,804.7, which include expenses for emergency visits, outpatient clinic visits, and hospitalizations at general wards or intensive care units (Wong et al., 2018). Hospitalization may cost, on average, US\$2,127.10 per patient per admission (Li et al., 2019). Thus, the high prevalence of type 2 diabetes and the high cost of treating the related complications ascribe a huge economic burden on health systems worldwide, ranging from US\$1,000 per capita annually in low-income countries to more than US\$10,000 for high-income countries (Seuring et al., 2015). Not surprisingly, these costs increased considerably if there were comorbidities or complications leading to hospitalizations (Chen et al., 2017).

Individuals with poor glycemic control have accelerated the progression of diabetic retinopathy (Osathaphan et al., 2017). According to the Diabetes Complication Severity Index, within 10 years of non-glycemic control, patients with A1c over 8% have a 16% greater risk of developing micro and macrovascular complications, such as cardiovascular disease and nephropathy, and a higher mortality risk (Pantalone et al., 2018). Controlling blood glucose levels is crucial to reducing costs and improving the quality of life of people living with DM. Some strategies optimize control, such as multidisciplinary protocols (Henriques et al., 2018), new methods of insulin administration (Roze et al., 2019), new drugs (Durdin et al., 2016), telemonitoring of patients (Warren et al., 2018), weight loss and exercising (Karkare et al., 2019), and increasing the number of medical consultations (Schwab et al., 2016). Despite these efforts, without the A1c test, it is difficult to timely identify individuals who are out of their glycemic target and adjust their therapy, which would prevent the advancement of vascular lesions, hospitalizations, and early death. However, the cost of an A1c test, along with travel to a centralized laboratory,

collecting a blood sample, and returning later for the test result, before the medical appointment in primary care, may lead to failures in individual follow-up (Alonso-Fernández et al., 2015).

The increased reliability of point-of-care (POC) devices for A1c testing has been shown to improve individual monitoring of blood glucose levels, because they can be used directly at primary care units (PCU), just before visiting the physician. With immediate access to the A1c test result, in many cases, changes in therapy can be made promptly to quickly improve glycemic control. Moreover, using POC devices at PCU could probably increase access to A1c tests for underserved and rural populations living with DM. However, POC devices and cartridges for A1c tests are expensive, which may be an obstacle for widespread use. The aim of this study was to evaluate the cost-effectiveness of a POC device for A1c dosage vs. traditional laboratory dosage in a primary care setting for people living with type 2 diabetes.

MATERIALS AND METHODS—STUDY DESIGN

We developed a Markov-based economic model to evaluate the cost-effectiveness of POC-A1c for the municipal government perspective, for routine monitoring of people living with type 2 diabetes. Our main assumptions are: 1) Improved control of glycemic levels results in risk reduction of diabetes-related complications (Huang et al., 2011); and 2) A1c control directly reflects glycemic control (Yazdanpanah et al., 2017).

Funding and Organization of Primary Care in Brazil

In Brazil, primary care is part of the public Unified Health System (SUS) funded by the federal government, states, and municipalities. The resources are managed by municipalities, which are responsible for local health policies and providing services. Hospitalizations in municipal or state hospitals caused by DM or hypertension are funded by municipalities. Each healthcare team in a PCU comprises a physician, nurse, dentist, nurse technician, and a group of community health workers, who are responsible for 2,000–3,500 people (generally, this number is higher). DM and hypertension management is managed mainly by urban and rural PCUs. At the local PCU where this study was conducted, A1c tests are conducted in a central laboratory after being requested by physicians. The collection of blood samples requires that people living with DM travel to the laboratory. As the demand for appointments at the PCU and the demand for laboratory tests is high, even when all goes well, the results may take 8–12 weeks to reach the physician, which could keep the individual out of their glycemic target for a longer period than desired (Brasil, 2017).

Data Sources for the Economic Model

This study evaluated data from people living with DM who were seen at the 16 PCUs in the urban zone of Vitória da Conquista.

TABLE 1 | Costs and probabilities of type 2 diabetes-related complications used in the economic model.

Complications	Value/patient/year (US\$)	Source of data (Ref.)
Costs		
Cardiovascular disease	1,529.00	Rosa et al. (2018)
Retinopathy	621.00	Bahia et al. (2019)
Nephropathy	1,602.00	Bahia et al. (2019)
Hospitalization	3,917.00	Henriques et al. (2018)
Diabetic foot with healing ^a	162.10	Rezende et al. (2008)
Diabetic foot with minor amputation ^a	112.90	Rezende et al. (2008)
Diabetic food with major amputation ^a	223.80	Rezende et al. (2008)
Diabetes general cost	1,844.00	Borges et al. (2014)
Probability of occurrence		
Cardiovascular disease	0.129	Santos et al. (2015)
Retinopathy	0.1340	Henriques et al. (2018)
Nephropathy	0.1680	Henriques et al. (2018)
Hospitalization	0.1895	Li et al. (2018)
Diabetic foot	0.0310	Bao et al. (2017)
Probability of death		
Cardiovascular disease	0.2840	Bujang et al. (2018)
Retinopathy	0.0000	Schmidt et al. (2015)
Nephropathy	0.0381	Sinkeler et al. (2013)
Hospitalization	0.0617	Li et al. (2018)
Diabetic foot	0.0740	Vassallo et al. (2019)

^aValues converted to USD according to the currency exchange on 07/26/2019 and updated to 2020 values, according to the World Bank annual deflator data.

Located in the northeast region of Brazil, this city has 338,480 inhabitants (Prefeitura Municipal de Vitória da Conquista, 2019) and a human development index of 0.708 (IBGE, 2017). The 18-month follow-up of participants was conducted by a research group as part of the HealthRise Program, which is a global initiative aimed at improving both access and quality care for individuals in underserved communities with DM and hypertension. The local project included support for workflow reorganization, purchasing medical and computing devices, implementing electronic medical records, training healthcare providers in protocols for DM and hypertension management, qualifying community health workers, conducting health fairs to detect target or undiagnosed people living with DM and hypertension, and monitoring the results of clinical test data such as A1c and blood pressure. Additionally, some new technologies, such as POC-A1c devices, were assessed in a real-life setting of primary care. A POC-A1c device was allocated to one PCU for 6 months. At that unit, individuals without recent A1c test results were tested prior to the physician's appointment. Individuals who presented an A1c test result above the target level were scheduled for a new test 3 months later, in accordance with the routine PCU workflow. Informed consent was required from all individuals. No direct physician-patient intervention was made. The work that the physicians did in relation to their patients was not interfered with. Unitary costs were US\$3,976.35 for the Roche Cobas b 101[®] POC device and US\$8.48 for the cartridge.

Literature Review

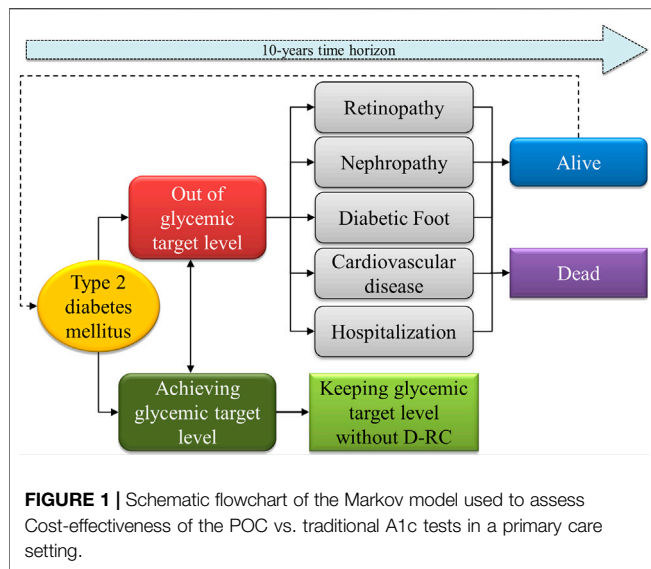
Data related to costs and the probabilities of controlling diabetes, developing complications, and death were searched in PubMed[®] and Science Direct[®]. The mesh terms and keywords used were

“type 2 diabetes,” “complications,” “Brazil,” “mortality,” “control rate,” “costs,” and “comorbidities”. They were mixed in several different combinations during the search. The search was filtered by title, and no time period was selected. When Brazilian data were not found for the probabilities, data were extracted from papers published for LMIC.

The costs and probabilities of each evaluated complication extracted from the literature are available in **Table 1**. The complications considered were cardiovascular disease (CVD), diabetic foot, retinopathy, nephropathy, and hospitalization. Most of the costs that are used refer to the reality in Brazil, which makes the model closer to an accurate result. However, few studies have researched the probabilities of these selected complications in Brazil. For diabetic foot, the mean cost of three complications applied in the model was US\$166.27. The price for the A1c conventional laboratory test was extracted from national databases (US\$2.65). Costs which were available in different currencies were converted using the Purchasing power parity criteria based on the statistics from the World Bank.

Markov Model

A transitional Markov model was built to compare the cost-effectiveness of the POC-A1c device vs. traditional laboratory A1c testing (High Performance Liquid Chromatography–HPLC) method in a centralized municipal laboratory, considering the progression of a person with type 2 diabetes over a time horizon of 10 years. The structure of the economic model is detailed in **Figure 1**. Probabilities for transition states (complications) were extracted from the literature review. The control rate for the POC device group of A1c tests was extracted from the HealthRise dataset, corresponding to 0.14, while the control rate for the traditional laboratory test was 0.0738, according to previous literature (Brown



et al., 2017). The effectiveness for both groups were extracted from the cohort as 0.0335 for the POC device group and 0.3 for the traditional laboratory test. Each cycle of the Markov model was set at 3 months, according to the recommended A1c reassessment time frame. Effectiveness was defined as achieving target levels after a 6-month period. The target level was defined as an A1c of 7.5%. A discount rate of 4% per year was applied to costs and outcomes. A half-cycle correction was performed to reduce the bias of the model. It was assumed that all individuals entered the cohort out of the glycemic target level.

Sensitivity Analysis

A tornado diagram was drawn to understand the influence of each model input parameter. The probabilistic sensitivity analysis by the Monte Carlo simulation was conducted to check model reliability. The economic model and sensitivity analysis were performed using TreeAge Pro 2020 - R1.2 (TreeAge Software Inc., MA, United States).

RESULTS

For 18 months, the local HealthRise team monitored the records of 1,390 individuals with DM. Of these, 288 (20.7%) patients were seen in the PCU where the POC-A1c device was available, and 1,102 (79.3%) were seen in 15 other PCUs. Baseline characteristics of the individuals included in the POC-A1c device group vs. the traditional laboratory test group were, respectively, as follows: 1) individuals with results for A1c available [219 (76%) vs. 397 (36%), $p < 0.0001$]; 2) sex [81 (37%) male and 138 (63%) female vs. 91 (23.4%) and 304 (76.6%), $p < 0.001$]; 3) mean age in years (standard deviation) [61.9 (0.91) vs. 56.8 (0.55), $p < 0.001$]; 4) hypertension as comorbidity [201 (91.7%) vs. 371 (93.5%), $p = 0.544$]; 5) A1c median (interquartile range) [7.8% (6.7%–9.5%) vs. 7.9% (6.8%–10.6%), $p = 0.025$]; and 6) number of medical appointments–mean (standard deviation) [1.19 (0.05) vs. 1.42 (0.06), $p = 0.005$]. The endline, as the effectiveness of the A1c target is achieved, was 0.14.

In the cost-effectiveness analysis, no dominance was observed between the two strategies. POC-A1c presented a mean cost of US\$10,503.48 per individual and an effectiveness of 0.35, vs. US\$9,992.35 and 0.09, respectively, for the traditional laboratory test in the 10-year time horizon. Consequently, POC-A1c device presented an incremental cost of US\$511.13 for an incremental effectiveness of 0.26, resulting in an incremental cost-effectiveness ratio of US\$1,947.10.

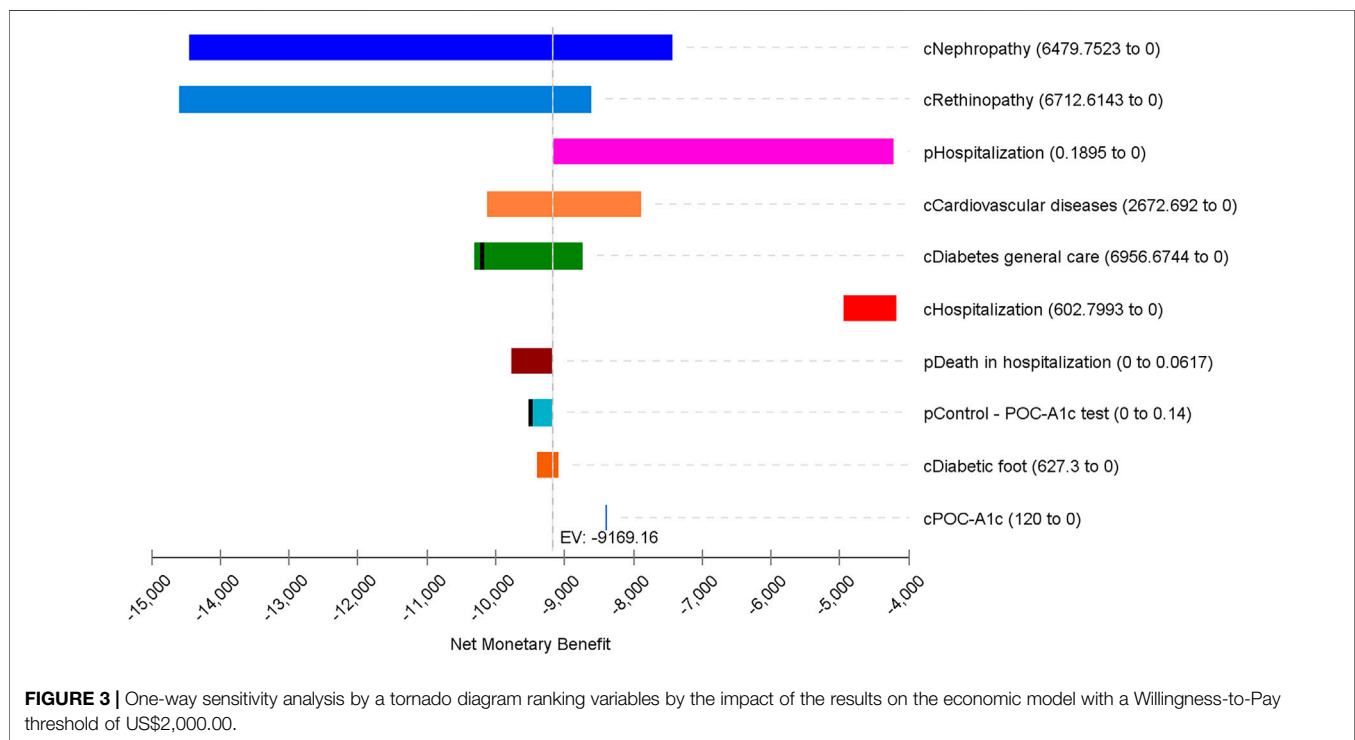
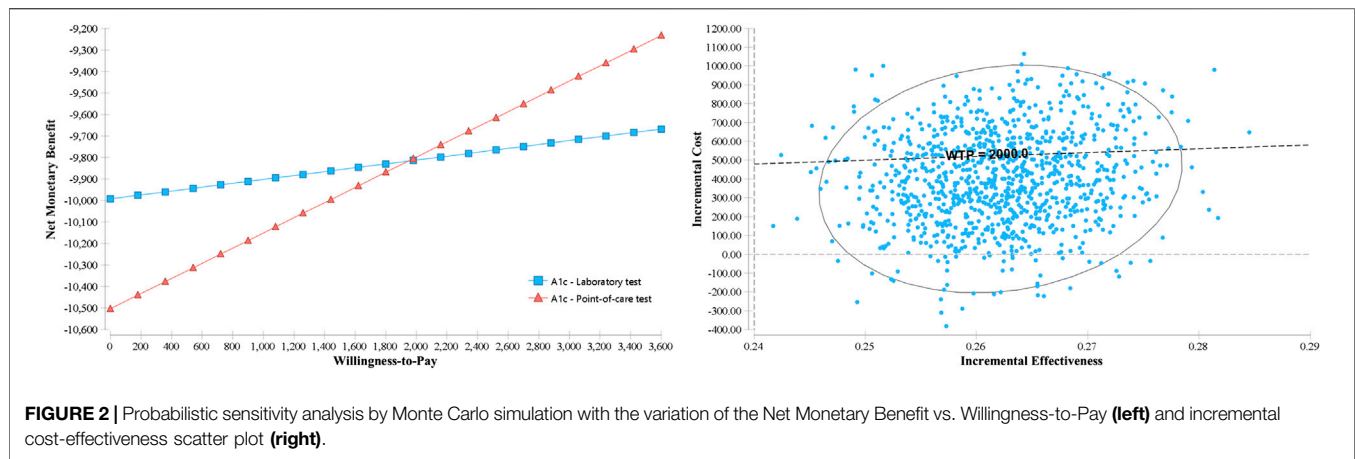
In the sensitivity analysis by Monte Carlo simulation with 1,000 random trials, the net monetary benefit (NMB) reached by the POC-A1c test overcomes the traditional laboratory test at a willingness-to-pay (WTP) value of US\$2,000 per person in the 10-year period (Figure 2). The same WTP threshold applied in the scatter plot (Figure 2) shows how each iteration between incremental effectiveness and incremental cost happened in the model. The tornado diagram (Figure 3) shows the main variables affecting the results of the economic model. The cost of nephropathy, retinopathy, and CVD, and the probability of hospitalization due to diabetes-related complications had the greatest impact on the cost-effectiveness of the comparators.

DISCUSSION

Despite being more expensive than the laboratory method, we found in our setting that the POC-A1c device is an equivalent alternative for monitoring the blood glucose levels of patients with type 2 diabetes. The POC-A1c device is faster in providing results compared to the traditional laboratory test. When the device is available at the PCU, more individuals can be tested prior to an appointment with a physician. The results indicate that, for a 10-year period, the total cost of caring for people living with type 2 diabetes is slightly higher if A1c tests were performed by the POC-A1c device. These data suggest that timely access to the exam, observed by inserting POC-A1c in primary care routine, may lead to the faster achievement of the desired A1c target, potentially minimizing diabetes-related complications, which result in health, economic, and social burdens.

The periodic monitoring of A1c directly affects decisions regarding possible changes in medication, diet, alternative therapies, and assessment adherence, which should promptly be implemented if out-of-target results are obtained (Nerat et al., 2016; Laiteerapong et al., 2018). However, a lack of the monitoring test leaves professionals and individuals without a control assessment parameter, which delays the achievement of treatment goals. This time loss harms the quality of life, increases health and social costs, and exacerbates early deaths. This study demonstrates that providing tests directly in PCU by using POC-A1c devices may expand access for proper monitoring of DM, especially for underserved populations assisted by the public healthcare system. These individuals encounter a stressful treatment process due to the high frequency of travel between the PCU and the laboratory.

Previous studies have examined the use of POC-A1c devices in hospitals (Patzer et al., 2018) or for early diagnosis in tertiary care (Gomez-Peralta et al., 2016). It was found to improve blood glucose levels in primary care (Motta et al., 2017). Although POC-A1c



devices are convenient and reliable for diabetes management (Grant et al., 2017), the costs of the devices and the supplies for A1c tests discourage their widespread use, and these costs are accounted for only at the time of purchase. This study found that the costs of purchase are offset by savings from decreased hospitalizations, heart attacks, strokes, amputations, ophthalmic procedures, blindness, dialysis, or other DM-related complications.

The sensitivity analysis indicates that the cost of general care, the POC-A1c device, and DM-related complications impacted the results of the model by increasing costs, while the probability of DM control observed in the POC device group was the main factor that led to lower costs. The cost of the POC-A1c device is probably the most sensitive factor, depending on the device manufacturer, the number of devices, and test cartridges. Thus, purchasing more

devices and cartridges could reduce prices and increase the cost-effectiveness of the POC-A1c device. Large municipalities, states, or the ministry of health may be the only parties capable of purchasing multiple devices. Therefore, the results may not be applicable to smaller settings. Additionally, if laboratory tests are more easily accessible than in this study, or if the costs of diabetes care and the rates of complications are lower than those in this study, then these results have to be applied with caution.

This study has some limitations. First, the model does not consider the costs paid by the individuals to travel to the centralized laboratory for testing, receiving results, and having a follow-up consultation. This oversight may impact the results and is a possible avenue for future research. Second, the study uses observational and secondary data rather than a clinical trial

to test effectiveness. However, by assessing the POC-A1c device as close as possible to an actual scenario, we believe that our results can sufficiently provide a snapshot of what really happens if physicians receive A1c test results on time and are, therefore, able to detect out-of-target individuals and promptly review their treatment plan. Using a clinical trial to test cost-effectiveness is a possible avenue for future research. Other difficulties that could possibly be faced in a real-life scenario include the distance from home to laboratories, the overload of primary healthcare, the shortage of antidiabetic drugs, limited therapeutic arsenal (unavailability of new drugs), individual non-adherence, and economic conditions restraining healthy habits. Third, different data sources were used to define probabilities and costs in transition states of DM-related complications, with an approximation to LMIC. Finally, some costs included in the modeling refer only to hospitalization due to diabetes-related complications, because wider data were not available. However, we believe this approach covers a substantial part of the costs assumed by the municipal governments in our setting, in addition to the costs of the local primary care system.

The adoption of the POC for glycemic control through A1c measurement helps overcome clinical inertia, as it leads to the earlier-than-expected use of oral antidiabetic drugs or insulin. Additionally, this adoption can lead to the start of new healthcare policies for managing type 2 diabetes in the public health system, emphasizing individualized follow-up, education, and empowerment tactics to change behaviors and improve lifestyles. Clinical inertia increases the risk of comorbidities and mortality due to diabetes, especially for patients with poor glycemic control, which increases the costs associated with type 2 diabetes. Increased delays in getting the right medications would decrease the prognoses of people living with diabetes (Reach et al., 2017; Ali et al., 2020).

CONCLUSION

This study showed that using POC-A1c devices in primary care settings is a cost-effective alternative for monitoring glycated hemoglobin A1c as a marker of blood glucose control in people

living with type 2 diabetes. Compared to a centralized laboratory test, the use of the POC-A1c device in a healthcare unit increased the chance of the early control of type 2 diabetes and reduced costs in relation to DM-related outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa do Instituto Multidisciplinar em Saúde da Universidade Federal da Bahia, Vitória da Conquista, Bahia, Brazil. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM, MO, and LR contributed to the study conception and design. Data acquisition, analysis and interpretation, and the manuscript draft were performed by SM and LR. MB, CK, KS, MC, DM, DS, JL, VB, WA, and LP actively contributed to the critical revision of the manuscript.

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REFERENCES

- Ali, S. N., Dang-Tan, T., Valentine, W. J., and Hansen, B. B. (2020). Evaluation of the clinical and economic burden of poor glycemic control associated with therapeutic inertia in patients with type 2 diabetes in the United States. *Adv. Ther.* 37, 869–882. doi:10.1007/s12325-019-01199-8
- Alonso-Fernández, M., Mancera-Romero, J., Mediavilla-Bravo, J. J., Comas-Samper, J. M., López-Simarro, F., Pérez-Unanua, M. P., et al. (2015). Glycemic control and use of A1c in primary care patients with type 2 diabetes mellitus. *Prim. Care Diabetes* 9, 385–391. doi:10.1016/j.pcd.2015.01.006
- Bahia, L. R., da Rosa, M. Q. M., Araujo, D. V., Correia, M. G., Dos Rosa, R. D. S., Duncan, B. B., et al. (2019). Economic burden of diabetes in Brazil in 2014. *Diabetol. Metab. Syndr.* 11, 54. doi:10.1186/s13098-019-0448-4
- Bao, X., Yang, C., Fang, K., Shi, M., Yu, G., and Hu, Y. (2017). Hospitalization costs and complications in hospitalized patients with type 2 diabetes mellitus in Beijing, China. *J. Diabetes* 9, 405–411. doi:10.1111/1753-0407.12428
- Borges, N. B., Ferraz, M. B., and Chacra, A. R. (2014). The cost of type 2 diabetes in Brazil: evaluation of a diabetes care center in the city of São Paulo, Brazil. *Diabetol. Metab. Syndr.* 6 (1), 122. doi:10.1186/1758-5996-6-122
- Brasil (2017). Portaria nº 2.436, de 21 de setembro de 2017. Brasília: Ministério da Saúde. Available at: http://www.in.gov.br/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/19308123/do1-2017-09-22-portaria-n-2-436-de-21-de-setembro-de-2017-19308031 (Accessed December 27, 2019).
- Brown, K., Fortenberry, K., Gren, L., Gunning, K., and McAdam-Marx, C. (2017). Achievement of adequate glycemic control in patients with type 2 diabetes and comorbid mental health conditions treated in a primary care setting. *Diabetes Spectr.* 30 (4), 277–287. doi:10.2337/ds16-0038
- Bujang, M. A., Kuan, P. X., Tiong, X. T., Saperi, F. E., Ismail, M., Mustafa, F. I., et al. (2018). The all-cause mortality and a screening tool to determine high-risk patients among prevalent type 2 diabetes mellitus patients. *J. Diabetes Res.* 4638327. doi:10.1155/2018/4638327

- Camargos, A. M. T., Gonçalves, A. C. O., Cazarim, M. S., Sanches, C., Pereira, L. R. L., and Baldoni, A. O. (2018). Patients lacking glycemic control place more burdens on health services with the use of medications. *Diabetes Metab. Syndr.* 12 (3), 279–283. doi:10.1016/j.dsx.2017.12.010
- Chen, D., Liu, S., Tan, X., and Zhao, Q. (2017). Assessment of hospital length of stay and direct costs of type 2 diabetes in Hubei Province, China. *BMC Health Serv. Res.* 17, 199. doi:10.1186/s12913-017-2140-4
- Durden, E., Lenhart, G., Lopez-Gonzalez, L., Hammer, M., and Langer, J. (2016). Predictors of glycemic control and diabetes-related costs among type 2 diabetes patients initiating therapy with liraglutide in the United States. *J. Med. Econ.* 19 (4), 403–413. doi:10.3111/13696998.2015.1131703
- Gomez-Peralta, F., Abreu, C., Andreu-Urioste, L., Antolí, A. C., Rico-Fontsaré, C., Martín-Fernández, D., et al. (2016). Point-of-care capillary HbA1c measurement in the emergency department: a useful tool to detect unrecognized and uncontrolled diabetes. *Int. J. Emerg. Med.* 9 (1), 7. doi:10.1186/s12245-016-0107-6
- Grant, D. A., Dunseath, G. J., Churm, R., and Luzio, S. D. (2017). Comparison of a point-of-care analyser for the determination of HbA1c with HPLC method. *Pract. Lab. Med.* 8, 26–29. doi:10.1016/j.plabm.2017.04.001
- Henriques, R. S., Steimbach, L. M., Baptista, D. R., Lenzi, L., Tonin, F. S., Pontarolo, R., et al. (2018). Direct costs of type 2 diabetes: a Brazilian cost-of-illness study. *Int. J. Technol. Assess. Health Care* 34 (2), 180–188. doi:10.1017/s026646231800017x
- Hirst, J. A., McLellan, J. H., Price, C. P., English, E., Feakins, B. G., Stevens, R. J., et al. (2017). Performance of point-of-care HbA1c test devices: implications for use in clinical practice—a systematic review and meta-analysis. *Clin. Chem. Lab. Med.* 55 (2), 167–180. doi:10.1515/cclm-2016-0303
- Huang, E. S., Liu, J. Y., Moffet, H. H., John, P. M., and Karter, A. J. (2011). Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care* 34 (6), 1329–1336. doi:10.2337/dc10-2377
- IBGE (2017). Vitória da Conquista. Available at: <https://cidades.ibge.gov.br/brasil/ba/vitoria-da-conquista/panorama> (Accessed April 19, 2019).
- International Diabetes Federation. (2019). IDF diabetes Atlas, 9th Edn. Brussels, Belgium. Available at: <https://www.diabetesatlas.org>.
- Karkare, S., Fridman, M., Dang-Tan, T., Lu, J., Smolarz, B. G., DeKoven, M., et al. (2019). Effect of weight change on economic outcomes among persons with type 2 diabetes mellitus in the United States: beyond glycemic control. *J. Manag. Care Spec. Pharm.* 25 (6), 658–668. doi:10.18553/jmcp.2019.18321
- Laiterapong, N., Cooper, J. M., Skandari, M. R., Clarke, P. M., Winn, A. N., Naylor, R. N., et al. (2018). Individualized glycemic control for U.S. Adults with type 2 diabetes: a cost-effectiveness analysis. *Ann. Intern. Med.* 168 (3), 170–178. doi:10.7326/m17-0537
- Li, T. C., Li, C. I., Liu, C. S., Lin, W. Y., Lin, C. H., Yang, S. Y., et al. (2018). Development and validation of prediction models for the risks of diabetes-related hospitalization and in-hospital mortality in patients with type 2 diabetes. *Metabolism* 85, 38–47. doi:10.1016/j.metabol.2018.02.003
- Li, X., Xu, Z., Ji, L., Guo, L., Liu, J., Feng, K., et al. (2019). Direct medical costs for patients with type 2 diabetes in 16 tertiary hospitals in urban China: a multicenter prospective cohort study. *J. Diabetes Investig.* 10 (2), 539–551. doi:10.1111/jdi.12905
- Motta, L. A., Shephard, M. D. S., Brink, J., Lawson, S., and Rheeder, P. (2017). Point-of-care testing improves diabetes management in a primary care clinic in South Africa. *Prim. Care Diabetes* 11, 248–253. doi:10.1016/j.pcd.2016.09.008
- Nerat, T., Locatelli, I., and Kos, M. (2016). Type 2 diabetes: cost-effectiveness of medication adherence and lifestyle interventions. *Patient Prefer. Adherence* 10, 2039–2049. doi:10.2147/ppa.s114602
- Osataphan, S., Chalermchai, T., and Ngasuwana, K. (2017). Clinical inertia causing new or progression of diabetic retinopathy in type 2 diabetes: a retrospective cohort study. *J. Diabetes* 9, 267–274. doi:10.1111/1753-0407.12410
- Pantalone, K. M., Misra-Hebert, A. D., Hobbs, T. M., Wells, B. J., Kong, S. X., Chagin, K., et al. (2018). Effect of glycemic control on the Diabetes Complications Severity Index score and development of complications in people with newly diagnosed type 2 diabetes. *J. Diabetes* 10, 192–199. doi:10.1111/1753-0407.12613
- Patzner, K. H., Ardjomand, P., Göhring, K., Klempt, G., Patzelt, A., Redzich, M., et al. (2018). Implementation of HbA1c point of care testing in 3 German medical practices: impact on workflow and physician, staff, and patient satisfaction. *J. Diabetes Sci. Technol.* 12, 687–694. doi:10.1177/1932296818759690
- Prefeitura Municipal de Vitória da Conquista (2019). Dados Estatísticos online. Available at: <https://www.pmvc.ba.gov.br/dados-estatisticos/> (Accessed April 19, 2019).
- Reach, G., Pechtner, V., Gentilella, R., Corcos, A., and Ceriello, A. (2017). Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. *Diabetes Metab.* 43, 501–511. doi:10.1016/j.diabet.2017.06.003
- Rezende, K. F., Nunes, M. A. P., Melo, N. H., Malerbi, D., Chacra, A. R., and Ferraz, M. B. (2008). Internações por pé diabético: comparação entre o custo direto estimado e o desembolso do SUS. *Arq. Bras. Endocrinol. Metabol.* 52 (3), 523–530. doi:10.1590/S0004-27302008000300013
- Rosa, M. Q. M., Rosa, R. D. S., Correia, M. G., Araujo, D. V., Bahia, L. R., and Toscano, C. M. (2018). Disease and economic burden of hospitalizations attributable to diabetes mellitus and its complications: a nationwide study in Brazil. *Int. J. Environ. Res. Publ. Health* 15 (2), 294. doi:10.3390/ijerph15020294
- Roze, S., Smith-Palmer, J., Delbaere, A., Bjornstrom, K., de Portu, S., Valentine, W., et al. (2019). Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections in patients with poorly controlled type 2 diabetes in Finland. *Diabetes Ther.* 10, 563–574. doi:10.1007/s13300-019-0575-9
- Santos, Ade. L., Cecílio, H. P., Teston, E. F., de Arruda, G. O., Peternella, F. M., and Marcon, S. S. (2015). Microvascular complications in type 2 diabetes and associated factors: a telephone survey of self-reported morbidity. *Cien. Saude Colet.* 20, 761–770. doi:10.1590/1413-81232015203.12182014
- Schmidt, M. I., Duncan, B. B., Ishitani, L., da Conceição Franco, G., de Abreu, D. M., Lana, G. C., et al. (2015). Trends in mortality due to diabetes in Brazil, 1996–2011. *Diabetol. Metab. Syndr.* 7, 109. doi:10.1186/s13098-015-0105-5
- Schwab, P., Saundankar, V., Bouchard, J., Wintfeld, N., Suehs, B., Moretz, C., et al. (2016). Early treatment revisions by addition or switch for type 2 diabetes: impact on glycemic control, diabetic complications, and healthcare costs. *BMJ Open Diabetes Res. Care* 4 (1), e000099. doi:10.1136/bmjdr-2015-000099
- Seuring, T., Archangelidi, O., and Suhrcke, M. (2015). The economic costs of type 2 diabetes: a global systematic review. *Pharmacoeconomics* 33, 811–831. doi:10.1007/s40273-015-0268-9
- Sinkeler, S. J., Kwakernaak, A. J., Bakker, S. J. L., Shahinfar, S., Esmatjes, E., de Zeeuw, D., et al. (2013). Creatinine excretion rate and mortality in type 2 diabetes and nephropathy. *Diabetes Care* 36, 1489–1494. doi:10.2337/dc12-1545
- Vassallo, I. M., Gatt, A., Cassar, K., Papanas, N., and Formosa, C. (2019). Healing and mortality rates following toe amputation in type 2 diabetes mellitus. *Exp. Clin. Endocrinol. Diabetes* [Epub ahead of print]. doi:10.1055/a-0942-1789
- Warren, R., Carlisle, K., Mihala, G., and Scuffham, P. A. (2018). Effects of telemonitoring on glycaemic control and healthcare costs in type 2 diabetes: a randomized controlled trial. *J. Telemed. Telecare* 24 (9), 586–595. doi:10.1177/1357633x17723943
- Wong, C. K. H., Jiao, F., Tang, E. H. M., Tong, T., Thokala, P., and Lam, C. L. K. (2018). Direct medical costs of diabetes mellitus in the year of mortality and year preceding the year of mortality. *Diabetes Obes. Metab.* 20, 1470–1478. doi:10.1111/dom.13253
- Yazdanpanah, S., Rabiee, M., Tahriri, M., Abdolrahim, M., Rajab, A., Jazayeri, H. E., et al. (2017). Evaluation of glycated albumin (GA) and GA/HbA1c ratio for diagnosis of diabetes and glycemic control: a comprehensive review. *Crit. Rev. Clin. Lab. Sci.* 54, 219–232. doi:10.1080/10408363.2017.1299684
- Zheng, Y., Ley, S. H., and Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* 14, 88–98. doi:10.1038/nrendo.2017.151

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Feasibility of De-Escalation Implementation for Positive Blood Cultures in Patients With Sepsis: A Prospective Cohort Study

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Purpose: The aim of the present study was to determine whether de-escalation guided by blood cultures for patients with a diagnosis of sepsis, severe sepsis or septic shock reduces mortality, and antimicrobial drug resistance (ADR).

Methods: A prospective, single-center, cohort study was conducted with adults admitted to the ICU with a diagnosis of sepsis, severe sepsis, or septic shock at a public hospital in Sorocaba, State of São Paulo, Brazil, from January 2013 to December 2013. We excluded patients who had negative blood cultures. Patients who had replaced the initial empirical broad-spectrum antibiotic therapy (EAT) by the antibiotic therapy guided by blood cultures were compared with those who continued receiving EAT. The outcome included mortality and antimicrobial drug resistance. We used the Cox regression (proportional hazards regression) and the Poisson regression to analyze the association between antibiotic therapy guided by blood cultures (ATGBC) and outcomes. The statistical adjustment in all models included the following variables: sex, age, APACHE II (Acute Physiology And Chronic Health Evaluation II) score and SOFA (Sequential Organ Failure Assessment) score.

Results: Among the 686 patients who were admitted to the intensive care unit, 91 were included in this study. The mean age of the patients was 52.7 years (standard deviation = 18.5 years) and 70.3% were male. EAT was replaced by ATGBC in 33 patients (36.3%) while 58 patients (63.7%) continued receiving EAT. Overall hospital mortality decreased from 56.9% in patients who received EAT to 48.5% in patients who received ATGBC [Hazard ratio- HR 0.44 (95% CI 0.24–0.82), $p = 0.009$]. There was no association between ATGBC and ADR [HR 0.90 (95% CI 0.78 – 1.03) $p = 0.15$].

Conclusions: Although the early and appropriate empirical EAT is undoubtedly an important factor prognostic, ATGBC can reduce the mortality in these patients.

Keywords: sepsis, antimicrobial stewardship, antimicrobial drug resistance, intensive care units, anti-bacterial agents [MeSH]

INTRODUCTION

Sepsis remains a serious public health problem with high morbidity and mortality. In 2017, the most recent global estimates for sepsis incidence reported 48, 9 million incident cases of sepsis and 11 million sepsis-related deaths, representing 19.7% of all global deaths (Rudd et al., 2020). Studies based on data for adults admitted to hospital show that mortality rates of sepsis range from 26.4% to 55.7% (Vincent et al., 2006; Engel et al., 2007; Machado et al., 2017; Strandberg et al., 2020; Xie et al., 2020), contributing to one-third to half of the deaths of hospitalized patients. Although therapeutic measures with considerable positive impacts have been widely emphasized, the management of sepsis in critically ill patients is challenging.

Empirical broad-spectrum antibiotic therapy (EAT) for treating sepsis, severe sepsis, and septic shock, when appropriate, reduces mortality; however, there is a risk that this treatment may expose patients to the overuse of antibiotics. It can lead to increases in antibiotic resistance, costs, and drug-associated adverse events (Martínez et al., 2020; Rhee et al., 2020). Thus, studies investigating the association between EAT and mortality among patients with sepsis have reported different findings (Paul et al., 2010). In addition, there is a relatively small number of studies that directly address the impact of the appropriate selection of antibiotic therapy in these patients (Sherwin et al., 2017).

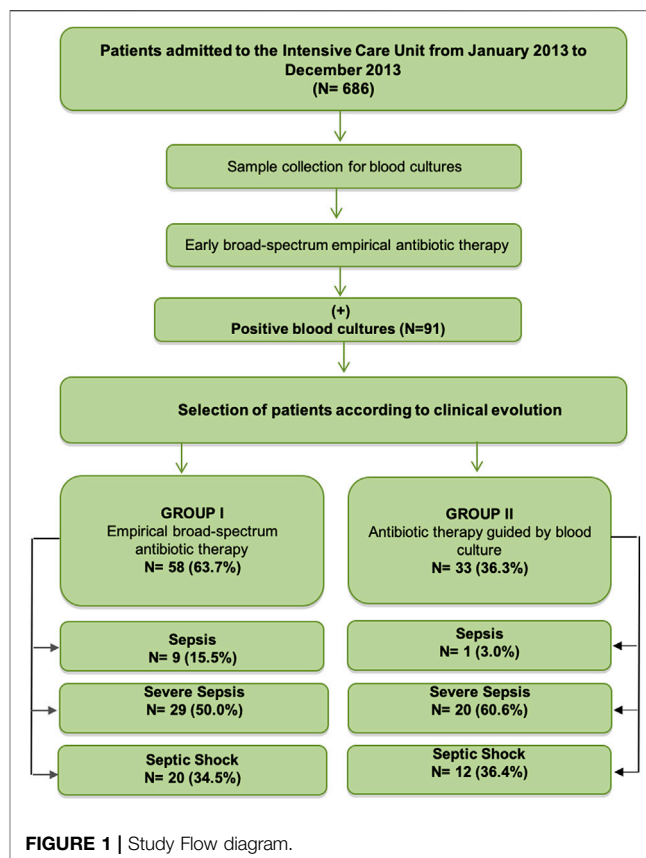
One of the main concerns on the management of patients with sepsis is the increase in the number of infections due to multidrug-resistant pathogens which limits the treatment options. Strategies focusing on the rational use of antibiotics are essential to ensure successful outcomes and to prevent adverse antibiotic effects, and the spread of antimicrobial drug resistance (ADR) (Pradipta et al., 2013; Denny et al., 2019). In this context, antibiotic therapy guided by blood culture (ATGBC) has been proposed as a strategy to reduce unnecessary exposure to antibiotics. Even if it appears beneficial, the impact of this strategy on mortality outcomes are uncertain (Lambrechts et al., 2019).

In light of these uncertainties, investigating and improving the management of antimicrobial therapy in critically ill patients with sepsis is crucial to ensure high quality and safe patient care (Mathur, 2019). Moreover, there is limited data on the impact of these strategies in patients with sepsis in low and middle-income countries such as Brazil. Therefore, this study aims to determine whether antibiotic therapy guided by blood cultures for adult patients with a diagnosis of sepsis, severe sepsis, or septic shock reduces mortality and length of hospital stay, considering relevant factors such as sex, age, and severity of sepsis.

METHODS

Study Design

A prospective, single-center, cohort study was conducted to compare mortality and length of stay in a hospital between patients who have had initial empiric therapy replaced by blood culture-guided therapy and those patients who continue receiving EAT for treatment of sepsis or sepsis severe at a public hospital in Sorocaba, State of São



Paulo, Brazil, from January 2013 to December 2013. This study was registered at Brazilian Clinical Trials Registry (ReBEC number 98.772, UTM: U1111-1,142-1806) and it was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Von Elm et al., 2014).

Setting

This study was carried out in the Intensive Care Unit (ICU) of the Conjunto Hospitalar de Sorocaba (CHS), Brazil. This public hospital is part of the fourth administrative region of the State of São Paulo (Regional Health Division XVI), which serves around three million inhabitants from 48 municipalities. The CHS is a tertiary university hospital with 28 beds destined to the ICU where patients are treated by a multidisciplinary healthcare team including 30 physicians and 20 residents in clinical and surgical clinical, the technical nurse responsible and 60 nursing technicians. It is also a hospital qualified as a Teaching Institution supported by the Faculty of Medical and Health Sciences of the Pontifical Catholic University of São Paulo.

Study Population

Study subjects included hospitalized adult patients (aged ≥ 18 years) with a diagnosis of sepsis, severe sepsis, or septic shock according to American College of Chest Physicians (ACCP) infection criteria, who were admitted to the ICU from January

TABLE 1 | Characteristics of patients with sepsis, severe sepsis or septic shock admitted to Intensive Care Unit (ICU) in a Public Hospital according to antibiotic therapy, Sorocaba city, State of São Paulo, Brazil, 2013 (*N* = 91).

	Empirical antibiotic therapy (EAT) <i>N</i> = 58 (63.7%)	Antibiotic therapy guided by blood culture (ATGBC) <i>N</i> = 33 (36.3%)	<i>p</i> > Value
Age (years)			0.68 ^a
Mean ± sd	53.5 ± 17.7	51.9 ± 18.3	
Age group (years)			1.00 ^b
≤65	41 (70.7)	23 (69.7)	
>65	17 (29.3)	10 (30.3)	
Sex			0.42 ^b
Men	42 (72.4)	25 (75.7)	
Women	16 (27.6)	8 (24.2)	
Ethnicity			0.80 ^b
Caucasian	44 (75.9)	28 (84.8)	
Black	14 (24.1)	5 (15.1)	
Severity			0.29 ^b
Sepsis	9 (15.5)	1 (3.0)	
Severe sepsis	29 (50.0)	20 (60.6)	
Septic shock	20 (34.5)	12 (36.4)	
Comorbidities			
Presence of comorbidity	33 (56.9)	20 (60.6)	0.82 ^b
Respiratory disease	4 (6.9)	1 (3.0)	1.00 ^b
Cardiovascular disease	17 (29.3)	8 (13.8)	0.63 ^b
Gastric disease	7 (12.0)	2 (6.0)	0.47 ^b
Kidney disease	7 (12.0)	6 (18.2)	0.53 ^b
Neurological disease	2 (3.5)	2 (6.0)	0.61 ^b
Autoimmune disease	2 (3.5)	2 (6.0)	0.61 ^b
Diabetes Mellitus	8 (13.8)	5 (15.2)	0.99 ^b
Malignancy	5 (8.6)	2 (6.0)	1.00 ^b
Coma on admission to the ICU	40 (68.9)	22 (66.6)	0.81 ^b
Ventilator-associated pneumonia	13 (22.4)	11 (33.3)	0.54 ^b
Apache II			0.83 ^a
First day of ICU admission Mean ± sd	24.8 ± 7.4	24.1 ± 5.9	
Last observation ^c Mean ± sd	20.6 ± 9.9	23.5 ± 6.8	
SOFA			0.71 ^a
First day of ICU admission Mean ± sd	8.4 ± 3.7	7.5 ± 2.9	
Last observation ^c Mean ± sd	5.6 ± 4.1	6.0 ± 3.2	
Length of hospitalization before the admission to ICU			0.44 ^a
Mean ± sd	7.3 ± 10.9	5.6 ± 8.8	
Median (range)	2.5 (0 – 58)	2.0 (0 – 35)	

^a*t* test.^bFisher's exact test.^cLast observation carried on before death or before ICU discharged.

2013 to December 2013. All patients who had positive results in at least two blood culture were included in order to avoid errors related to colonization/contamination of surgical sites.

Definitions

Blood samples, secretion cultures (according to their origin), and blood cultures (at least three different sites) were collected for routine admission exams according to the protocols adopted by the CHS.

Blood cultures were performed by an automated process using the Bact-Alert system manufactured by bioMérieux, Inc (100 Rudolph Wtreet, Durham, NC 27712).

EAT was defined as an initial antibiotic treatment before the microorganism was identified and antimicrobial susceptibility test results were obtained. EAT was initiated for all patients included. After the result of blood cultures, the subjects were

classified into two groups, according to clinical evolutionary criteria (Bone et al., 1992). Patients who were progressing satisfactorily remained on broad-spectrum EAT and those who did not show clinical improvement had their therapy replaced by an antibiotic therapy guided by blood culture which was based on blood culture and antibiotic susceptibility results.

Clinical and laboratory follow-up was carried out by attending physicians and infectious disease specialists, with an adaptation to the most specific antimicrobial therapy (smaller or larger generation), if possible for monotherapy and a shorter period of therapy.

Data Collection

We developed a software in the Access platform in order to collect data from patients included in this study. This software was divided into six stages of completion: patient's registration, symptoms, clinical and laboratory results, antibiogram,

TABLE 2 | Microorganisms isolated in patients with sepsis, severe sepsis or septic shock obtained on admission to Intensive Care Unit (ICU) in a Public Hospital according to antibiotic therapy, Sorocaba city, State of São Paulo, Brazil, 2013 (N = 91).

Microorganisms	Empirical antibiotic therapy (EAT) N = 58		Antibiotic therapy guided by blood cultures (ATGBC) N = 33		p value
	Total	% MR ^a	Total	% MR ^a	
Gram-positive	44 (75.8)		29 (87.9)		0.18 ^b
<i>Enterococcus</i> spp	9 (20.4)	1 (2.2)	7 (24.1)	1 (3.4)	
<i>Staphylococcus</i> sp coag neg	28 (63.6)	26 (59.0)	21 (72.4)	17 (58.6)	
<i>Staphylococcus aureus</i>	5 (11.3)	1 (2.2)	6 (20.6)	3 (10.3)	
<i>Streptococcus pneumoniae</i>	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	
Gram-negative	26 (44.8)		13 (39.4)		0.83 ^b
<i>Enterobacter aerogenes</i>	9 (34.6)	4 (15.4)	3 (23.1)	2 (15.4)	
<i>Escherichia coli</i>	2 (7.7)	1 (3.8)	1 (7.7)	0 (0.0)	
<i>Klebsiella pneumoniae</i>	9 (34.6)	4 (15.3)	5 (38.4)	3 (23.0)	
<i>Morganella morganii</i>	1 (3.8)	0 (0.0)	1 (7.7)	0 (0.0)	
<i>Pseudomonas aeruginosa</i>	6 (23.0)	3 (11.5)	3 (23.0)	2 (15.3)	
<i>Serratia marcescens</i>	0 (0.0)	0 (0.0)	1 (7.7)	1 (7.7)	
<i>Acinetobacter baumannii</i>	12 (46.1)	11 (42.3)	6 (46.1)	6 (46.1)	
<i>Citrobacter freundii</i>	0 (0.0)	0 (0.0)	2 (15.3)	1 (7.7)	
<i>Citrobacter koseri</i>	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	
<i>Burkholderia cepacia</i>	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	

^aMR = Multi-resistance.^bFisher's exact test.

comorbidities, list of antibiotics. Data were collected prospectively, and patients were followed up until death or until hospital discharge. All data collected were confirmed by two specialists (José Victor Miranda Pedroso and Eduardo Leite Croco) and were cross-checked with laboratory information which was obtained directly from the laboratory's database.

Outcomes

The primary outcome was hospital mortality. The secondary outcome was an antimicrobial drug resistance. Antimicrobial drug resistance was defined as the ability of microorganisms, especially bacteria, to resist or to become tolerant to chemotherapeutic agents, antimicrobial agents, or antibiotics. This resistance may be acquired through gene mutation or foreign DNA in transmissible plasmids.

Variables

The following data were collected prospectively for all included patients from the time of admission into the ICU: age, sex, length of hospital stay, the origin of infection, chronic diseases, and comorbidities, type of sepsis (sepsis, severe sepsis, and septic shock), need for mechanical ventilation, hemodialysis, surgical interventions, drainage, blood cultures, and antibiotic therapy. The severity of the disease was assessed using the APACHE II index (Acute Physiology And Chronic Health Evaluation II). The development of organ failures was accompanied by the SOFA index (Sequential Organ Failure Assessment). Both APACHE II index and SOFA were estimated on the first day of ICU admission and the last observation carried on before death or before ICU discharged.

Statistical Analysis

Analyses were performed using Stata v.12 (Stata Corp., College Station, TX, United States). For descriptive statistics, we

examined characteristics among patients who received EAT vs. patients who received therapy guided by blood culture. Based on distribution data we used unpaired *t*-test, chi-squared test, or Fisher's exact test.

The data were described using proportions and contingency tables for categorical variables and measures of central tendency and dispersion for continuous variables (age, Apache II, SOFA).

Hazard ratios (HRs) and 95% confidence intervals (CIs 95%) were obtained using Cox regression (proportional hazards regression) in order to estimate the effect of therapy directed by blood culture on mortality and hospital mortality. With regard to acquired antimicrobial drug multi-resistance, the relative risk and CIs 95% were calculated using Poisson regression. The statistical adjustment in all models included the following variables: sex, age, APACHE score, and SOFA score. All tests with *p*-values <0.05 were considered statistically significant.

RESULTS

During the study period, 686 adults were admitted to the ICU, 91 eligible patients with sepsis, severe sepsis, or septic shock were included, according to the inclusion and exclusion criteria (Figure 1). The mean age of the patients was 52.7 years (standard deviation = 18.5 years) and 70.3% were male. They were classified into two groups: the broad-spectrum EAT group (58 patients) and the ATGBC group (33 patients).

Characteristics of the patients included in this study according to antibiotic therapy received are detailed in Table 1. There was no significant difference between patients who received EAT and the ATGBC with respect to sociodemographic characteristics such as age, sex, and ethnicity.

TABLE 3 | The most common Multidrug Resistant Bacteria isolated in the blood cultures of patients with sepsis, severe sepsis or septic shock admitted to Intensive Care Unit (ICU) in a Public Hospital, Sorocaba city, State of São Paulo, Brazil, 2013 (N = 91).

	<i>Enterobacter aerogenes</i>		<i>Staphylococcus sp coag neg</i>		<i>Klebsiella pneumoniae</i>		<i>Pseudomonas aeruginosa</i>		<i>Acinetobacter baumannii</i>	
Antibiotic	Na	Rb (%)	Na	Rb (%)	Na	Rb (%)	Na	Rb (%)	Na	Rb (%)
Penicillins										
Penicillin G	—	—	54	51 (94.4)	—	—	—	—	—	—
Oxacillin	—	—	56	54 (96.4)	—	—	—	—	—	—
Ampicillin	12	12 (100.0)	—	—	16	16 (100.0)	—	—	4	4 (100.0)
Amoxicillin	10	10 (100.0)	—	—	14	9 (64.3)	—	—	—	—
Piperacillin	13	11 (84.6)	—	—	16	11 (68.7)	11	7 (70.7)	18	17 (94.4)
Cephalosporins										
1st Generation										
Cephalothin	12	12 (100.0)	—	—	15	11 (73.3)	—	—	—	—
Cephalexin	—	—	—	—	—	—	—	—	—	—
2nd Generation										
cefoxitin	12	12 (100.0)	—	—	17	12 (70.6)	—	—	—	—
3rd Generation										
ceftazidime	12	10 (83.3)	—	—	15	10 (66.6)	—	—	—	—
ceftriaxone	12	10 (83.3)	—	—	12	11 (91.6)	11	8 (72.7)	18	18 (100.0)
4th Generation										
cefepime	12	10 (83.3)	—	—	16	11 (68.7)	11	8 (72.7)	17	16 (94.1)
Carbapenems										
Meropenem	11	0 (0.0)	—	—	15	1 (11.2)	11	7 (63.6)	18	15 (83.3)
Imipenem	12	0 (0.0)	—	—	15	0 (0.0)	11	7 (63.6)	18	14 (77.7)
Ertapenem	12	1 (8.3)	—	—	15	0 (0.0)	—	—	—	—
Quinolones										
Ciprofloxacin	12	6 (50.0)	51	45 (88.2)	16	10 (62.5)	11	8 (72.7)	18	16 (88.8)
Aminoglycosides										
Amikacin	12	3 (25.0)	—	—	16	2 (12.5)	10	6 (60.0)	18	14 (77.7)
Gentamycin	12	9 (75.0)	56	49 (87.5)	16	7 (43.8)	11	8 (72.7)	18	16 (88.8)
Tobramycin	—	—	—	—	—	—	11	7 (63.6)	18	16 (88.8)
Sulfonamides										
Sulfamethoxazole	11	7 (63.6)	54	44 (81.5)	16	10 (62.5)	—	—	18	16 (88.8)
Macrolides										
Erythromycin	—	—	54	51 (94.4)	—	—	—	—	—	—
Chloramphenicol										
Chloramphenicol	12	7 (58.3)	55	32 (58.2)	16	8 (50.0)	—	—	—	—
Glycopeptides										
Vancomycin	—	—	54	1 (1.8)	—	—	—	—	—	—
Lincosamides										
Clindamycin	—	—	52	48 (92.3)	—	—	—	—	—	—
Monobactams										
Aztreonam	12	10 (83.3)	—	—	14	11 (78.6)	11	8 (72.7)	18	17 (94.4)
Polymyxins										
Polymyxin B	—	—	—	—	—	—	10	1 (10.0)	18	1 (5.5)
Oxazolidinones										
Linezolid	—	—	56	0 (0.0)	—	—	—	—	—	—

^aN = number of positive blood cultures where specific antibiotic was tested.^bR = number of positive blood cultures where the causative agent was resistant to the antibiotic.

TABLE 4 | Number of days of antibiotic use in patients with sepsis, severe sepsis or septic shock admitted to Intensive Care Unit (ICU) in a Public Hospital according to antibiotic therapy, Sorocaba city, State of São Paulo, Brazil, 2013 (N = 91).

Types of antibiotic	Empirical antibiotic therapy (EAT)		Antibiotic therapy guided by blood culture (ATGBC)	
	N = 58 (%)	Number of days Mean $\pm$ sd	N = 33 (%)	Number of days Mean $\pm$ sd
Penicillins	22 (37.9)		22 (66.6)	
Penicillin G	0 (0.0)	0.0 $\pm$ 0.0	1 (3.0)	8.0 $\pm$ 0.0
Oxacillin	1 (1.7)	12.0 $\pm$ 3.4	3 (9.1)	3.0 $\pm$ 1.5
Amoxicillin	0 (0.0)	0.0 $\pm$ 0.0	1 (3.3)	2.0 $\pm$ 0.0
Piperacilin + Tazobactam	21 (36.2)	10.4 $\pm$ 5.3	17 (51.5)	10.5 $\pm$ 3.5
Cephalosporins	39 (67.1)		24 (75.7)	
1st Generation				
Cefazolin	11 (18.9)	7.6 $\pm$ 4.2	3 (9.1)	1.6 $\pm$ 0.8
2nd Generation				
Cefuroxime	1 (1.7)	1.0 $\pm$ 0.0	0 (0.0)	0.0 $\pm$ 0.0
3rd Generation				
Ceftazidime	0 (0.0)	0.0 $\pm$ 0.0	1 (3.0)	4.9 $\pm$ 0.0
Ceftriaxone	20 (34.5)	8.15 $\pm$ 2.1	10 (30.3)	5.6 $\pm$ 2.5
4th Generation				
cefepime	7 (12.0)	7.1 $\pm$ 3.0	11 (33.3)	5.4 $\pm$ 3.5
Carbapenems	18 (31.0)		19 (57.6)	
Meropenem	9 (15.5)	15.2 $\pm$ 1.3	9 (27.3)	10.4 $\pm$ 4.1
Imipenem	5 (8.6)	10.6 $\pm$ 3.5	6 (18.2)	24.6 $\pm$ 2.0
Ertapenem	4 (6.8)	11.25 $\pm$ 2.8	4 (12.1)	8.5 $\pm$ 3.5
Quinolones	6 (10.3)		1 (3.0)	
Ciprofloxacin	5 (8.6)	7.0 $\pm$ 2.6	0 (0.0)	0.0 $\pm$ 0.0
Levofloxacin	0 (0.0)	0.0 $\pm$ 0.0	1 (3.0)	5.0 $\pm$ 0.0
Moxiflocin	1 (1.7)	3.0 $\pm$ 0.0	0 (0.0)	0.0 $\pm$ 0.0
Aminoglycosides	5 (8.6)		5 (15.2)	
Amikacin	4 (6.8)	7.5 $\pm$ 2.2	4 (12.1)	9.7 $\pm$ 1.5
Gentamycin	1 (1.7)	11.0 $\pm$ 0.0	1 (3.0)	21.0 $\pm$ 0.0
Sulfonamides	3 (5.2)		3 (9.1)	
Sulfamethoxazole	2 (3.4)	14.0 $\pm$ 0.0	2 (6.1)	3.0 $\pm$ 0.0
Sulfadiazine	1 (1.7)	7.0 $\pm$ 0.0	1 (3.0)	36.0 $\pm$ 0.0
Macrolides	2 (3.4)		2 (6.1)	
Rifampicin	2 (3.4)	17.5 $\pm$ 1.2	2 (6.1)	23.0 $\pm$ 0.0
Amphenicols	1 (1.7)		2 (6.1)	
Chloramphenicol	1 (1.7)	1.0 $\pm$ 0.0	2 (6.1)	0.0 $\pm$ 0.0
Glycylcyclines	1 (1.7)		1 (3.0)	
Tigecycline	1 (1.7)	19.0 $\pm$ 0.0	1 (3.0)	21.0 $\pm$ 0.0
Glycopeptides	19 (32.8)		30 (90.9)	
Vancomycin	18 (31.0)	13.6 $\pm$ 3.1	30 (90.9)	14.0 $\pm$ 5.2
Teicoplanin	1 (1.7)	1.0 $\pm$ 0.0	0 (0.0)	0.0 $\pm$ 0.0
Lincosamides	10 (17.2)		5 (15.2)	
Clindamycin	10 (17.2)	8.3 $\pm$ 2.4	5 (15.2)	11.0 $\pm$ 3.5
Polymyxins	3 (5.1)		7 (21.2)	
Polymyxin B	3 (5.1)	8.6 $\pm$ 1.2	7 (21.2)	9.8 $\pm$ 2.5
Oxazolidinones	1 (1.7)		3 (9.1)	
Linezolid	1 (1.7)	18.0 $\pm$ 0.0	3 (9.1)	12.0 $\pm$ 2.0

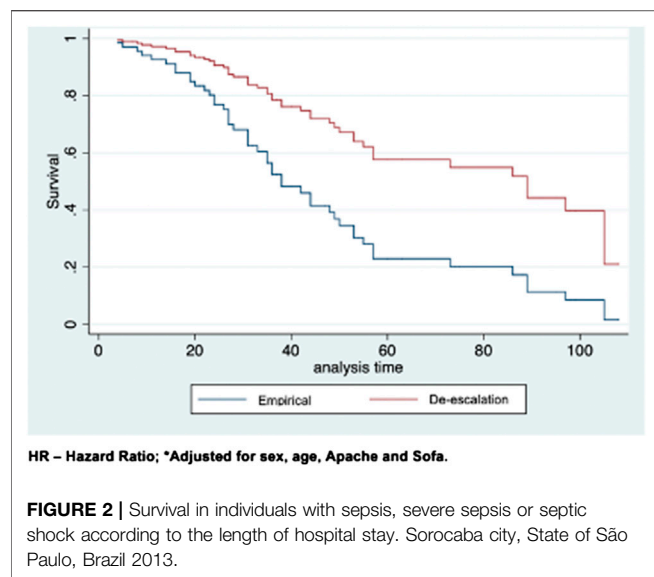
Furthermore, statistically significant differences were not detected in the proportion of comorbidities, coma ($p = 0.81$), pneumonia associated with mechanical ventilation ($p = 0.54$) and in the median values of Apache II ($p = 0.83$) and SOFA ($p = 0.71$) and length of hospital stay before the ICU ($p = 0.44$) between the two groups.

The frequency of identified pathogens in the blood cultures according to antibiotic therapy received are presented in **Table 2**. Gram-positive was the most common in both types of antibiotic therapy (75.8% of patients with EAT vs. 87.9% of patients with ATGBC therapy, $p = 0.18$). *Staphylococcus* sp coag neg (63.6%) was the most frequently Gram-positive microorganism isolated,

followed by *Enterococcus* spp. (34.6%). Among Gram-negative microorganisms, *Acinetobacter baumannii* (46.1%) was the most commonly isolated, followed by *Klebsiella pneumonia* (34.6%) and *Enterobacter erogenes* (34.6%).

The most frequent multidrug-resistant bacteria isolated in critically ill patients were *Staphylococcus* sp, followed by *Acinetobacter baumannii* and *Klebsiella pneumoniae* (**Table 3**). Oxacillin-resistant *Staphylococcus* sp and Penicillin G-resistant *Staphylococcus* sp are the most commonly identified.

Table 4 shows the antibiotics and number of days used according to intervention adopted. Piperacillin (36.2%), ceftriaxone (34.5%) and vancomycin (31.0%) were the antibiotics most used in EAT.



About 90% of ATGBC patients used vancomycin, followed by piperacillin (51.5%) and cefepime (33.3%).

Mortality

In the study sample of 91 individuals, 49 deaths were reported, resulting in a mortality rate of 53.8%. Mortality for patients who continued receiving EAT was 56.9% vs. 48.5% for patients receiving ATGBC. **Figure 2** presents a survival analysis for patients during hospitalization. The hospital mortality rate of patients receiving ATGBC was statistically lower than the mortality rate of patients who continued receiving empirical treatment after adjustment for sex, age, APACHE II, and SOFA [HR 0.44 (IC 95% 0.24 – 0.82), $p = 0.009$] (**Table 5**).

Antimicrobial Drug Resistance

The prevalence of ADR was high in both types of Antimicrobials therapy (93.5% ATGBC vs. 84.5% EAT). There was no association between ATGBC and ADR [HR 0.90 (95% CI 0.78 – 1.03) $p = 0.15$] (**Table 5**).

DISCUSSION

Although the safety and effectiveness of the strategy of de-escalation in the use of antibiotics in severe sepsis and septic shock were questioned in a previous systematic review (Silva et al., 2013), this prospective cohort study verified that the substitution of the EAT by an ATGBC increased survival of patients with sepsis when compared to the continuation of EAT, after adjusting for potentially confounding factors such as age, sex, APACHE. Currently, The Surviving Sepsis Campaign recommends that the antibiotic spectrum should be narrowed as soon as causative pathogens and their antibiotic susceptibility profile is available. In addition, some

observational studies (Garnacho-Montero et al., 2014; Tabah et al., 2016) and a meta-analysis (Gutiérrez-Pizarra et al., 2017) have also found that de-escalation therapy was associated with lower mortality rates in patients with severe sepsis and septic shock. It is important to highlight that although there is no consensus regarding the definition of de-escalation, switching from a broad to narrow therapy based on culture data constitutes one important strategy of this process (Tabah et al., 2016).

In this study, the alteration of initial empirical therapy was applied in one-third of patients. Although the severity of the disease did not influence the decision to use the ATGBC, some physicians may be reluctant to switch from a broad-spectrum antibiotic to narrow therapy when caring for patients with sepsis, especially when the infections are caused by multidrug-resistant bacteria. Furthermore, the applicability of antimicrobial therapy to infections caused by multidrug-resistant pathogens where the use of combined broad-spectrum therapy is recommended by most specialists, makes this choice very difficult to be adopted (Kollef et al., 2011).

Gram-positive bacteria were the most frequently involved microorganisms. These findings are consistent with the literature (Martin et al., 2003). *Staphylococcus* sp and *Acinetobacter baumannii* were the most prevalent multidrug-resistant bacteria. This result is similar to other studies about infections in Brazil (De Oliveira et al., 2012) and in other countries (Garnacho-Montero and Amaya-Villar, 2010; Teerawattana et al., 2018).

Despite the presence of ESKAPE organisms, the alteration of broad-spectrum empirical therapy by the narrow therapy did not influence the emergence of multidrug resistance pathogens. Although de-escalation is often presented as an effective strategy to reduce multidrug resistance, previous observational study (De Bus et al., 2016) and randomized clinical trial (Leone et al., 2014) found that the de-escalation did not affect the emergence of multidrug-resistant (MDR) pathogens. Only one study that evaluated the carbapenem de-escalation has found significant differences in resistant *Acinetobacter* spp. colonization (Lew et al., 2015). According to De Waele et al. (2020) other studies with large numbers of patients are probably required to evaluate the impact of de-escalation on ADR in ICU patients.

In 2016, the new definitions of sepsis and septic shock have changed. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This definition uses the Sequential Organ Failure Assessment (SOFA ≥ 2) score to discriminate sepsis from uncomplicated infection, replacing SIRS criteria that were criticized for being inaccurate. SIRS criteria are present in many hospitalized patients, including those who never develop infection (Singer et al., 2016). Although our study followed the criteria established in 2001, all patients included in this study had SOFA ≥ 2 . In addition, we only included patients with at least two positive blood cultures in order to ensure the diagnosis of sepsis in the patients included in this study.

TABLE 5 | Mortality and Antimicrobial Drug Resistance (ADR) in *p* patients with sepsis, severe sepsis or septic shock admitted to Intensive Care Unit (ICU) in a Public Hospital according to antibiotic therapy, Sorocaba city, State of São Paulo, Brazil, 2013 (N = 91).

	Antibiotic therapy guided by blood cultures N (%)	Empirical antibiotic therapy (EAT) N (%)	Adjusted HR ^a (95% CI ^b)	<i>p</i> value ^c
Mortality rate	16 (48.5)	28 (56.9)	0.44 (0.24–0.82)	0.009
Antimicrobial drug resistance	31 (93.9)	49 (84.5)	0.90 (0.78 – 1.03)	0.15

^aHR–Hazard Ratio.^bCI–Confidence interval.^cAdjusted for sex, age, Apache e Sofa.

Limitations and Strength of This Study

To our knowledge, this study adds valuable information on the management of antibiotic therapy in patients with sepsis since there are few data or recommendations that assess effective approaches to sepsis treatment in resource-limited low-income and middle-income countries such as Brazil. The development of local studies that analyze the use of antimicrobials, as well as ADR in hospital settings, is important since the causes of sepsis and available infrastructure can be different from those described in high-income countries. It is also important to highlight that this research included the application of a robust methodology. During the entire study period, the authors made sure that the initial empirical therapy and their alteration were based on protocol established by Hospital Infection Control Committee (HICC) which monitor the use of antibiotics and resistant strains in the hospital. The local policy regarding empiric therapy was based on antimicrobial resistant patterns present in the hospital and followed the Surviving Sepsis Campaign guideline (Dellinger et al., 2013) and used the criteria of evolutionary clinicians according to Bone et al. (1992). Furthermore, this study compared two types of therapies using robust outcome measures (mortality of hospital and antimicrobial drug resistance). Data collection was prospective and cross-checked with laboratory information which was obtained directly from the laboratory's database. In addition, there was no loss of patients in this sample, all the results collected were analyzed within the original patient group and the outcomes were adjusted by confusing factors such as sex, age, APACHE II, and SOFA.

However, some limitations of our study should be acknowledged. First, the de-escalation practice was based on physician preference. Second, this study involved a small number of patients from a single public hospital. In addition, although the all patients included in this study have the possibility of de-escalation, the number of patients who had alteration of initial empirical therapy was limited. It is important to emphasize that this work was a cohort study, patients were not randomised to the two options. Thus, the de-escalation was based on clinical decision making.

Third, we initially used medical records to collect data from patients which these are not designed for research purposes. Thus, in order to reduce memory bias or lack of data in medical records any question or absence of data was requested to the team in real-time, and all variables collected were confirmed by two specialists. Finally,

only patients with positive blood cultures were included in order to reduce the colonization/contamination bias due to the presence of bacteria in catheters and other access points in patients. Despite the blood culture remains the reference standard for the diagnosis of sepsis, contaminations represent up to 50% of positive blood cultures (Dargère et al., 2018). This limitation implied that, for all patients, the possibility of de-escalation existed. On the other hand, this inclusion criterion increases the specificity of the diagnosis of sepsis since the SIRS has limited specificity.

Implications for Clinical Practice

In order to improve antibiotic prescribing patterns, it is well established that accurate knowledge of the pathogens associated, and their susceptibility profile allows for a more rational selection of antibiotics for treatment of patients with sepsis. In clinical practice, however, antibiotics are often used, even when culture results are not available. The challenge for intensive care physicians is to obtain microbiological cultures before starting antimicrobial therapy (Schurink et al., 2004).

Although the early and appropriate EAT is undoubtedly an important prognostic factor in critically ill patients with sepsis, our findings clearly support the use of empirical antibiotics should be reviewed according to the susceptibility profile, when blood culture results are available. Thus, the ideal approach for the treatment of patients with sepsis, severe sepsis and septic shock admitted to the ICU should include the early administration of broad-spectrum antibiotics, together with reassessment and narrowing or discontinuation of subsequent treatment based on the results of blood cultures and antibacterial susceptibility. However, further studies are needed in order to evaluate the impact of the implementation of this practice on antibiotic resistance.

On the other hand, it is important to highlight that routine microbiological cultures and sensitivity tests may not be performed in some hospitals from most low- and middle-income countries, such as Brazil, due to a lack of personnel trained, equipment and financial resources (Taniguchi et al., 2019; Kakkar et al., 2020; Mathew et al., 2020). Without this information, clinicians do not have sufficient information to prescribe the narrowest-spectrum antibiotic needed to treat patients with sepsis. Therefore, the transferability of our findings to hospitals with more limited resources within Brazil or to other low- and middle-income countries will largely depend on the availability of laboratory support and financial resources.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was reviewed and approved by Research Ethics Committee of the University of Sorocaba and Research Ethics Committee of the Conjunto Hospitalar de Sorocaba (CHS). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP contributed to the conception and design of the study. JP, SK, and MC collected and organized the data. LL participated

in the design of the project and drafted the manuscript. MS and FM performed the statistical analysis. MT and FF analyzed the results of antimicrobial drug resistance. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

- Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., et al. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. the ACCP/SCCM consensus conference committee. american college of chest physicians/society of critical care medicine. *Chest* 101 (6), 1644–1655. doi:10.1378/chest.101.6.1644
- Dargère, S., Cormier, H., and Verdon, R. (2018). Contaminants in blood cultures: importance, implications, interpretation and prevention. *Clin. Microbiol. Infect.* 24 (9), 964–969. doi:10.1016/j.cmi.2018.03.030
- De Bus, L., Denys, W., Catteeuw, J., Gadeyne, B., Vermeulen, K., Boelens, J., et al. (2016). Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study. *Intensive Care Med.* 42 (6), 1029–1039. doi:10.1007/s00134-016-4301-z
- Dellinger, R. P., Levy, M. M., Rhodes, A., Annane, D., Gerlach, H., Opal, S. M., et al. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit. Care Med.* 41 (2), 580–637. doi:10.1097/CCM.0b013e31827e83af
- De Oliveira, A. C., Damasceno, Q. S., Piscocoy, M., and Nicoli, J. R. (2012). Epidemiologic characteristics of resistant microorganisms present in reserves from an intensive care unit. *Am. J. Infect. Contr.* 40 (2), 186–187. doi:10.1016/j.ajic.2011.04.010
- De Waele, J. J., Schouten, J., Beovic, B., Tabah, A., and Leone, M. (2020). Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions—a viewpoint of experts. *Intensive Care Med.* 46 (2), 236–244. doi:10.1007/s00134-019-05871-z
- Denny, K. J., Gartside, J. G., Alcorn, K., Cross, J. W., Maloney, S., and Keijzers, G. (2019). Appropriateness of antibiotic prescribing in the emergency department. *J. Antimicrob. Chemother.* 74 (2), 515–520. doi:10.1093/jac/dky447
- Engel, C., Brunkhorst, F. M., Bone, H.-G., Brunkhorst, R., Gerlach, H., Grond, S., et al. (2007). Epidemiology of sepsis in germany: results from a national prospective multicenter study. *Intensive Care Med.* 33 (4), 606–618. doi:10.1007/s00134-006-0517-7
- Garnacho-Montero, J., and Amaya-Villar, R. (2010). Multiresistant acinetobacter baumannii infections: epidemiology and management. *Curr. Opin. Infect. Dis.* 23 (4), 332–339. doi:10.1097/QCO.0b013e32833ae38b
- Garnacho-Montero, J., Gutiérrez-Pizarra, A., Escobedo-Ortega, A., Corcia-Palomo, Y., Fernández-Delgado, E., Herrera-Melero, I., et al. (2014). De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med.* 40 (1), 32–40. doi:10.1007/s00134-013-3077-7
- Gutiérrez-Pizarra, A., Leone, M., Garnacho-Montero, J., Martin, C., and Martin-Loeches, I. (2017). Collaborative approach of individual participant data of prospective studies of de-escalation in non-immunosuppressed critically ill patients with sepsis. *Expet Rev. Clin. Pharmacol.* 10 (4), 457–465. doi:10.1080/17512433.2017.1293520
- Kakkar, A. K., Shafiq, N., Singh, G., Ray, P., Gautam, V., Agarwal, R., et al. (2020). Antimicrobial stewardship programs in resource constrained environments: understanding and addressing the need of the systems. *Front. Public Health.* 8, 140. doi:10.3389/fpubh.2020.00140
- Kollef, M. H., Golan, Y., Micek, S. T., Shorr, A. F., and Restrepo, M. I. (2011). Appraising contemporary strategies to combat multidrug resistant gram-negative bacterial infections—proceedings and data from the gram-negative resistance summit. *Clin. Infect. Dis.* 53 (Suppl. 2), S33–S55. doi:10.1093/cid/cir475
- Lambrechts, M. M. C., Bernards, A. T., van der Beek, M. T., Visser, L. G., and de Boer, M. G. (2019). Time to positivity of blood cultures supports early re-evaluation of empiric broad-spectrum antimicrobial therapy. *PloS One* 14 (1), e0208819. doi:10.1371/journal.pone.0208819
- Leone, M., Bechis, C., Baumstarck, K., Lefrant, J.-Y., Albanèse, J., Jaber, S., et al. (2014). De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med.* 40 (10), 1399–1408. doi:10.1007/s00134-014-3411-8
- Lew, K. Y., Ng, T. M., Tan, M., Tan, S. H., Lew, E. L., Ling, L. M., et al. (2015). Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an ESBL-endemic setting. *J. Antimicrob. Chemother.* 70 (4), 1219–1225. doi:10.1093/jac/dku479
- Machado, F. R., Cavalcanti, A. B., Bozza, F. A., Ferreira, E. M., Angotti Carrara, F. S., Sousa, J. L., et al. (2017). The epidemiology of sepsis in brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. *Lancet Infect. Dis.* 17 (11), 1180–1189. doi:10.1016/s1473-3099(17)30322-5
- Martin, G. S., Mannino, D. M., Eaton, S., and Moss, M. (2003). The epidemiology of sepsis in the united states from 1979 through 2000. *N. Engl. J. Med.* 348 (16), 1546–1554. doi:10.1056/NEJMoa022139
- Martínez, M. L., Plata-Menchaca, E. P., Ruiz-Rodríguez, J. C., and Ferrer, R. (2020). An approach to antibiotic treatment in patients with sepsis. *J. Thorac. Dis.* 12 (3), 1007–1021. doi:10.1177/0885066618784861
- Mathew, P., Ranjalkar, J., and Chandy, S. J. (2020). Challenges in implementing antimicrobial stewardship programmes at secondary level hospitals in India: an exploratory study. *Front. Public Health* 8, 493904. doi:10.3389/fpubh.2020.493904
- Mathur, A. (2019). What's new in critical illness and injury science? Antibiotics in critical care: therapeutic toolbox. *Int. J. Crit. Illness Injury Sci.* 9 (3), 105–109. doi:10.4103/IJCIIS.IJCIIS_81_19
- Paul, M., Shani, V., Muchtar, E., Kariv, G., Robenshtok, E., and Leibovici, L. (2010). Systematic review and meta-analysis of the efficacy of appropriate empiric

- antibiotic therapy for sepsis. *Antimicrob. Agents Chemother.* 54 (11), 4851. doi:10.1128/AAC.00627-10
- Pradipta, I. S., Sodik, D. C., Lestari, K., Parwati, I., Halimah, E., Diantini, A., et al. (2013). Antibiotic resistance in sepsis patients: evaluation and recommendation of antibiotic use. *N. Am. J. Med. Sci.* 5 (6), 344–352. doi:10.4103/1947-2714.114165
- Rhee, C., Kadri, S. S., Dekker, J. P., Danner, R. L., Chen, H.-C., Fram, D., et al. (2020). Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. *JAMA Network Open* 3 (4), e202899. doi:10.1001/jamanetworkopen.2020.2899
- Rudd, K. E., Johnson, S. C., Agesa, K. M., Shackelford, K. A., Tsoi, D., Kievlan, D. R., et al. (2020). Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet* 395 (10219), 200–211. doi:10.1016/S0140-6736(19)32989-7
- Schurink, C. A., Hoitsma, M., Rozenberg-Arska, M., Joore, J. C., Hoepelman, I. M., and Bonten, M. J. (2004). Do cultures contribute to optimisation of antibiotic therapy in the intensive care unit? *Int. J. Antimicrob. Agents* 23 (4), 325–331. doi:10.1016/j.ijantimicag.2003.08.013
- Sherwin, R., Winters, M. E., Vilke, G. M., and Wardi, G. (2017). Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? *J. Emerg. Med.* 53 (4), 588–595. doi:10.1016/j.jemermed.2016.12.009
- Silva, B. N., Andriolo, R. B., Atallah, A. N., and Salomão, R. (2013). De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst. Rev.* 2013 (3), Cd007934. doi:10.1002/14651858.CD007934.pub3
- Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., et al. (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315 (8), 801–810. doi:10.1001/jama.2016.0287
- Strandberg, G., Walther, S., Agvald Ohman, C., and Lipcsey, M. (2020). Mortality after severe sepsis and septic shock in swedish intensive care units 2008–2016–A nationwide observational study. *Acta Anaesthesiol. Scand.* 64 (7), 967–975. doi:10.1111/aas.13587
- Tabah, A., Cotta, M. O., Garnacho-Montero, J., Schouten, J., Roberts, J. A., Lipman, J., et al. (2016). A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. *Clin. Infect. Dis.* 62 (8), 1009–1017. doi:10.1093/cid/civ1199
- Taniguchi, L. U., Azevedo, L. C. P., Bozza, F. A., Cavalcanti, A. B., Ferreira, E. M., Carrara, F. S. A., et al. (2019). Availability of resources to treat sepsis in Brazil: a random sample of brazilian institutions. *Revista Brasileira de Terapia Intensiva* 31 (2), 193–201. doi:10.5935/0103-507x.20190033
- Teerawattanapong, N., Panich, P., Kulpokin, D., Na Ranong, S., Kongpakwattana, K., Saksinanon, A., et al. (2018). A systematic review of the burden of multidrug-resistant healthcare-associated infections among intensive care unit patients in southeast asia: the rise of multidrug-resistant acinetobacter baumannii. *Infect. Contr. Hosp. Epidemiol.* 39 (5), 525–533. doi:10.1017/ice.2018.58
- Vincent, J. L., Sakr, Y., Sprung, C. L., Ranieri, V. M., Reinhart, K., Gerlach, H., et al. (2006). Sepsis in european intensive care units: results of the SOAP study*. *Crit. Care Med.* 34 (2), 344–353. doi:10.1097/01.ccm.0000194725.48928.3a
- Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotsche, P. C., and Vandembroucke, J. P. (2014). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int. J. Surg.* 12 (12), 1495–1499. doi:10.1016/j.ijsu.2014.07.013
- Xie, J., Wang, H., Kang, Y., Zhou, L., Liu, Z., Qin, B., et al. (2020). The epidemiology of sepsis in chinese ICUs: a national cross-sectional survey. *Crit. Care Med.* 48 (3), e209–e218. doi:10.1097/ccm.0000000000004155

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What Matters Most to Lung Cancer Patients? A Qualitative Study in Italy and Belgium to Investigate Patient Preferences

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Background: The potential value of patient preference studies has been recognized in clinical individual treatment decision-making between clinicians and patients, as well as in upstream drug decision-making. Drug developers, regulators, reimbursement and Health Technology Assessment (HTA) bodies are exploring how the use of patient preference studies could inform drug development, regulatory benefit risk-assessment and reimbursement decisions respectively. Understanding patient preferences may be especially valuable in decisions regarding Non-Small Cell Lung Cancer (NSCLC) treatment options, where a variety of treatment options with different characteristics raise uncertainty about which features are most important to NSCLC patients. As part of the Innovative Medicines Initiative PREFER project, this qualitative study aimed to identify patient-relevant lung cancer treatment characteristics.

Methods: This study consisted of a scoping literature review and four focus group discussions, 2 in Italy and 2 in Belgium, with a total of 24 NSCLC patients (Stages III-IV). The focus group discussions sought to identify which treatment characteristics patients find most relevant. The discussions were analyzed thematically using a thematic inductive analysis.

Results: Patients highlighted themes reflecting: 1) positive effects or expected gains from treatment such as greater life expectancy and maintenance of daily functioning, 2) negative effects or adverse events related to therapy that negatively impact patients' daily functioning such as fatigue and 3) uncertainty regarding the duration and type of treatment effects. These overarching themes were consistent among patients from Belgium and Italy, suggesting that treatment aspects related to efficacy and safety as well as the psychological impact of lung cancer treatment are common areas of concern for patients, regardless of cultural background or country.

Discussion: Our findings illustrate the value of using qualitative methods with patients to identify preferred treatment characteristics for advanced lung cancer. These could inform a subsequent quantitative preference survey that assesses patient trade-offs regarding treatment options.

Keywords: patient preferences, drug decision-making, drug development, patient-centered research, lung cancer, benefit-risk assessment, focus group discussions

INTRODUCTION

Non-Small Cell Lung Cancer (NSCLC) represents approximately 85% of the lung cancer forms worldwide (Jemal et al., 2011). Traditional medical treatments for advanced stages of NSCLC consist of a combination of chemotherapy and/or targeted therapy (Zappa and Mousa, 2016; Planchard et al., 2018; Hanna et al., 2020). Recently, new NSCLC treatments have been introduced, such as immunotherapy, the combination of immunotherapy and chemotherapy, and local stereotactic body radiotherapy (Ellis and Vandermeer, 2011; Aumann et al., 2016; Novello et al., 2016; Reck et al., 2016; Planchard et al., 2018; Shafique and Tanvetyanon, 2019; Hanna et al., 2020). Different treatments have both different benefits in terms of progression-free survival, overall survival and objective response rate and different risks or side-effects. For example, frequent side-effects of chemo-immunotherapy are weight increase, hair loss, pain, nausea, vomiting, breathing problems and fatigue. All of these may negatively impact patients' body image perception (Bahrami et al., 2017) and health-related quality of life (Blinman et al., 2010; Grassi et al., 2017).

This variety of lung cancer treatment options (chemotherapy, immunotherapy, chemotherapy-immunotherapy, targeted therapy), their benefits (e.g., progression-free survival, overall survival, response rate), and risks (e.g., fatigue, negative body perception) underscore the need for informed clinical treatment decision-making that takes into consideration patients' preferences¹. Such decisions require patients and their clinicians to trade-off between more aggressive treatments, with a more negative impact on their quality of life, and alternatives that may be less effective but which carry fewer adverse events, and hence less negatively affect health-related quality of life (Blinman et al., 2010; Hajjaj et al., 2010).

In view of this large variety of NSCLC treatment options that are associated with a range of different characteristics, decisions concerning lung cancer treatments may be classified as

“preference sensitive” (Lillie et al., 2014). In such decisions, the “right” decision depends the value that patients place on particular health outcomes. The potential value of patient preferences has not only been recognized in the clinical individual (“micro”) decision-making context, but also in upstream (“macro”) drug decision-making. Drug developers, regulators, reimbursement and Health Technology Assessment (HTA) bodies are exploring how the use of patient preferences could improve drug development, regulatory benefit risk-assessment and reimbursement decisions respectively (Cook et al., 2019; Hines et al., 2020; PPI, 2019).

Patient preferences can be investigated through patient preference studies via qualitative methods (e.g., interviews, focus group discussions) and/or quantitative methods (surveys using specific preference elicitation techniques, such as discrete choice experiment or swing weighting) (Van Overbeeke et al., 2019). Whereas qualitative methods are generally exploratory (see for example Bailo et al., (2019)), quantitative methods often require patients to choose between treatment alternatives and provide quantitative preference evidence (PPI, 2019). Researchers have stressed the importance of qualitative methods for investigating patient preferences; qualitative methods have been described to generate richer information than quantitative methods as they permit sensitive topics to be discussed (Coast et al., 2012; Hollin et al., 2020).

Several patient preference studies have been performed among lung cancer patients with three systematic reviews summarizing a portion of this. A first systematic review by Blinman et al., (2010) summarizes five studies between 1997 and 2009 on the subject of survival benefits that NSCLC patients expect to make the chemotherapeutic toxicity worthwhile. However, the emphasis on chemotherapy makes it difficult to generalize the findings to other therapies. In addition, the studies included in this systematic review were conducted before newer treatments such as immunotherapy were available, which may affect patients' preferences. Furthermore, the studies were all quantitative, which suggests that the attributes included in these studies were not selected by patients, but rather by clinicians and researchers. This absence of qualitative research for attribute development also contrasts with the recent recommendation of Hollin et al., (2020) and Coast et al., (2012) to use qualitative research for developing attributes included in subsequent preference surveys. Schmidt et al., (2016) conducted a more recent systematic review, which includes 17 studies between 2000 and 2012. The scope of this review was broader than the one of Blinman et al.; however, the majority of the included studies focused on chemotherapy and had a quantitative approach. Another recent systematic review

¹The FDA refers to “patient preference information” as “qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions” (<https://www.fda.gov/media/92593/download>). Attributes include types of benefits and risks associated with medical interventions. Attributes may also include other clinical and nonclinical aspects that can influence desirability or acceptability of medical interventions. (<https://www.fda.gov/about-fda/cdrh-patient-engagement/patient-preference-sensitive-areas-using-patient-preference-information-medical-device-evaluation>). In other words, patient preferences reveal what treatments or treatment characteristics patients find most important and how important they find them in comparison to each other.

(Sugitani et al., (2020)) found 15 studies published from 2000 to 2020, nine of them specifically on lung cancer patients. Finally, another systematic review found that health literacy, numeracy, and locus of control have an impact on health-related preferences and decisions (Russo et al., 2019). The included studies considered chemotherapy and surgery or radiation, and results from the systematic review suggested that, according to patients, health-related quality of life and overall survival were the most important features of a therapy. Besides these three systematic reviews, other patient preference studies have been conducted with conflicting results. This could be attributable to the fact that the scopes of these studies differ greatly. Most of them have an emphasis on a particular goal, such as a specific patient group (Hirose et al., 2005; Hirose et al., 2009; Schmidt et al., 2017), specific treatment (Peeters et al., 2012) or specific interest in characteristics such as emotional wellbeing (Mosher et al., 2017). In contrast, the present qualitative study aimed to identify patient-relevant lung cancer treatment characteristics across different therapies (including newer types of therapies such as immunotherapies) according to advanced lung cancer patients.

MATERIALS AND METHODS

Study Context

This study was conducted as part of the *Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle* (PREFER) project. PREFER aims to develop evidence-based recommendations to guide industry, regulatory authorities, and HTA bodies (including reimbursement agencies and payers) on how and when patient preference studies should be performed and when the results can be assessed and used in order to support and inform medical product decision-making ("Including the patient perspective", 2020).

Qualitative Approach, Data Collection Methods and Sources

This study aimed to identify patient-relevant lung cancer treatment characteristics. The qualitative study design involved a scoping literature review and focus group discussions with patients (Durosini et al., 2021). The literature review informed the list of treatment characteristics used in the subsequent focus group discussions, in which patients were first asked openly about which treatment characteristics (such as potential improvements and side-effects) matter most to them, and afterwards reflect on examples of treatment characteristics retrieved via the literature search. (Supplementary Appendix SA). The literature review extracted treatment characteristics from: 1) previously performed preference studies among lung cancer patients, 2) benefits and risks of treatments already being prescribed to lung cancer patients, and 3) treatment characteristics of medicines that are currently being studied in clinical trials for the treatment of lung cancer patients. Searches involved two electronic databases (Web of Science and PubMed) and used free text terms and Medical Subject Headings (MeSH). Variations of the following key search terms were adopted: "Lung Cancer" AND "Patient preferences".

Only research papers published in English were considered. Both reviews and meta-analyses including original articles were evaluated for inclusion in the scoping review. The results were screened using a twofold process. First, the title and abstract were screened based on the inclusion criteria that the studies had to: 1) assess the treatment of lung cancer and 2) assess patient preferences for lung cancer treatments. Afterwards, the full text of the selected article were reviewed to ensure that the article was relevant to the scoping review based on the above inclusion criteria. If the article met the inclusion criteria, it was included in the review and information from the study was extracted for analysis. Based on the review, a final table including both positive aspects (improvements) and side-effects related to cancer therapies was developed (See Supplementary Appendix SA).

The focus group discussions sought to identify which treatment characteristics patients found most relevant and why (Supplementary Appendix SC). Focus group discussions were selected as the method for data collection because they allow for interactivity between participants, active discussions guided by the researchers, and thereby may generate topics that researchers were previously unaware of (see Durosini et al., 2021).

Sampling Strategy and Process

Advanced stage lung cancer patients were included because they often have received different kinds of treatments and are thus able to reflect on a broad range of different characteristics from different therapies. Moreover, uncertainty on behalf of decision-makers (clinicians, patients, regulators, HTA/bodies and reimbursement agencies) seems to be particularly present in the context of advanced stage lung cancer. This is caused by the increasing amount of treatment options and treatment combinations for all stages of NSCLC, but for advanced stage lung cancer in particular as described in the introduction (see also Supplementary Appendix SB).

Participants were recruited by the treating oncologists at the Thoracic Oncology Division of the European Institute of Oncology in Milan and at the Respiratory Oncology Department of the KU Leuven University Hospital in Leuven.

Inclusion and exclusion criteria were defined and described in the protocol paper of the study (Durosini et al., 2021). A formal invitation letter was sent to those patients expressing interest in the study and who met the inclusion criteria. Those interested in participating were then contacted by telephone to plan the date and time of the focus group discussions. Ethical approval was obtained from both study centers before starting participants recruitment² and participants signed a written informed consent before participation.

Data Collection and Tools

From August 2019 to October 2019, participants were invited for the scheduled focus group discussions. At the beginning of each

²In Belgium, the "Ethische Commissie Onderzoek UZ/KU Leuven" approved the study (reference S63007). In Italy, the Ethical Committee of the European Institute of Oncology IRCCS IEO approved the study (reference 1027/19-IEO 1093)

discussion, an informed consent process took place and a consent form was signed by each participant. The discussion consisted of the following steps (see Supplementary Appendix SC):

- Welcome time, provision of the information sheet and signing of the consent form;
- Introduction of the focus group discussion including an explanation of some basic discussion 'rules' such as the importance of listening to each other, the aims of the study;
- Introduction of the main topics of the discussion and time for participants to introduce themselves;
- Introduction and discussion on the first question/topic: *"when you undergo a treatment for lung cancer, what type of improvement do you expect from it? With improvement, we mean benefits or desirable effects. Why?"*;
- Introduction and explanation of examples of improvements from the literature review (see **Supplementary Appendix SA**) and time for participants to reflect on the list;
- Break;
- Introduction and discussion on the second question/topic: *"When you undergo a treatment for lung cancer, what type of side-effects would make you want to doubt whether you want to keep on taking the treatment? Why? What type of these side-effects would make you stop taking the treatment? Why?"*;
- Introduction and explanation of potential examples of side-effects from the literature review (see **Supplementary Appendix SA**) and time for participants to reflect on the list;
- Introduction and discussion on the third question/topic: *"What type of side-effects would make you want to reconsider whether you want to continue the treatment? What type of improvements would make you want to accept more of the side-effects we just talked about?"*;
- Introduction and discussion on the fourth question/topic: *"Are there any other aspects of lung cancer treatment, besides the different side-effects and improvements we just talked about that would influence your choice to take or stop taking a lung cancer treatment? Why?"*
- Summary, Conclusions and Final Greetings.

The full discussion guide can be retrieved in the Supplementary Appendix SC. During the discussion, the moderator probed about whether a specific point was found important across participants, whether there was consensus or disagreement on certain aspects. The overall duration of the discussions ranged from 1.5 to 2.5 h and the discussions were conducted by the authors of this paper (SP, SO, ID, PG in Italy and RJ, RA, IH in Belgium), who have experience with qualitative research approaches and conducting focus group discussions. The moderator facilitated the discussion, allowing participants to respond spontaneously to the issues raised. The discussions were conducted in person in a silent and comfortable room, and they were audio recorded with participants' permission. To increase procedural comparability among the discussions conducted by the two different teams, both teams used the same discussion guide and weekly meetings between moderators and other members of the research team were organized before and after

the discussions took place. In all discussions, participants were asked to complete a short questionnaire (Supplementary Appendix SD) to gather information on socio-demographics and health literacy via the Chew Brief Literacy scale (Chew et al., 2008).

As for the sample size, it is worth noting that data collection for qualitative research does not have clear guidelines on how much data should be included in a study (Brod et al., 2009). Several authors indicate that qualitative data should be collected until "data saturation", which has been defined as the point when "no new information or themes are observed in the data", when redundancy is reached in data analysis and signals to researchers that data collection may cease. Several studies found that data saturation can be achieved after conducting four to six focus groups (Morgan, 1996; Brod et al., 2009; Kerr et al., 2010; Hennink et al., 2019), especially when the goal is to identify "core" issues. Since the aim of the present study was indeed to identify "core" attributes among lung cancer patients with regard to their treatment, we estimated that four focus groups across two different countries (Italy and Belgium) would be sufficient to reach data saturation (see also Durosini et al., 2021). Following qualitative data collection, it appeared that the same themes were observed across the focus group discussions. Hence, it was decided that no additional data was needed.

Data Processing and Data Analysis

U Mann-Whitney tests were carried out to investigate possible differences between Italian and Belgian participants in terms of stage of disease, treatment characteristics, socio-demographics, and health literacy. The audio-recordings were transcribed verbatim in the original language and then translated into English by a professional translation company. Transcripts and notes from the focus group discussions were thematically analyzed using an iterative approach as described in the framework method by Lacey and Luff (2009) (see **Table 1**) and using Nvivo v.11.

An inductive thematic analysis was conducted, allowing the transcripts to determine the themes. Four researchers, two in Italy and two in Belgium, independently coded all the transcripts. A first phase of familiarization involved reading the material, taking initial notes, and getting familiar with the data. Using Nvivo v.11, the second phase involved the data coding, highlighting sections of the text and labeling them with a short code to describe the content. The codes are those aspects that emerged from the discussions and were found to be relevant across group members. In the third phase, the codes were then grouped in themes, in which every theme is a combination of several codes. The final phase involved defining and naming the themes. Throughout the analysis, an iterative, constant comparative analysis approach was used to enable continuous modifications and extensions of the themes to ensure that all key aspects could be incorporated through these modifications. The lists of themes was then compared and combined across Italy and Belgium to generate a comprehensive list. During this phase, overarching themes were detected, whilst considering similarities or potential differences in the sub-themes identified.

TABLE 1 | Iterative steps of the framework method followed for the thematic analysis of the focus group discussions. The charting step (i.e., summarizing of the data based on the themes identified through the analysis), as described by Lacey and Luff (2009), was performed during the writing of this paper and is therefore not mentioned in the table.

1. Familiarization	SP, SO, RJ, and RA thoroughly read and re-read the transcripts. They used the margins of the transcripts to write down analytical notes, thoughts or impressions (e.g., when focus group participants expressed exceptionally strong or contrasting views)
2. Identifying a thematic framework	To identify an initial thematic framework, SP, SO, RJ, and RA independently coded the text, meaning that they attached specific themes or concepts to particular paragraphs, based on the research aims of the study. These codes were different factors such as treatment outcomes, side-effects and symptoms patients mentioned during the focus group discussions
3. Coding	SP, SO, RJ, and RA discussed these preliminary codes to assess whether they interpreted the focus group discussions in the same manner and to reach consensus about the final coding list. The final coding list (i.e. framework) consisted of the final list of characteristics, each with examples of what ideas or elements could be summarized under that code. NVivo (QSR international) was used to code the transcripts using the final coding list
4. Mapping and interpretation	Meetings were organized between SP, SO, RJ, and RA to discuss their coding. This process took into consideration the differences between the Italian and Belgian focus group discussions but also between the focus group discussions within one country

RESULTS

Literature Review

From the literature review, a list of examples of treatment characteristics included in the focus group discussions was derived (see **Supplementary Appendix SA**).

Focus Group Discussions

Participants' Characteristics

Twenty-four advanced stage lung cancer patients participated in the focus group discussions (age range: 42–78, Mage = 61, SDage = 8.5; 62% men), equally distributed in Belgian ($n = 12$) and Italian ($n = 12$) discussions (6 patients in each discussion). Mean age of patients at the time of diagnosis was 58 years ($SD = 8$; Age range: 41–73). Response rates ranged between 50% and 57% in Italy and Belgium and across the four focus group discussions. Reasons for refusal to participate were: 1) extreme psychological suffering due to NSCLC diagnosis, 2) painful physical symptoms, 3) long distance from the hospital, 4) too little time available, 5) not interested and 6) preference to stay at home whenever they were not necessarily expected to be in the hospital (for quality of life). The majority of participants had a high-school degree (41.6%), whereas 37.5% did not finish the High School, and 20.8% had a university degree. U Mann-Whitney tests indicated that Belgian participants were significantly older than Italian participants ($U = 111.5$, $p = 0.020$), and significantly longer diagnosed with lung cancer than Italian participants ($U = 109$, $p = 0.039$). Gender and education distributions were not significantly different in the two groups of participants. Comparing Belgian and Italian patients, there was no difference even in the number of participants who were on treatment. Additionally, U Mann-Whitney tests revealed a significant difference between Italian and Belgian participants on the first question of the literacy scale ("How often do you have someone, like a family member, friend, hospital/clinic worker, or caregiver, help you read hospital materials?" retrieved from Chew et al., (2008)) ($U = 108.5$, $p = 0.025$) with Italian participants relying more on family members than the Belgian patients. There were no differences between the two groups on the other two questions included in the Chew Brief Literacy scale. **Table 2** reports all participants' characteristics.

Qualitative Results From Thematic Analysis

A thematic analysis was conducted on the focus group discussion transcripts. Data revealed differences in the specific side-effects experienced by NSCLC patients. More specifically, episodes of diarrhea, vomiting, and sexual impotence emerged in Italian focus group discussions, while they were not raised during the discussions in Belgium. In addition, the importance patients gave to specific side-effects (e.g. hair loss, cognitive limitations) varied between individual patients. However, there were apparent overarching themes of treatment characteristics where patients agreed upon during the discussion. In particular, three overarching themes emerged from the thematic analysis: 1) positive effects or expected gains from treatment, 2) negative effects or adverse events that patients want to avoid, and 3) uncertainty regarding the duration and type of treatment effects. These themes are described below.

Positive Effects or Expected Gains From Treatment

The first theme emerging in the four focus group discussions consisted of positive treatment effects such as greater life expectancy, decrease in cancer growth, cancer remission, and maintenance of daily functioning. Patients reported that one important reason to prefer a particular treatment is that it increases their life expectancy and prolongs the patient's life. Another important feature for patients was that the treatment ensures that the cancer grows less rapidly or stops growing.

Cancer remission was another important feature of the treatment. Patients expected to see their cancer stop growing, and reduce in size. Lastly, participants highlighted the importance of being able to perform their daily activities. Participants stated they wanted to live as much as possible a normal life, and be able to continue their activities like before their cancer. In **Table 3**, we report on several quotes related to this theme.

Negative Effects or Adverse Events Related to Treatment

The second theme consists of categories related to common side-effects or adverse events of advanced stage lung cancer treatments (i.e., severe skin problems, nausea, hair loss, infections, and infusion reaction, gravity of edema, fatigue, and weight fluctuations) and categories related to less common side-effects (i.e., probability of renal failure, having pain, hearing impairment,

TABLE 2 | Participants' characteristics distinguished by country. LC = lung cancer.

	Italy	Belgium
Age		
M (sd) - range	57.33 (8.56)–42–72	64.92 (6.82)–52–78
Gender		
Males	41.6%	83.3%
Females	58%	16.7%
Education		
Did not finish high school	58%	16.7%
High school Diploma	41.6%	41.7%
Higher education or university degree	-	41.7%
Currently on LC treatment		
No treatment or only symptomatic treatment	-	33.3%
Immunotherapy	33.3%	41.7%
Chemotherapy	16.7%	16.7%
Chemotherapy and immunotherapy	16.7%	8.3%
Biological therapy	33.3%	-
Number of treatment lines		
M (sd) - range	2.42 (3.6)–0–12	2.33 (1.44)–0–5
Health literacy - M (sd)		
Item 1	2.58 (1.8)	4.33 (0.89)
Item 2	3.83 (1)	3.92 (0.79)
Item 3	3.67 (0.77)	3.83 (0.58)

cognitive limitations, difficulty in breathing). **Table 2** shows examples of the discussions regarding those themes. Both Italian and Belgian participants stressed the importance of these effects because of their negative impact on patients' possibility to maintain their daily functioning or their psychological wellbeing. In contrast, diarrhea, vomiting, and sexual impotence emerging in Italian focus group discussions, were not raised by Belgian patients. Conversely, weeping eyes was only mentioned in the Belgian discussion.

Uncertainty Regarding the Duration and Type of Treatment Effects

The third theme relates to the uncertainty that patients experience regarding the long-term effects of their current treatment. Participants argued that both the uncertainty of the duration and type of negative effects and the uncertainty regarding the duration of positive effects were difficult for them to cope with. They stressed the role of patient-friendly but accurate treatment information and good communication with their healthcare providers as possible ways to help them cope with these uncertainties (**Table 3**).

DISCUSSION

This qualitative study identified patient-relevant characteristics of lung cancer treatment. The strength of this qualitative study is the involvement of advanced stage lung cancer patients, who already experienced the main benefits vs. negative consequences of NSCLC therapies, including immunotherapy, chemotherapy, or a combination of both. For this reason, these persons can easily reflect and give their opinion on the outcomes of different therapies. The overarching themes reflecting treatment

characteristics highlighted by patients in the focus group discussions were: 1) positive effects or expected gains from treatment such as greater life expectancy and maintenance of daily functioning, 2) negative effects or adverse events related to therapy that impact patients' daily functioning and 3) uncertainty regarding the duration and type of treatment effects (**Table 3**). These overarching themes were consistent across patients from both Belgium and Italy, suggesting that treatment aspects related to efficacy and safety and the psychological effects of lung cancer and treatments are common areas of concern for advanced lung cancer patients, regardless of cultural background or country.

In contrast, differences regarding specific side-effects experienced by individual patients and how they had been experienced by individual patients were observed between participants within and across different focus group discussions in Italy and Belgium. More specifically, diarrhea, vomiting and sexual impotence were not raised by Belgian patients and weeping eyes was only mentioned in the Belgian discussion.

Although there is nothing in the published research literature to date suggesting that there are systematic differences between Italian and Belgian lung cancer patients concerning these side-effects, as with all qualitative research, it is possible that these differences were idiosyncratic to the specific group of patients who participated in the focus group discussions. In addition, it is possible that hitherto unstudied cultural differences in how side-effects and/or symptoms are experienced, acknowledged and expressed may account for these differences. For these reasons, conducting this study with other patients, and for example in additional countries, could lead to the identification of additional specific characteristics. Likewise, conducting this study when newer NSCLC treatment algorithms or newer (combinations of) medications become available could also lead to the identification of additional treatment characteristics.

TABLE 3 | Examples of qualitative evidence of the themes.

Overarching Themes	Themes	Italy	Belgium
Positive effects or expected gains from treatment	Greater life expectancy	P6-Focus 1: "Oh, [I expect] that he makes me live a little more" P4-Focus 1: "It would be enough for me to know that it [the cancer] is blocked there. I've been fine so far and sometimes I don't realize I'm doing this So it would be enough for me to stop it." P3-Focus 1: "Live as long as possible! When they say you have cancer it is not like when you break an arm that you say "heal"."	P5-Focus 1: "I hope that the treatment prolongs my life so that I can see my grandchildren grow up" P2-Focus 1: "If you feel bad one day That is nothing in comparison to living a day longer" P5-Focus 1: "P5: Well, I've always continued to move forward. I even started sorting out my funeral two months ago. Hoping of course, that I can stay alive for a long time, and so that my wife does not have any problems later on. that everything is arranged and that she can be at ease. So that is how rational I am and yes I just carry on with my life."
	Decrease in cancer growth	P6-Focus 1: "I expect that maybe it [the cancer] regresses a little and that he stays there as it is."	P1-Focus 1: "Healing will not be possible, so limiting the progression is our goal" P1-Focus 2: "For most people, it is already too late to be able to cure them, all you can do at that point is reduce it"
	Cancer remission	P1-Focus 1: "I expect healing" P2-Focus 2: "I immediately tell you loud and clear: to heal. Which unfortunately did not happen. Do not do more treatments and do nothing. To heal"	P2-Focus 1: "The focus must always remain on the primary - on healing, and the rest is nice to have" P4-Focus 1 "If they say: 'we are going to give you chemo and radiation'. 'Yeah, go ahead'. What am I supposed to do? 1/3 chance of success, of healing"
	Maintenance of daily functioning	P3-Focus 1: "Try to live my life as normal as possible, as similar as possible to the previous one" P3-Focus 2: "It's not just a matter of not wanting to die, it's also a question of how you want to live, rather than not wanting to die" P5-Focus 2: "P5: I can't even ride a bicycle, imagine that. It is not that I can't ride it, it is that I can't get on it"	P5-Focus 2: "I think it depends on how livable your side-effects are, how enjoyable your life then still is" P2-Focus 1: "Being a bit more active than I am now. Sitting about at home isn't easy if you've always worked. I mean it's really driving me crazy" P2-Focus 1: "I would stop the treatment if my quality of life fell so low that it made me say: 'why keep going?'"
Uncertainty regarding the duration and type of treatment effects		P3-Focus 2: "Beforehand it lasted 1 h or 1 h and 10 min. Now I see that things have changed the initial phases were analysis, study and now the protocols have changed a bit... Beforehand I was doing it in 1 h and 10 min, now in 40 min. I am also used to it, I did it today. I am also used to it, apart from the first 24 h which" P1-Focus 2: "but the path is a bit long, you don't recover straight away it takes a bit of time, it takes some years, at least that is the case in the experiences that I have encountered up until now"	P6-Focus 1: "It's so new and long term, will it keep working, will it stop?" P7-Focus 1: "I had to wait 5 months for the results of a scan. That's too long for me there's too much uncertainty" P2-Focus 1: "If they would have told me beforehand: 'Sir, your sense of taste will change and nothing will be tasty anymore Then you can say: 'That is the way it has to be So that you know what you are up against'" P1-Focus 2: "What could be the cause, what are the remedies, what are the chances of survival, what stages. there is unfortunately very little to be found, let's say at the Benelux level, of information. I have been lucky from day one to have had a very good communication, in my case with the professor" (treating physician)

(Continued on following page)

TABLE 3 | (Continued) Examples of qualitative evidence of the themes.

Overarching Themes	Themes	Italy	Belgium
Negative effects or expected loss from treatment	Severity of skin problems	P2-Focus 2: "Every day. One pill that I take every day. I find that this pill, compared to the other one, the other one really killed me. In the first few months I lost all of the skin from my hands, face, spots"	P7-Focus 1: "That's a side-effect of the immunotherapy; it starts to itch, then I began to scratch it, but you keep scratching until you start bleeding"
	Severity of nausea	P1-Focus 1: I haven't had any side-effects, apart from in January when I had chemo, nausea at the thought of eating fish, but zero side-effects	P2-Focus 1: "the misery that comes with it; being sick, feeling nauseous"
	Severity of diarrhea	P2-Focus 2: "The first treatment that I had, I had diarrhoea problems"	No example of this theme emerged in the Belgian focus groups
		P2-Focus 2: "Better to die and then I was unless I had stomach sickness, diarrhoea, spots all over, blood coming out of here especially"	
	Severity of vomiting	P2-Focus 1: "They brought me to accident and emergency because I could not eat any more, I vomited twenty times, after two times I had to stop it because it was highly"	No example of this theme emerged in the Belgian focus groups
		P2-Focus 1: "Yes, I couldn't even manage to take Plasil, the side-effect was fainting, or almost.. it was vomiting, continuing and continuing and nothing ever came up because I wasn't able to hydrate myself"	
	Severity of hair loss	P3-Focus 1: "Yes I the history of hair, who loses them all on a personal level is devastating, okay you put on the wig but maybe if you could create something that controls this or that stimulates growth"	P5-Focus 1: "Losing my hair is the least of concerns"
		P2-Focus 1: "I practically just eat fish, fruit, chicken. I have eliminated almost everything, pasta they tell me that I have a low immune system"	P2-Focus 1: "If I would go completely bald. I'm almost certain that that is something I absolutely cannot live with. Then I'd say 'I stop'"
	Severity of infections		P2-Focus 1: "My daughter says 'your immune system is at its lowest now. Don't stand near ill people in the shop, stay away from the bakery, because if there is one person that is ill, then you will get ill too' (..) you only have to catch a disease once and your treatment is completely ruined"
	Severity of infusion reactions	P3-Focus 2: "Look, because among those that I see thrombocytopenia colitis nausea reaction to the infusion"	P1-Focus 1: "The very first time, I had an internal reaction to the therapy. So I was shivering because I was so cold, then fever, forty degrees, and they were panicking at home saying: 'you have to go to the hospital'"
	Gravity of the edema	P3-Focus 1: "One thing that I would find hard to accept is too much swelling"	P1-Focus 2: "Those first two years, I didn't have any (side-effects) apart from my edema but I could live with that just fine"
	Gravity of fatigue	P6-Focus 2: "Yes, I get tired easily"	P7-Focus 1: "The only thing that I actually have, since I get that immunotherapy, yes tired, tired, tired, tired, I am always tired. I could always sleep. It is unbelievable"
	Gravity of weight fluctuations	P6-Focus 1: "With chemo I was so tired, like that lady, I have always walked, I have climbed so many stairs and steps in my life and, conversely, since I have had chemo I have found it difficult to walk, to cook"	
		P5-Focus 1: "I would not accept 120 kg because this weight gain is so frustrating for me that it really destroys me. I got to the point of not going out"	P1-Focus 1: "I've gained 20 kilos and I really don't feel good about it If I want to go out, then it is like: 'is my tummy not too big?' And then I try to wear clothing that fit me as loosely as possible so that I can be a bit more comfortable."
	Probability of renal failure	P3-Focus 2: "This is to say that if we stay on the topic of the side-effects, if we have therapy which makes the cancer chronic but creates additional new illnesses such as kidney failure"	P1-Focus 1 "Then you get your test results and then you see that something about the kidney function is slightly less and that is - there were too few white blood cells in the urine"
	Probability of sexual impotence	P3-Focus 2: "P3: For me, as a man, impotence would certainly be of a different weight compared to the tube tube all my life but this, why? Because certain psychological problems of dissatisfaction would be triggered for a man; impotence and the impossibility of working are almost in the collective imagination."	No example of this theme emerged in the Belgian focus groups
	Probability of having pain	P2-Focus 2: "I would do everything that I have done again, despite all the pain."	P1-Focus 2: "There are an awful lot of kinds of lung cancer that give you really bad pain, where not even morphine is enough for the pain - yes and that's something."

(Continued on following page)

TABLE 3 | (Continued) Examples of qualitative evidence of the themes.

Overarching Themes	Themes	Italy	Belgium
Probability of having hearing impairment	Probability of having weeping eyes	P4-Focus 2: "Well, I don't know How can I say that? Besides, on the same day I lost my hearing, I don't know if it was also linked to the first drug that I took I don't know."	P3-Focus 1: "But that was the decision: did I want to go deaf or did I want - well yes, that wasn't an option for me"
		No example of this theme emerged in the Italian focus groups	P5-Focus 1: "The only nasty side-effect I have are tears and a runny nose. I eat with my fork in my right hand and I always need to have a tissue in my left hand"
		P1 - Focus 2: It has really been more of a mental illness than a physical one	P3-Focus 2: "If they tell me I will get dementia, I will still continue to get treatment."
		P3-Focus 2: "Extreme conditions, you were talking about euthanasia and extreme conditions before, like in the case of the [name of a TV show] about [name of a well-known person in Italy who did euthanasia], that is an extreme condition, there is no point living like that."	P1-Focus 2: "I will undergo every treatment as long as my brain functions."
Probability of having difficulty in breathing		P5-Focus 2: "My only fear was not breathing, the thing that I tried the two previous nights in hospital. But now I still have my breath. At the start I was doing three stairs and stopping with a fit, not now."	P1-Focus 1: "but after an hour or an hour and a half - Then it's like: 'that's enough for me, because you are so tired.'"

Further research could assess the impact of treatment experience by setting-up a longitudinal design; conducting additional focus group discussion with the same patients in the beginning, in middle and at the end of their therapy to assess whether additional characteristics would emerge. Other patient and contextual factors that could influence their opinions and preferences are: 1) patients' individual knowledge and need for information concerning therapies; some patients may want to learn about therapies whereas others not and the characteristics raised by these patients could differ between those groups of patients; 2) the way patients are supported and educated could also explain differences in opinions; e.g. participants with a supportive primary caregiver at home base might raise other aspects of the therapy vs. someone with difficult access to the hospital and/or a very small social network and 3) the time frame patients have (or need) to reflect on treatment decisions. It would therefore be interesting to further investigate heterogeneity in preferences and explain potential differences and the impact of these factors and patient characteristics on patient preferences. For example, it would be interesting to perform a further analysis of cross-country similarities and differences between Italian and Belgian patients and try to explain the impact of treatment experience on our findings. For the same reason, it would be interesting to apply the same methodology in additional countries to assess further if cultural aspects or other patient characteristics affect patient preferences. These are clearly important topics deserving further research in this regard, especially due to their implications for product manufacturers who are seeking to develop products, in most instances, for global markets, and regulatory and reimbursement decision-makers whose decisions impact multiple patients in one or more countries.

However, in view of limited evidence from lung cancer patient preferences regarding newer lung cancer therapies, we believe that this study may be informative for healthcare stakeholders interested in using patient preferences to inform the development, evaluation and prescription of lung cancer treatments. Firstly, lessons from applying this qualitative methodology may inform the development of PREFER's evidence-based guidelines for future preference study developers and assessors on how to perform qualitative preference research that aims to inform decision-making across the drug life cycle. Secondly, the results may inform the development of a quantitative preference survey that elicits patients' trade-offs for the characteristics of lung cancer treatment.

Thirdly, the identified treatment characteristics may inform healthcare stakeholders involved in the development and evaluation of lung cancer treatments (academia, clinicians, drug developers, patient organizations, regulators and HTA/reimbursement bodies) to understand the value of lung cancer treatment outcomes according to patients. More specifically, these characteristics may inform academia, patient organizations and drug developers on the design of patient-centered clinical trials, e.g. via the identification of clinical trial endpoints and patient-reported outcome measures beyond those that have traditionally been included in lung cancer treatment trials. For example, we identified that uncertainty and psychological aspects of lung cancer and lung cancer therapy are

important to patients. It may therefore be appropriate to include a measure in clinical trials that assesses the psychological impact of the therapy on patients. In addition, evidence on how important patients find these different treatment outcomes may be used in marketing authorization and reimbursement ("macro") decision-making. Patient preferences may add the available evidence on benefits and risks already considered during the decision process as well as complement existing decision criteria for marketing authorization and reimbursement.

Finally, in individual (micro) decision-making, the ethical and legal mandate for patient involvement in medical care is well-accepted as is the importance of patients expressing their preferences, and in engaging in informed choice in treatment decision-making (O'Connor et al., 1997; Say and Thomson, 2003). However, it has been highlighted that the preference elicitation process poses a challenge for doctors (Say and Thomson, 2003) in terms of time to spend to collect patients' preferences and doctors' abilities to elicit patients' preferences. Our research may inform healthcare providers and clinicians of important factors on patients' preferences, outside the traditional ones (e.g. age, performance status, comorbidities, histology and molecular pathology) (Novello et al., 2016). More specifically, these characteristics may be incorporated in decision aids that aim to improve shared decision-making between clinicians and patients as therapeutic decisions require value judgements of each of the treatments' benefits and risks by doctors and patients combined together. An understanding of patients' preferences could facilitate medical decision-making and promote more patient-centered health care.

LIMITATIONS

Firstly, it is important to reflect on the representativeness of our sample. Care was taken to include different types of participants (with various disease and treatment histories, and inclusive of those patients in a relatively good condition as well as further progressed in the disease and who are typically harder to reach) to ensure that the eventually found characteristics are important to different types of patients. Notwithstanding, it is important to note that our results are not meant to be generalized to a population broader than the included sample and that they should not be viewed as representing the entire population from which the included patients were sampled, in this case, all stage III-IV NSCLC patients. As for any qualitative research, we also have to underline that we cannot make any conclusive statements regarding how the sample size may have affected the generalization of the results. However, we could speculate that the inclusion of additional patients and additional countries beyond the two included, could affect the derived themes. Secondly, the participants were selected by clinicians. This could be deemed as "cherry picking" certain types of patients that the clinician thinks would be most suitable for the study, e.g. those with the worst experiences, or those that are in a relatively good condition. Therefore, if only a certain type of patients was included, this could bias the outcomes of the study. However, as mentioned above, the clinicians took care to select different types of participants regarding current disease status and treatment

history. Secondly, we found it useful to source patients with the clinicians' involvement, both because of their knowledge of the overall health status of the patients, and thus how to include different types of patients, as well as from a practical point of view. A last limitation of the study is the lack of a quantitative evaluation of the relevant themes. However, further quantitative research has been planned with the aim to complement and quantify the findings of the present qualitative study; the prioritized characteristics emerged from the present research will be ranked by patients using the Nominal Group Technique (Hilgsmann et al., 2013). In addition, a subsequent online survey has been planned to quantify the relevance of the treatment characteristics identified in this study, across a larger sample of lung cancer patients. This survey will also compare different quantitative methods for the elicitation and study of patient preferences.

CONCLUSION

Our findings illustrate the value of using qualitative study methods with patients to identify preferred treatment characteristics for advanced lung cancer. These findings could inform a subsequent quantitative preference survey to assess patient trade-offs regarding treatment options. Previous preference research in this area, which relied predominantly on clinician-nominated treatment characteristics, used a comparatively limited set of characteristics that focused on survival and the severity of toxicity. In contrast, our preference study results indicate that patients consider a broader range of characteristics as being highly salient to their decision-making regarding cancer treatment options. Future research should examine whether our findings are transferable to other clinical settings.

The themes emerged from the present qualitative study may also inform: 1) drug developers on the design of patient-centered clinical trials and more specifically for the identification of clinical trial endpoints and patient-reported outcome measures, 2) regulators and HTA/reimbursement to understand whether the treatment being evaluated targets (clinical) outcomes that are relevant for patients and 3) healthcare providers when deciding on treatment options (e.g., via the development of decision aids that aim to improve shared decision-making between clinicians and patients).

DATA AVAILABILITY STATEMENT

The data are not publicly available because they contain information that could compromise interviewees' privacy and consent. Requests to access the datasets should be directed to serena.petrocchi@ieo.it.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the "Ethische Commissie Onderzoek UZ/KU Leuven" (reference S63007) in Belgium and the Ethical Committee of the European Institute of Oncology IRCCS IEO

(reference 1027/19-IEO 1093) in Italy. All participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Writing of focus group guidelines: RJ, RA, KN, EL, MV, MS. Data collection and recruitment: SP, RJ, RA, PG, SO, ID, IH, GP, KN, EL, MV, GG, LG, FM. Analysis of results and interpretation: SP, RJ, IH, RA, SO, ID, KN, GP, EL, MV, GG, LG, FM. Writing the paper: SP, RJ, RA. Revision of the paper and final approval: SP, RJ, RA, SO, ID, IH, GP, KN, EL, MV, GG, LG, FM.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.602112/full#supplementary-material>.

REFERENCES

- Aumann, I., Kreis, K., Damm, K., Golpon, H., Welte, T., and Graf von der Schulenburg, J. M. (2016). Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis. *Health Expect.* 19 (6), 1226–1236. doi:10.1111/hex.12417
- Bahrami, M., Mohamadirizi, M., Mohamadirizi, S., and Hosseini, S. A. (2017). Evaluation of body image in cancer patients and its association with clinical variables. *J. Educ. Health Promot.* 6, 81. doi:10.4103/jehp.jehp_4_15
- Bailo, L., Guidi, P., Vergani, L., Marton, G., and Pravettoni, G. (2019). The patient perspective: investigating patient empowerment enablers and barriers within the oncological care process. *Ecancermedicalscience* 13, 912. doi:10.3332/ecancer.2019.912
- Blinman, P., Alam, M., Duric, V., McLachlan, S. A., and Stockler, M. R. (2010). Patients' preferences for chemotherapy in non-small-cell lung cancer: a systematic review. *Lung Canc.* 69 (2), 141–147. doi:10.1016/j.lungcan.2010.05.001
- Brod, M., Tesler, L. E., and Christensen, T. L. (2009). Qualitative research and content validity: developing best practices based on science and experience. *Qual. Life Res.* 18, 1263–1278. doi:10.1007/s11136-009-9540-9
- Castellanos, E. H., Chen, S. C., Drexler, H., and Horn, L. (2015). Making the grade: the impact of low-grade toxicities on patient preference for treatment with novel agents. *J. Natl. Compr. Canc. Netw.* 13 (12), 1490–1495. doi:10.6004/jnccn.2015.0177
- Chew, L. D., Griffin, J. M., Partin, M. R., Noorbaloochi, S., Grill, J. P., Snyder, A., et al. (2008). Validation of screening questions for limited health literacy in a large VA outpatient population. *J. Gen. Intern. Med.* 23 (5), 561–566. doi:10.1007/s11606-008-0520-5
- Coast, J., Al-Janabi, H., Sutton, E. J., Horrocks, S. A., Vosper, A. J., Swancutt, D. R., et al. (2012). Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. *Health Econ.* 21 (6), 730–741. doi:10.1002/hec.1739
- Cook, N. S., Cave, J., and Holtorf, A. P. (2019). Patient preference studies during early drug development: aligning stakeholders to ensure development plans meet patient needs. *Front. Med.* 6, 82. doi:10.3389/fmed.2019.00082
- Durosini, I., Janssen, R., Arnou, R., Veldwijk, J., Smith, M. Y., Monzani, D., et al. (2021). Patient preferences for lung cancer treatment: a qualitative study protocol among advanced lung cancer patients. *Front. Public Health* 9 (27).
- Ellis, P. M., and Vandermeer, R. (2019). Delays in the diagnosis of lung cancer. *J. Thorac. Dis.* 3 (3), 183–188. doi:10.3978/j.issn.2072-1439.2011.01.01
- Grassi, L., Spiegel, D., and Riba, M. (2017). Advancing psychosocial care in cancer patients, *F1000Res.* 6, 2083. doi:10.12688/f1000research.11902.1
- Hajjaj, F. M., Salek, M. S., Basra, M. K., and Finlay, A. Y. (2010). Non-clinical influences on clinical decision-making: a major challenge to evidence-based practice. *J. R. Soc. Med.* 103 (5), 178–187. doi:10.1258/jrsm.2010.100104
- Hanna, N. H., Schneider, B. J., Temin, S., Baker, S., Brahmer, J., Ellis, P. M., et al. (2020). Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO and OH (CCO) Joint guideline update. *J. Clin. Oncol.* 38 (14), 1608–1632. doi:10.1200/JCO.19.03022
- Hennink, M. M., Kaiser, B. N., and Weber, M. B. (2019) What influences saturation? Estimating sample sizes in focus group research. *Qual. Health Res.* 29, 1483–1496. doi:10.1177/1049732318821692
- Hilgsmann, M., van Durme, C., Geusens, P., Dellaert, B. G., Dirksen, C. D., van der Weijden, T., et al. (2013). Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. *Patient Prefer. Adherence* 7, 133. doi:10.2147/PPA.S38408
- Hines, P. A., Janssens, R., Gonzalez-Quevedo, R., Lambert, A. I., and Humphreys, A. J. (2020). A future for regulatory science in the European Union: the European Medicines Agency's strategy. *Nat. Rev. Drug. Discov.* 19, 293–294. doi:10.1038/d41573-020-00032-0
- Hirose, T., Horichi, N., Ohmori, T., Kusumoto, S., Sugiyama, T., Shirai, T., et al. (2005). Patients preferences in chemotherapy for advanced non-small-cell lung cancer. *Intern Med.* 44, 107–113. doi:10.2169/internalmedicine.44.107
- Hirose, T., Yamaoka, T., Ohnishi, T., Sugiyama, T., Kusumoto, S., Shirai, T., et al. (2009). Patient willingness to undergo chemotherapy and thoracic radiotherapy for locally advanced non-small cell lung cancer. *Phychooncology* 18 (5), 483–489. doi:10.1002/pon.1450
- Hollin, I. L., Craig, B. M., Coast, J., Beusterien, K., Vass, C., DiSantostefano, R., et al. (2020). Reporting formative qualitative research to support the development of quantitative preference study protocols and corresponding survey instruments: guidelines for authors and reviewers. *Patient* 13 (1), 121–136. doi:10.1007/s40271-019-00401-x
- Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., and Forman, D. (2011). Global cancer statistics. *CA Cancer J Clin.* 61 (2), 69–90. doi:10.3322/caac.20107
- Kerr, C., Nixon, A., and Wild, D. (2010). Assessing and demonstrating data saturation in qualitative inquiry supporting patient-reported outcomes research. *Expert Rev. Pharmacoecon. Outcomes Res.* 10, 269–281. doi:10.1586/erp.10.30
- Lacey, A., and Luff, D. (2009). *Qualitative data analysis: the NIHR research design service for Yorkshire and the Humber*. National Institute for Health Research.
- Lillie, S. E., Partin, M. R., Rice, K., Fabbri, A. E., Greer, N. L., Patel, S. S., et al. (2014). The effects of shared decision making on cancer screening—a systematic review. *VA ESP Project* #09-009.
- Mosher, C. E., Ott, M. A., Hanna, N., Jalal, S. I., and Champion, V. L. (2017). Qualitative feedback from advanced lung cancer patients and their family caregivers. *Cancer Nurs.* 40, 66–75. doi:10.1097/NCC.0000000000000350

- Morgan, D. L. (1996). Focus groups. *Annu. Rev. Sociol.* 22, 129–152. doi:10.1146/annurev.soc.22.1.129
- Novello, S., Barlesi, F., Califano, R., Cufer, T., Ekman, S., Levra, M. G., et al. (2016). Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 27 (Suppl. 1–5), v1–v27. doi:10.1093/annonc/mdw326
- O'Connor, A. M., Llewellyn-Thomas, H. A., Sawka, C., Pinfold, S. P., To, T., and Harrison, D. E. (1997). Physicians' opinions about decision aids for patients considering systematic adjuvant therapy for axillary-node negative breast cancer. *Patient Educ. Counsel.* 30, 143–153. doi:10.1016/s0738-3991(96)00948-2
- PPI (2019). Patient preference information (PPI) in medical device decision-making Available at: <https://www.fda.gov/about-fda/cdrh-patient-engagement/patient-preference-information-ppi-medical-device-decision-making>
- Peeters, L., Sibille, A., Anrys, B., Oyen, C., Dooms, C., Nackaerts, K., et al. (2012). Maintenance therapy for advanced non-small-cell lung cancer: A pilot study on patients' Preceptions. *J. Thorac Oncol.* 7, 1291–1295. doi:10.1097/JTO.0b013e31825879ea
- Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., et al. (2018). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 29 (Suppl. 4), iv192–iv237. doi:10.1093/annonc/mdy275
- Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csösz, T., Fülöp, A., et al. (2016). Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375 (19), 1823–1833. doi:10.1056/NEJMoa1606774
- Russo, S., Jongerius, C., Faccio, F., Pizzoli, S. F. M., Pinto, C. A., Veldwijk, J., et al. (2019). Understanding patients' preferences: a systematic review of psychological instruments used in patients' preference and decision studies. *Value Health* 22 (4), 491–501. doi:10.1016/j.jval.2018.12.007
- Say, R. E., and Thomson, R. (2003). The importance of patient preferences in treatment decisions--challenges for doctors. *Bmj* 327 (7414), 542–545. doi:10.1136/bmj.327.7414.542
- Schmidt, K., Damm, K., Prenzler, A., Golpon, H., and Welte, T. (2016). Preferences of lung cancer patients for treatment and decision-making: a systematic literature review. *Eur. J. Cancer Care* 25 (4), 580–591. doi:10.1111/ecc.12425
- Schmidt, K., Damm, K., Vogel, A., Golpon, H., Manns, M. P., Welte, T., et al. (2017). Therapy preferences of patients with lung and colon cancer: A discrete choice experiment. *Patient prefer Adherence* 11, 1647–1656. doi:10.2147/PPA.S138863
- Shafique, M., and Tanvetyanon, T. (2019). Immunotherapy alone or chemo-immunotherapy as front-line treatment for advanced non-small cell lung cancer. *Expert Opin. Biol. Ther.* 19 (3), 225–232.
- Sugitani, Y., Sugitani, N., and Ono, S. (2020). Quantitative preferences for lung cancer treatment from the patients' perspective: a systematic review. *Patient* 13 (5), 521–536. doi:10.1007/s40271-020-00434-7
- Van Overbeeke, E., Janssens, R., Whichello, C., Schölin Bywall, K., Sharpe, J., Nikolenko, N., et al. (2019). Design, conduct, and use of patient preference studies in the medical product life cycle: a multi-method study. *Front. Pharmacol.* 10, 1395. doi:10.3389/fphar.2019.01395
- Zappa, C., and Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. *Transl. Lung Cancer Res.* 5 (3), 288. doi:10.21037/tlcr.2016.06.07
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Risks of Adverse Neonatal Outcomes in Early Adolescent Pregnancy Using Group Prenatal Care as a Strategy for Public Health Policies: A Retrospective Cohort Study in Brazil

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Background: Adolescent pregnancy is a public health concern and many studies have evaluated neonatal outcomes, but few have compared younger adolescents with older using adequate prenatal care.

Objective: To compare the risks of adverse neonatal outcomes in younger pregnant adolescents who are properly followed through group prenatal care (GPC) delivered by specialized public services.

Methods: This retrospective cohort study followed pregnant adolescents (aged 10–17 years) who received GPC from specialized public services in Brazil from 2009 to 2014. Data were obtained from medical records and through interviews with a multidisciplinary team that treated the patients. The neonatal outcomes (low birth weight, prematurity, Apgar scores with 1 and 5 min, and neonatal death) of newborns of adolescents aged 10–13 years were compared to those of adolescents aged 14–15 years and 16–17 years. Incidence was calculated with 95% confidence intervals (CIs) and compared over time using a chi-squared test to observe trends. Poisson Multivariate logistic regression was used to adjust for confounding variables. The results are presented as adjusted relative risks or adjusted mean differences.

Results: Of the 1,112 adolescents who were monitored, 758 were included in this study. The overall incidence of adverse neonatal outcomes (low birth weight and prematurity) was measured as 10.2% (95% CI: 9.7–11.5). Apgar scores collected at 1 and 5 min were found to be normal, and no instance of fetal death occurred. The incidence of low birth weight was 16.1% for the 10–13 age group, 8.7% for the 14–15 age group and 12.1% for the 16–17 age group. The incidence of preterm was measured at 12, 8.5, and 12.6% for adolescents who were 10–13, 14–15, and 16–17 years of age, respectively. Neither low birth weight nor prematurity levels significantly differed among the groups ($p > 0.05$). The infants born to mothers aged 10–13 years presented significantly ($p < 0.05$) lower Apgar scores than other age groups, but the scores were within the normal range.

Conclusions: Our findings showed lower incidence of neonatal adverse outcomes and no risk difference of neonatal outcomes in younger pregnancy adolescents. It potentially suggests that GPC model to care pregnant adolescents is more important than the age of pregnant adolescent, however further research is needed.

Keywords: pregnant, prematurity, low birth weight, prenatal care, adolescents

INTRODUCTION

Adolescent pregnancy is a public health concern due to the complexities and impacts of problems related to it (1). Among adolescents, pregnancy is seldom planned or desired; in many cases, it results from abuse or sexual violence, causing permanent changes in their lives and creating a cycle of inequality, social exclusion, difficulty attending school, job loss, or reductions in work hours and the potential development of emotional disorders (2). The adolescent's life course changes, eventually leading to school dropouts and the perpetuation of poverty, inequality, and exclusion (3).

Approximately 12 million adolescents aged 15–19 years and 770 thousand of whom are under 15 years give birth each year in developing world (4). In Brazil, the rate of adolescent pregnancy is 400 thousand cases each year (5).

Adolescent pregnancy may be a risk factor for adverse obstetric, maternal, or neonatal outcomes such as prematurity, low birth weight, low Apgar scores, and neonatal and maternal mortality, mainly in mothers under 15 years of age (6, 7). One study reported an increase in maternal and fetal complications occurring during all stages of pregnancy among pregnant adolescents (8, 9). However, according to other research, such complications are more closely associated with newborns, particularly for cases of prematurity, low birth weight and death (8, 10, 11).

Factors potentially associated with adverse neonatal outcomes include a reduced number of prenatal visits being made, late or inadequate access to prenatal care, race, marital status, low education level, smoking and poverty (12, 13).

Preventive interventions to address preterm low birth weight and mortality include efforts to improve the quality of prenatal care in the intrapartum and postpartum periods (14). Although Brazil maintains elevated levels of prenatal care coverage across the country, quality, and adequacy rates are low, ranging from 4.5 to 66.1% in several regions (12). This is attributed to individuals not making the ideal number of consultations or using early assistance services, to failures of basic procedures and to a lack of content designed for consultations (15).

Recently, group prenatal care models in general, both for adult women with risk factors and for adolescents, have been growing in popularity internationally, mainly in high-income settings; such models may offer advantages over the traditional individual model of care (16). Complete prenatal care is provided in a group setting and integrates pregnancy health assessments and education on nutrition; potential problems with pregnancy or childbirth; child care; the prevention or detection of disease; skills building services; and peer support (14). This model has

been adopted in Brazil and allows for significantly more time compared to models of traditional individual prenatal care, provides pregnancy care to ~12 women simultaneously over up to 10, 90–120-min group visits and follows American Congress of Obstetricians and Gynecologists guidelines (17, 18).

A recent overview shows that compared to findings associated with individual care, group prenatal care is associated with a decreased rate of low birth weight overall and with a reduction in risk for preterm birth among African-American women (16). A systematic review (with only two high quality randomized studies conducted on women with high-risk pregnancies) suggests that compared to standard individual care, group prenatal care decreases rates of preterm births and cesarean sections and increases the prevalence of breastfeeding and satisfaction with care (19). These improved outcomes may be due to reduced levels of stress and enhanced knowledge, and stronger effects have been observed with women who experience higher levels of stress (20).

The data are conflicting, and evidence of benefits in low- and middle-income countries (where resources are scarce) is limited (21). More researches are needed to demonstrate the health impact and effects of group prenatal care in these settings.

Considering the high prevalence of adolescent pregnancy and its consequences in Brazil, the aim of the present study was to compare the risks of adverse neonatal outcomes in younger pregnant adolescents who are properly followed through group prenatal care delivered by specialized public services.

METHODS

Design and Setting

This is a retrospective cohort study of pregnant adolescents cared for in the public health system in Sorocaba city, State of São Paulo, Brazil.

The study was conducted at the Edward Maluf Municipal Polyclinic (EMMP), Sorocaba, using medical records for pregnant women who received prenatal care from 2009 to 2014. As a specialized service, the Municipal Polyclinic is a reference center for adolescent prenatal care located in the city of Sorocaba. Sorocaba is located in the state of São Paulo, and according to the last census performed by the Brazilian Institute of Geography and Statistics (IBGE), its estimated population in 2013 was 629,231 inhabitants (22).

In 2000, after some changes to women's health policies were made, the Brazilian Health Ministry launched the Prenatal and Birth Humanization Program to improve the coverage and quality of and access to prenatal, delivery and postpartum care for women and newborns (23). The Prenatal and Birth

Humanization Program follows a protocol involving several tests, follow-up routines, recording of prenatal visits, laboratory and imaging tests, and registration of all pregnant women during their respective visits using specific software. Furthermore, the program follows recommendations from the American Congress of Obstetricians and Gynecologists on group prenatal care (17, 18).

Public health services offered by the EMMP for pregnant adolescents (23) apply principles and best features of the group prenatal care model, including three main elements: (i) health assessment, (ii) education and skills building (focusing on nutrition, exercise, pregnancy issues, infant care and feeding, pregnancy comfort measures, childbirth preparation, etc.) and (iii) peer support (15, 24, 25). Generally, the groups meet eight to 10 times during the pregnancy period, and care is provided to groups of 8–12 women through 120-min sessions.

The service is provided by a multidisciplinary team that includes obstetricians, obstetric nurses, psychologists, social workers, and dentists. In addition, as the polyclinic is a specialized healthcare service, referrals to other medical specialists and for emergency obstetric ultrasounds are easily available. To promote adherence to prenatal care, various social activities are offered to pregnant women to promote their social and occupational inclusion. For women who live far away and have difficulty attending visits, transportation assistance is provided through municipal buses. Whenever a woman misses an appointment, she receives a phone call on the day of the appointment to identify her reason for missing the appointment and to schedule a new visit.

Participants

As explained in the previous item, the EMMP is referenced by all outpatient clinics who refer pregnant women at risk and adolescents for this follow-up. Thus, all pregnant adolescents cared by the public health system in Sorocaba and the region performed their prenatal care at the EMMP. This study included all adolescents who use public health services, at any stage of pregnancy under 18 years of age and who received care at the EMMP. From this, we excluded miscarriage cases or records with missing data.

Among adolescents, pregnancy is classified in girls of up to 15 years of age and in girls older than 16 years of age. Pregnancy adolescents up to 15 years are considered to be at a high risk of adverse maternal, obstetric, and neonatal outcomes (26). In the present study, the adolescents were intentionally divided into three age groups to achieve a stronger understanding of differences observed within narrower age ranges. We were also interested in analyzing the youngest participants (those younger than 13 years of age) to address a lack of data in the literature on this population.

Variables and Data Source

All of the adolescents included in the study were followed up until the end of the pregnancy period. The participants were divided by age as follows: 10–13, 14–15, and 16–17 years of age.

The extraction of variables was done using an electronic form developed specifically for this study. The investigator DPH, filled

out each electronic form extracting information directed from the medical record and cross-checked with the information in the database of the EMMP. When necessary, the multidisciplinary teams were interviewed to address any questions about the medical records.

General and socio-demographic characteristics (enrolment date, birth date, employment status of the head of the family, having a partner, literacy level, having another child under 2 years of age, receiving child benefits and whether the pregnancy was desired) were collected from the polyclinic's follow-up service enrolment form at the time of prenatal care enrolment.

The following information was collected from the participants' medical records: (i) prenatal and pregnancy-related characteristics (referring ambulatory unit, prenatal care start date, gestational weeks at the start of prenatal care, number of prenatal visits, last menstrual period, expected delivery date and infant's gestational age at delivery); (ii) birth-related characteristics (delivery date, place and type; preterm or full-term birth; Apgar score at 1 and 5 min; and neonate's birth weight); (iii) clinical characteristics (presence of comorbidities such as human immunodeficiency virus (HIV) or venereal disease and findings on serology tests); and (iv) obstetric characteristics (vaginal birth, cesarean section and forceps assisted).

Risky neonatal outcomes were defined as follows: low birth weight: <2,500 g; prematurity: birth that occurs after the 22nd week of gestation and before the 37th; mean Apgar score at 1 and 5 min; and neonatal death.

Statistical Analysis

The variables of interest were summarized as descriptive statistics; frequency was calculated for categorical variables, and the mean and standard deviation were calculated for continuous variables.

The differences in demographic, clinical, and obstetric characteristics, low weight, and prematurity between age groups were calculated using the chi-square test or Fisher's exact test (expected values <5). Differences in Apgar scores at 1 and 5 min were calculated by ANOVA.

The association between maternal age and Apgar score was determined by calculating coefficients generated from a multiple regression model adjusted for covariables infant gender, maternal comorbidities, delivery type, positive HIV status and positive VDRL.

The association between maternal age and the outcomes of low birth weight and preterm birth was estimated by Poisson regression (27). For this purpose, the incidences of low weight and preterm between the groups were calculated and proceeded with adjustments with the variables of the newborn's sex and mother's comorbidities.

To minimize chance effects, sensitivity analyses were performed by repeating the same calculations on random subsamples (bootstrapping) (27). Bonferroni correction was used to conservatively estimate the statistically significant variables. Imputation was not performed for missing data; in such cases, the corresponding information was excluded from the multivariate analysis. All analyses were performed in STATA

(version 14) with a 95% confidence interval (95% CI); the significance level (alpha error) was set to 5%.

Ethical Approval

This study was approved by the Research Ethics Committee of the University of Sorocaba, which is accredited by the National Research Ethics Commission according to stipulations of the National Health Council Ordinance 466/2012; it was also approved according to Platform Brazil Protocol no. 985.590 for March 13, 2015. EMMP also approved the protocol and personal information of the participants was kept blinded to investigators. Waiver of parental permission (Written informed consent from the participants' legal guardian) was requested and authorized by Research Ethics Committee.

RESULTS

During the 5-year study period, 795 adolescents enrolled in the Sorocaba municipal government's high-risk prenatal care program were identified, and 758 were included in the final sample. A total of 37 (4.6%) pregnant adolescents were excluded because they had miscarried, or because their medical records had missing data. None of the studied adolescents ($n = 758$) were lost to analysis (Figure 1).

Table 1 describes socio-demographic, clinical and obstetric characteristics of the sample. Approximately 79.8% of the participants started prenatal care during the first trimester of pregnancy, and 96% made six visits or more. Vaginal birth was the most frequent delivery type across all of the groups (68.6%). There was a difference in the distribution between the hospitals ($p = 0.003$) and the presence of comorbidities ($p < 0.001$) between the age groups. There was no statistical difference between lower

preterm birth rates and the hospitals: hospital A ($p = 0.383$); hospital B ($p = 1.00$); hospital C ($p = 0.406$).

Prematurity occurred in 10.2% of the newborns, a proportion similar to that found for low birth weight (10.4%). The incidence of low birth weight was 16.1% for the 10–13 age group, 8.7% for the 14–15 age group and 12.1% for the 16–17 age group. The incidence preterm risk was measured as 12, 8.5, and 12.6% for adolescents that were 10–13, 14–15, and 16–17 years of age, respectively.

The Apgar scores at 1 and 5 min were found to be slightly lower for the infants of mothers aged 10–13 years (Table 2).

Table 3 describes the outcomes of infants born to the adolescent mothers. Neither low birth weight nor prematurity levels significantly differed among the groups ($p > 0.05$). Vitality by Apgar score is lower in ages 10–13 group than ages 16–17 group. Ages 14–15 group did not show differences between ages 16–17 group.

The infants born to mothers aged 10–13 years presented significantly lower Apgar scores, with a mean reduction of 0.69 points at 1 min and 0.26 points at 5 min. These results remained significant through the sensitivity analysis. No instance of neonatal death occurred.

DISCUSSION

Main Findings

The results of the study showed that pregnant adolescents, disaggregated across three thresholds of age at pregnancy, did not exhibit difference between the adverse neonatal outcomes. The overall incidences of low birth weight and prematurity were 10.4 and 10.2%, respectively. Vitality by Apgar scores at 1 and 5 min were normal (values of Apgar > 7) in all groups, although slightly lower for the infants of mothers aged 10–13 years. No fetal death

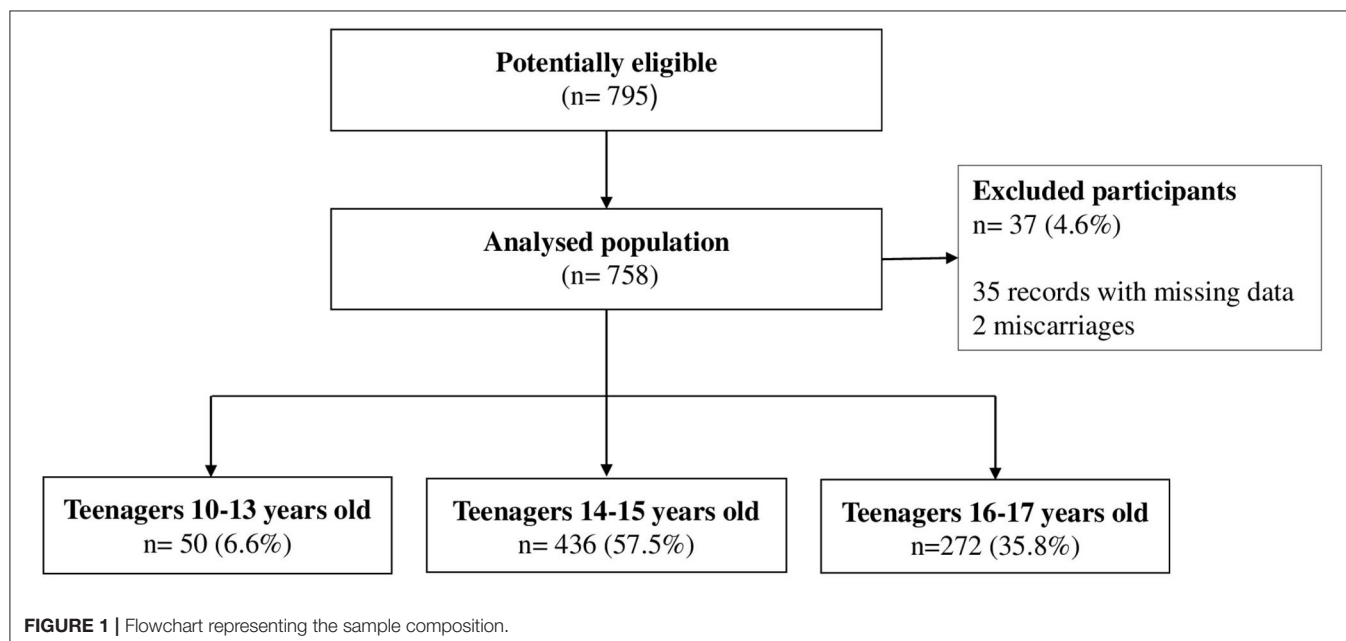


TABLE 1 | Socio-demographic, clinical, and obstetric characteristics of pregnant adolescents who received prenatal care services.

Variables	Total n (%)	Age 16–17 n (%)	Age 14–15 n (%)	Age 10–13 n (%)	p-value
	758 (100)	272 (35.8)	436 (57.5)	50 (6.6)	
SOCIO-DEMOGRAPHIC CHARACTERISTICS					
Unemployed head of family					
Yes	24 (3.2)	9 (3.3)	13 (3.0)	2 (4.0)	0.793
No	725 (96.8)	261 (96.7)	416 (97.0)	48 (96.0)	–
Has child <2 years of age					
Yes	21 (2.8)	8 (3.0)	12 (2.8)	1 (2.0)	1.000
No	733 (97.2)	261 (97.0)	423 (97.2)	49 (98.0)	–
Partner					
Yes	555 (73.2)	205 (75.4)	315 (72.2)	35 (70.0)	0.557
No	203 (26.8)	67 (24.3)	121 (27.8)	15 (30.0)	–
Self-reported literacy					
Yes	749 (99.1)	268 (98.9)	431 (99.1)	50 (100)	1.000
No	7 (0.9)	3 (1.1)	4 (0.9)	0.00	–
Desired infant					
Yes	754 (99.6)	270 (99.6)	434 (99.5)	50 (100)	1.000
No	3 (0.4)	1 (0.4)	2 (0.5)	0.00	–
Prenatal care start					
First trimester	554 (79.8)	208 (81.2)	308 (78)	38 (88.4)	0.369
Second trimester	121 (17.5)	39 (15.2)	77 (19.5)	5 (11.6)	–
Third trimester	19 (2.7)	9 (3.5)	10 (2.5)	0.00	–
Number of prenatal visits					
<six visits	30 (4.01)	9 (3.4)	16 (3.7)	5 (10.0)	0.106
Six or more visits	718 (96.0)	257 (96.6)	416 (96.3)	45 (90.0)	–
Delivery hospital					
Hospital A	435 (59.2)	158 (62.1)	239 (55.5)	38 (77.6)	0.003
Hospital B	176 (23.9)	47 (18.3)	121 (28.0)	8 (16.3)	–
Hospital C	124 (16.9)	50 (19.6)	71 (16.5)	3 (6.1)	–
CLINICAL CHARACTERISTICS					
Comorbidities	131 (17.3)	89 (32.7)	39 (8.9)	3 (6.0)	<0.001
VDRL positive	9 (1.2)	4 (1.5)	5 (1.2)	0.00	0.859
HIV positive	2 (0.2)	1 (0.4)	1 (0.2)	0.00	1.000
OBSTETRIC CHARACTERISTICS					
Vaginal birth	504 (68.6)	169 (66.2)	302 (70.1)	33 (67.4)	0.081
Cesarean section	203 (27.6)	81 (31.8)	110 (25.5)	12 (24.5)	–
Forceps assisted	28 (3.8)	5 (2.0)	19 (4.4)	4 (8.1)	–

occurred during the study period, and vaginal birth was the most frequent delivery type across all of the groups.

Relationship to Previous Studies

According to World Health Organization (WHO), prenatal care should start early, be universally available, be performed periodically and be integrated with all other preventive and therapeutic actions (28). Also, prenatal care should be adapted for adolescents in order to provide them easy access to multidisciplinary care to compensate for a lack of or delay in care (29). The success of prenatal care largely depends on its time of onset and on the number of prenatal visits made. Adolescents often have low adherence to prenatal care and fewer prenatal

visits, especially in the first trimester (29, 30). In the present study, we could assume higher adherence to the prenatal care compared with the national average due to high rate (82%) of time of onset in first semester and number of prenatal visits made (more than six) that we could assume higher adherence to the prenatal care compared with the national average.

Although not have compared to individualized care, we could suggest that the good engagement of these adolescents to this program is due the quality of prenatal care provided in primary care and the connection with the specialized services in this region, which comply with all recommendations established by the Brazilian Health Ministry and WHO (23, 28). In addition to routine tests, vaccinations, multidisciplinary care and social

TABLE 2 | Characteristics of infants born to mothers who received prenatal care.

Variables	Total	Ages 16–17	Ages 14–15	Ages 10–13	P-value
	<i>n</i> = 758 (100%)	<i>n</i> = 272 (35.8%)	<i>n</i> = 436 (57.5%)	<i>n</i> = 50 (6.6%)	
Gender					
Male	388 (52.8)	129 (50.6)	236 (54.8)	23 (46.9)	0.401
Female	347 (47.2)	126 (49.4)	195 (45.2)	26 (53.1)	
Apgar (mean ± standard deviation)					
Apgar at 1 min	7.83 ± 1.62	7.93 ± 1.50	7.84 ± 1.65	7.28 ± 1.96	0.035
Apgar at 5 min	8.99 ± 0.72	9.00 ± 0.73	9.01 ± 0.69	8.76 ± 0.94	0.056
Birth weight					
Low weight	79 (10.4)	33 (12.1)	38 (8.7)	8 (16.1)	0.132
Prematurity					
Term	676 (89.8)	236 (87.4)	396 (91.4)	44 (88)	0.197
Preterm	77 (10.2)	34 (12.6)	37 (8.5)	6 (12.0)	

TABLE 3 | Mean difference and relative risk of neonatal outcomes.

Outcome	Ages 16–17**	Ages 14–15*	P-value	Ages 10–13*	P-value
	<i>n</i> = 272	<i>n</i> = 436		<i>n</i> = 50	
Apgar coeff (95% CI)^{&c}					
At 1 min	Ref**	−0.10 (−0.36 to 0.15)	0.43	−0.69 (−1.19 to −0.19)	0.007
At 5 min	Ref**	0.03 (−0.09 to 0.14)	0.63	−0.26 (−0.49 to −0.04)	0.021
Birth weight RR (95% CI)					
Low weight	1.00	0.76 (0.47 to 1.23)	0.26	1.48 (0.68 to 3.23)	0.320
Prematurity RR (95% CI)					
Preterm	1.00	0.72 (0.44 to 1.16)	0.17	1.05 (0.45 to 2.60)	0.860

^{&c} Mean difference; RR, relative risk; CI, confidence interval.

*Analysis adjusted to infant gender, maternal comorbidities, delivery type, HIV-positive status, and VDRL positive status; **Reference group for multivariate analysis.

and educational activities, all of which are duly recorded in a universal open-access system, contribute to the satisfactory provision of services.

We cannot affirm with certainty that the positive outcomes obtained in this study is specifically due to the GPC model, nevertheless our results reinforce other findings (21, 31), which point out that an adequate adaptation in the implementation of the GPC model may generate robust adherence as demonstrated in this sample (>90% of the adolescents with more than six visits and ~80% starting the prenatal care in the first trimester) and contribute to better neonatal and obstetric outcomes.

Other studies revealed a high incidence and prevalence of adverse neonatal outcomes in adolescents (32, 33), mainly in pregnant with social disadvantage (34, 35). Although we have not investigated the socio-economic characteristics of these adolescents, most of the people assisted by the public health system in Brazil have lower economic conditions, but even so, they showed positive outcomes. Other researcher suggested that the prenatal care is more important than the woman's age (36), the fact that corroborates with this studied context.

Patients in group prenatal care are more satisfied and engaged in care services and adhere more to recommendations, which

could have reflected in the observed outcomes. The group model based on the premise that prenatal care is more effective when learning and support are enhanced by group resources through the guidance of a professional care provider and on the notion that high-quality care cannot be achieved through traditional care services, especially for high-risk groups such as adolescents pregnant women (17).

Making the difficult transition from individual to group prenatal care takes effort and a desire to work with innovation and multidisciplinary staff. The decision for changing to introduce group prenatal care to this region could improve the quality of care. Positive experiences of the implementation of group care have also been observed in New Haven, Atlanta, New York, Boston and Iran (17, 37, 38).

Prematurity and low birthweight, are outstanding factors related to perinatal morbidity and mortality rates. Premature births are those occurring after gestational week 22 and before week 37, and in the present study, the prematurity rate (10.2%) was found to be lower than rates reported in other studies on adolescents in Brazil (39–41); the exception is one study performed in Campinas (42), in which the rate was 7.5%. None of these studies found a prematurity rate lower than that of developed countries (7%). Furthermore, no significant

differences were observed in the proportion of preterm births among younger and older adolescents, in contrast to the results of other studies, in which younger adolescents were shown to have increased risk of preterm delivery (43–46).

Studies have found a correlation between low birth weight and maternal age, showing that the odds of delivering a low birth-weight infant are higher for mothers under the age of 16 (47–49). However, in the present study, we found no significant difference in the rate of low birth-weight infants as a function of the maternal age ranges studied. In addition, the rate of low birth weight infants was found to be lower than that reported by another study, where in adolescents aged 11–14 years had higher risks of infants with low and very low birth weights (46, 50).

Low birth weight and prematurity is reflected in the higher Apgar scores found for most of the newborns (51, 52). The Apgar scores reporting the status of the newborns' physiologies at 1 min and at 5 min immediately after birth summarize five components: respiratory effort, color, muscle tone, heart rate, and reflex (52). The gestational age affects this score and may be reflected in lower Apgar score, which in turn may increase the relative risk of neurologic disability (7, 52). But, the Apgar scores at 1 and 5 min were normal (>7) in all groups of this study.

Younger maternal age was associated with greater risk of fetal death in some studies (45, 53), which was different to our results. No instance of fetal death occurred during the study period and this may be attributed to the resulting outcomes and especially to the low frequency of prematurity and low birth weight.

The proportion of cesarean sections was measured at 27.6% in the present study, which is higher than the level of 15% recommended by the WHO for both adult and adolescent females. The WHO has not yet established a consensus on the ideal rate of cesarean sections for the total population of women, and thus, we are still far from identifying a specific recommendation for adolescents (54).

On the other hand, given that the bodies of girls under 13 years of age are still developing, a higher frequency of cephalopelvic disproportion would be expected with a consequently higher number of cesarean sections; however, the opposite was observed. The proportion of cesarean sections was found to be considerably lower among the youngest adolescents relative to the older adolescents, corroborating the results of other studies among younger adolescents (46, 50). This finding may be explained by the larger number of forceps-assisted vaginal births involved in the study.

Study Limitations and Strengths

The study reflects real-life data from representative sample of adolescents assisted by SUS through group prenatal care, which the results can be extrapolated to similar contexts. It is worth mentioning that the Brazilian public health system assists ~80% of country's population. Most studies investigate teenage pregnancy without considering the quality of prenatal care services. In addition to applying well-defined eligibility criteria and controlling confounders in the analysis, this study described data collected from the real-life conditions of a public health

service structured to follow up with pregnant teenagers in an adequate manner.

To ensure the internal validity of the study, we consider the following aspects. We included all pregnant adolescents assisted by the public sector in the study and only excluded those with incomplete data, which reduced the selection bias. We checked the consistency of the data contained in the medical records with the information obtained from the professionals' team and so, the memory bias was also reduced. Data were collected in the same way for all participants, avoiding performance and measurement bias. There was no misclassification of the outcomes because the adolescents were monitored from the beginning and the outcomes were not present at the beginning of the follow-up. We took care that the analyzes were made considering adjustments for confounders (sex infant, maternal comorbidities, type of delivery, HIV serology, and positive VDRL) and we performed a stratified analysis by subgroups and Poisson Multivariate logistic regression.

Although the total sample was relatively large, the subgroup analysis reduced its size, which might have influenced some of the assessed outcomes. This study also did not compare outcomes against those of adolescents not used group care or other external comparator, so it lacked a control group. We provided outcomes of internal comparisons of age groups within the adolescence age range. We also did not capture data from private sector. However, the public sector covers about 80% of the Brazilian population.

CONCLUSION

The neonatal outcomes, including Apgar scores, low frequencies of prematurity, and low birth weight were within the normal range and did not differ between the age groups of pregnant adolescents who were enrolled in GPC through specialized public services which were implemented in Sorocaba.

The results suggest that adherence to the prenatal model implemented in the public health care system in Brazil could among other factors, limit the occurrence of adverse neonatal and obstetrics outcomes, even among the youngest pregnant adolescents.

In addition, we would like to suggest that future research will overcome the challenges and limitations of our study design using: randomized controlled clinical trial or pragmatic clinical trial with a comparator control group with another type of prenatal care. It is also recommended that data on socioeconomic and cultural aspects and satisfaction with prenatal care be collected. We similarly advise that both children and mothers be followed for a prolonged period after childbirth to check for other important outcomes related to the education received at the GPC.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the University of Sorocaba, which is accredited by the National Research Ethics Commission according to stipulations of the National Health Council Ordinance 466/2012; it was also approved according to Platform Brazil Protocol no. 985.590 for March 13, 2015. It used only medical records, no identifiable data. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LL and DH developed the original idea and the study protocol. DH, LL, IF, and MS performed the data collection, data analysis, and drafted the manuscript. All authors read and provided critical revision and approved the final manuscript.

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REFERENCES

- WHO. (2016). *Adolescent Pregnancy*. World Health Organization. Available online at: <http://www.who.int/mediacentre/factsheets/fs364/en/> (accessed July 12, 2016).
- Halonen M, Apter D. Multiple challenges of teenage pregnancy and maternity. *Duodecim*. (2010) 126:881–7.
- Michelazzo D, Yazlle MEHD, Mendes MC, Patta MC, Rocha JSY, Moura MDD. Indicadores sociais de grávidas adolescentes: estudo caso-controle. *Rev Bras Ginecol Obstetr*. (2004) 26:633–9. doi: 10.1590/S0100-72032004000800007
- Darroch JE, Woog V, Bankole A, Ashford LS. *Adding It Up: Costs and Benefits of Meeting the Contraceptive Needs of Adolescents*. New York, NY: Guttmacher Institute (2016). Available online at: <https://www.guttmacher.org/report/adding-it-meeting-contraceptive-needs-of-adolescents> (accessed February 17, 2020).
- AMB. (2019). *Gravidez na Adolescência, são 400 Mil Casos por Ano No Brasil*. Associação Médica Brasileira. Available online at: <https://amb.org.br/noticias/gravidez-na-adolescencia/> (accessed February 5, 2020).
- Martins MDG, Santos GHND, Sousa MDS, Costa JEFBD, Simões VMF. Associação de gravidez na adolescência e prematuridade. *Rev Bras Ginecol Obstetr*. (2011) 33:354–60. doi: 10.1590/S0100-72032011001100006
- Vieira CL, Coeli CM, Pinheiro RS, Brandao ER, Camargo KRJR, Aguiar FP. Modifying effect of prenatal care on the association between young maternal age and adverse birth outcomes. *J Pediatr Adolesc Gynecol*. (2012) 25:185–9. doi: 10.1016/j.jpog.2011.12.070
- Nili F, Rahmati MR, Sharifi SM. Maternal and neonatal outcome in teenage pregnancy in Tehran Valiasr Hospital. *Acta Med Iran*. (2002) 40, 55–59. Available online at: <https://acta.tums.ac.ir/index.php/acta/article/view/2550/2537> (accessed 27 March, 2021).
- Del Ciampo LA, Junqueira MJG, Ricco RG, Daneluzzi JC, Ferraz IS, Junior CEM. Tendência secular da gravidez na adolescência. *Pediatrics*. (2004) 26:21–6. Available online at: https://www.researchgate.net/publication/237357760_Tendencia_secular_da_gravidez_na_adolescencia (accessed March 27, 2021).
- Markovitz BP, Cook R, Flick LH, Leet TL. Socioeconomic factors and adolescent pregnancy outcomes: distinctions between neonatal and post-neonatal deaths? *BMC Public Health*. (2005) 5:79. doi: 10.1186/1471-2458-5-79
- Neves Filho ADC, Leite ÁJM, Bruno ZV, Gomes B, Filho J, Silva CFD. Gravidez na adolescência e baixo peso ao nascer: existe associação? *Rev Paul Pediatr*. (2011) 29:489–94. doi: 10.1590/S0103-05822011000400004
- Rocha RCLD, Souza ED, Guazzelli C, Chambó Filho A, Soares EP, Nogueira ES, et al. Prematuridade e baixo peso entre recém-nascidos de adolescentes primíparas. *Rev Bras Ginecol Obstetr*. (2006) 28, 530–5. doi: 10.1590/S0100-72032006000900005
- Azevedo WFD, Diniz MB, Fonseca ESVBD, Azevedo LMRD, Evangelista CB. Complications in adolescent pregnancy: systematic review of the literature. *Einstein (São Paulo)*. (2015) 13:618–26. doi: 10.1590/S1679-45082015RW3127
- Mbuagbaw L, Medley N, Darzi AJ, Richardson M, Habiba Garga K, Ongolo-Zogo P. Health system and community level interventions for improving antenatal care coverage and health outcomes. *Cochrane Database Syst Rev*. (2015) 12:CD010994. doi: 10.1002/14651858.CD010994.pub2
- Nunes JT, Gomes KRO, Rodrigues MTP, Mascarenhas MDM. Qualidade da assistência pré-natal no Brasil: revisão de artigos publicados de 2005 a 2015. *Cad Saúde Coletiva*. (2016) 24:252–61. doi: 10.1590/1414-462X201600020171
- Byerley BM, Haas DM. A systematic overview of the literature regarding group prenatal care for high-risk pregnant women. *BMC Pregnancy Childbirth*. (2017) 17:329. doi: 10.1186/s12884-017-1522-2
- Massey Z, Rising SS, Ickovics J. Centering pregnancy group prenatal care: promoting relationship-centered care. *J Obstet Gynecol Neonatal Nurs*. (2006) 35:286–94. doi: 10.1111/j.1552-6909.2006.00040.x
- Cunningham SD, Lewis JB, Thomas JL, Grilo SA, Ickovics JR. Expect With Me: development and evaluation design for an innovative model of group prenatal care to improve perinatal outcomes. *BMC Pregnancy Childbirth*. (2017) 17:147. doi: 10.1186/s12884-017-1327-3
- Ruiz-Mirazo E, Lopez-Yarto M, McDonald SD. Group prenatal care versus individual prenatal care: a systematic review and meta-analyses. *J Obstet Gynaecol Can*. (2012) 34:223–9. doi: 10.1016/S1701-2163(16)35182-9
- Heberlein EC, Picklesimer AH, Billings DL, Covington-Kolb S, Farber N, Frongillo EA. The comparative effects of group prenatal care on psychosocial outcomes. *Arch Womens Ment Health*. (2016) 19:259–69. doi: 10.1007/s00737-015-0564-6
- Sharma J, O'Connor M, Rima Jolivet R. Group antenatal care models in low- and middle-income countries: a systematic evidence synthesis. *Reprod Health*. (2018) 15:38. doi: 10.1186/s12978-018-0476-9
- Brazil. (2010). *Censos Demográficos 2010*. Brazil: Instituto Brasileiro de Geografia e Estatística. Available online at: <http://www.ibge.gov.br> (accessed January 12, 2016).
- Brazil. (2015). *Humanização do Parto. Humanização no Pré-natal e Nascimento*. Brazil: Ministério da Saúde. Secretaria Executiva. Available online at: <http://bvsms.saude.gov.br/bvs/publicacoes/parto.pdf> (accessed May 10 2015).
- Alexander BT, Henry Dasinger J, Intapad S. Effect of low birth weight on women's health. *Clin Ther*. (2014) 36:1913–23. doi: 10.1016/j.clinthera.2014.06.026
- Munabi-Babigumira S, Glenton C, Lewin S, Fretheim A, Nabudere H. Factors that influence the provision of intrapartum and postnatal care by skilled birth attendants in low- and middle-income countries: a qualitative evidence synthesis. *Cochrane Database Syst Rev*. (2017) 11:CD011558. doi: 10.1002/14651858.CD011558.pub2
- Santos GHND, Martins MDG, Sousa MDS, Batalha SDJC. Impacto da idade materna sobre os resultados perinatais e via de parto. *Rev Bras Ginecol Obstetr*. (2009) 31:326–34. doi: 10.1590/S0100-72032009000700002
- Katz MH. *Multivariable Analysis. A Practical Guide for Clinicians and Public Health Researchers*. Cambridge: Medicine (2011).
- OPAS. *Organização Pan-Americana de Saúde. Mulheres Grávidas Devem ter Acesso aos Cuidados Adequados no Momento Certo, Afirma OMS* (2020). Available online at: https://www.paho.org/bra/index.php?option=com_

- content&view=article&id=5288:mulheres-gravidas-devem-ter-acesso-aos-cuidados-adequados-no-momento-certo-afirma-oms&Itemid=820 (accessed February 16, 2020).
29. Fleming N, Ng N, Osborne C, Biederman S, Yaseen AS 3rd, Dy J, et al. (2013). Adolescent pregnancy outcomes in the province of Ontario: a cohort study. *J Obstet Gynaecol Can.* 35, 234–45. doi: 10.1016/S1701-2163(15)30995-6
 30. Lena SM, Marko E, Nimrod C, Merritt L, Poirier G, Shein E. Birthing experience of adolescents at the Ottawa General Hospital Perinatal Centre. *CMAJ.* (1993) 148:2149–54.
 31. Finlayson K, Downe S. Why do women not use antenatal services in low- and middle-income countries? A meta-synthesis of qualitative studies. *PLoS Med.* (2013) 10:e1001373. doi: 10.1371/journal.pmed.1001373
 32. Marvin-Dowle K, Kilner K, Burley VJ, Soltani H. Impact of adolescent age on maternal and neonatal outcomes in the Born in Bradford cohort. *BMJ Open.* (2018) 8:e016258. doi: 10.1136/bmjopen-2017-016258
 33. Kassa GM, Arowojolu AO, Odukgbe AA, Yalew AW. Adverse neonatal outcomes of adolescent pregnancy in Northwest Ethiopia. *PLoS One.* (2019) 14:e0218259. doi: 10.1371/journal.pone.0218259
 34. Van der Klis KA, Westenberg L, Chan A, Dekker G, Keane RJ. Teenage pregnancy: trends, characteristics and outcomes in South Australia and Australia. *Aust N Z J Public Health.* (2002) 26:125–31. doi: 10.1111/j.1467-842X.2002.tb00904.x
 35. Abebe AM, Fitie GW, Jember DA, Reda MM, Wake GE. Teenage pregnancy and its adverse obstetric and perinatal outcomes at Lemlem Karl Hospital, Tigray, Ethiopia. *Biomed Res Int.* 2020:3124847. doi: 10.1155/2020/3124847
 36. Leppert PC, Namerow PB, Barker D. Pregnancy outcomes among adolescent and older women receiving comprehensive prenatal care. *J Adolesc Health Care.* (1986) 7:112–7. doi: 10.1016/S0197-0070(86)80006-7
 37. Jafari F, Eftekhari H, Fotouhi A, Mohammad K, Hantoushadeh S. Comparison of maternal and neonatal outcomes of group versus individual prenatal care: a new experience in Iran. *Health Care Women Int.* (2010) 31:571–84. doi: 10.1080/07399331003646323
 38. Earnshaw VA, Rosenthal L, Cunningham SD, Kershaw T, Lewis J, Rising SS, et al. Exploring Group Composition among Young, Urban Women of Color in Prenatal Care: implications for satisfaction, engagement, and group attendance. *Women's Health Issues.* (2016) 26:110–5. doi: 10.1016/j.whi.2015.09.011
 39. Simões VMF, Silva AAMD, Bettiol H, Lamy-Filho F, Tonial SR, Mochel EG. Características da gravidez na adolescência em São Luís, Maranhão. *Rev Saúde Públ.* (2003) 37:559–65. doi: 10.1590/S0034-89102003000500003
 40. Goldenberg P, Figueiredo MDCT, Silva RDSE. Gravidez na adolescência, pré-natal e resultados perinatais em Montes Claros, Minas Gerais, Brasil. *Cadernos Saúde Públ.* (2005) 21:1077–86. doi: 10.1590/S0102-311X2005000400010
 41. Chalem E, Mitsuhiko SS, Ferri CP, Barros MCM, Guinsburg R, Laranjeira R. Gravidez na adolescência: perfil sócio-demográfico e comportamental de uma população da periferia de São Paulo, Brasil. *Cadernos Saúde Públ.* (2007) 23:177–86. doi: 10.1590/S0102-311X2007000100019
 42. Carniel EDF, Zanolli MDL, Almeida CAA, Morcillo AM. Características das mães adolescentes e de seus recém-nascidos e fatores de risco para a gravidez na adolescência em Campinas, SP, Brasil. *Rev Bras Saúde Materno Infantil.* (2006) 6:419–26. doi: 10.1590/S1519-38292006000400009
 43. Olausson PM, Cnattingius S, Goldenberg RL. Determinants of poor pregnancy outcomes among teenagers in Sweden. *Obstet Gynecol.* (1997) 89:451–7. doi: 10.1016/S0029-7844(97)00009-4
 44. Gallo PR, Reis AOA, Leone C. Características de seguimento pré-natal, do parto e do recém-nascido de adolescentes grávidas, município de Joinville, Estado de Santa Catarina, Brasil, 1995. *Pediatrics (São Paulo).* (2000) 22:123–9. Available online at: <https://repositorio.usp.br/item/001175434> (accessed March 27, 2021).
 45. Malabarey OT, Balayla J, Klam SL, Shrim A, Abenheim HA. Pregnancies in young adolescent mothers: a population-based study on 37 million births. *J Pediatr Adolesc Gynecol.* (2012) 25:98–102. doi: 10.1016/j.jpag.2011.09.004
 46. Torvie AJ, Callegari LS, Schiff MA, Debiec KE. Labor and delivery outcomes among young adolescents. *Am J Obstet Gynecol.* (2015) 213:95.e1–95.e98. doi: 10.1016/j.ajog.2015.04.024
 47. Gama SGND, Szwarcwald CL, Leal MDC, Theme Filha MM. Gravidez na adolescência como fator de risco para baixo peso ao nascer no Município do Rio de Janeiro, 1996 a 1998. *Rev Saúde Públ.* (2001) 35:74–80. doi: 10.1590/S0034-89102001000100011
 48. Pardo RA, Nazer HJ, Cifuentes OL. Prevalencia al nacimiento de malformaciones congénitas y de menor peso de nacimiento en hijos de madres adolescentes. *Rev Méd Chile.* (2003) 131:1165–72. doi: 10.4067/S0034-98872003001000010
 49. Wallace JM, Aitken RP, Milne JS, Hay WW Jr. Nutritionally mediated placental growth restriction in the growing adolescent: consequences for the fetus. *Biol Reprod.* (2004) 71:1055–62. doi: 10.1095/biolreprod.104.030965
 50. Eure CR, Lindsay MK, Graves WL. Risk of adverse pregnancy outcomes in young adolescent parturients in an inner-city hospital. *Am J Obstet Gynecol.* (2002) 186:918–20. doi: 10.1067/mob.2002.123986
 51. Shah GS, Singh R, Das BK. Outcome of newborns with birth asphyxia. *JNMA J Nepal Med Assoc.* (2005) 44:44–6. doi: 10.31729/jnma.395
 52. Carvalho PID, Pereira PMH, Frias PGD, Vidal SA, Figueiroa JN. Fatores de risco para mortalidade neonatal em coorte hospitalar de nascidos vivos. *Epidemiol Serv Saúde.* (2007) 16, 185–94. doi: 10.5123/S1679-49742007000300005
 53. De Vienne CM, Creveuil C, Dreyfus M. Does young maternal age increase the risk of adverse obstetric, fetal and neonatal outcomes: a cohort study. *Eur J Obstet Gynecol Reprod Biol.* (2009) 147:151–6. doi: 10.1016/j.ejogrb.2009.08.006
 54. WHO. (2016). *Organização Mundial da Saúde. Declaração da OMS Sobre Taxas de Cesáreas.* Available online at: http://apps.who.int/iris/bitstream/10665/161442/3/WHO_RHR_15.02_por.pdf (accessed January 26, 2016).

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Community-Based Interventions to Improve the Control of Non-Communicable Diseases in Underserved Rural Areas in Brazil: A Before-and-After Study

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Background: Hypertension and diabetes mellitus are the second and third highest leading causes of disability-adjusted life-years (DALY), respectively, in Brazil. The clinical outcomes of chronic diseases are influenced by various factors. Therefore, there is a need for multifaceted interventions to achieve a decrease in the rate of DALY, with a better control of these diseases.

Objective: To verify whether sustainable long-term interventions, such as health worker training and provision of health education to the patients, contribute to health improvements in patients with hypertension and diabetes from rural communities.

Methods: Over a 6 month period, educational and medical interventions were provided to optimize the treatment of hypertension and diabetes. Furthermore, blood pressure and glycated hemoglobin (HbA1c) measurements were taken at baseline and after the interventions.

Results: The monitored hypertensive patients ($n = 276$) had a reduction of 13.4 mmHg ($p = 0.021$) and 5.8 mmHg ($p < 0.001$) in mean systolic and diastolic blood pressure, respectively. Diabetic patients who were followed-up ($n = 71$) achieved a 0.55% ($p = 0.185$) reduction in HbA1c level. The desired blood pressure level ($< 140/90$ mmHg) was achieved in 38.8% of patients with hypertension, whereas the desired level of HbA1c ($< 7.0\%$ for adults and $< 8.0\%$ for the elderly) was achieved in 16.9% of patients with diabetes; in addition, 38.0% had a reduction of HbA1c of at least 1%.

Conclusion: The results showed that the interventions improved the blood pressure and HbA1c levels in patients with hypertension and diabetes from rural communities in a municipality in Northeast Brazil.

Keywords: primary health care, hypertension, diabetes, glycated hemoglobin, rural population

INTRODUCTION

The prevalence of non-communicable diseases (NCDs) has been increasing worldwide and this significantly impacts the health systems (Flor et al., 2020). In Brazil, hypertension and diabetes are the second and third leading causes of disability-adjusted life-years (DALY) (Costa et al., 2017; Nascimento et al., 2020), a measure that combines information about premature death and disability due to a condition (Nascimento et al., 2020). The total number of deaths and DALY are increasing due to the aging of the population and the increased risk exposure; however, the DALY rates have decreased in Brazil, possibly reflecting an improvement in access and quality of health care (Nascimento et al., 2020).

The investment in the implementation and improvement of strategies to provide patients with NCDs in the primary health care settings has yielded good results by reducing the need for specialized care and health system expenses (Flor et al., 2020; American Diabetes Association, 2020). Given that a variety of factors can influence the clinical outcomes of chronic diseases, multifaceted interventions are required to achieve the desired results, either at the individual level with a timely medical diagnosis and appropriate drug treatment, or at the community level, with health education and monitoring (He et al., 2017; Flor et al., 2020; Silva-Tinoco et al., 2020). In other words, multicomponent community intervention programs are more successful than interventions based on a single activity (Philip et al., 2018).

The social determinants of health, including economic, environmental, political, and social conditions, also significantly affect the control of NCDs (American Diabetes Association, 2020). This is especially important for patients from rural communities because in addition to the factors mentioned above, this population encounters cost barriers when seeking transportation to access health services (Flor et al., 2020).

The demographic profile of rural environments has changed over time, with a higher proportion of older patients than in the urban areas. As birth rate decreases, the rural exodus of young people in search of better living conditions to urban areas increases, triggering the aging of rural populations, and consequently, an increase in the need for chronic diseases care (Crhisten, 2016).

The Brazilian Unified Health System (*Sistema Único de Saúde-SUS*) still faces organizational problems that are limiting access to adequate treatment of patients (Mendes et al., 2012). This is especially important for rural populations that have budgetary restrictions, which affect access to private health plans, and enhance dependency on public policies (Pessoa et al., 2018).

Therefore, we conducted this study considering 1) the scarcity of intervention studies of patients with hypertension and diabetes from rural communities in Brazil and 2) the greater need for access to health care in this population.

Thus, the aim of the study was to evaluate whether multicomponent interventions would improve the control of blood pressure (BP) and glycated hemoglobin (HbA1c)

level in four rural areas in Brazil where patients need more health care.

METHODS

Procedures

A before-and-after uncontrolled study was conducted in which the baseline and post-intervention BP (for hypertensive patients) and HbA1c (for diabetes patients) levels were compared, and the baseline levels for each patient served as the control for the subsequent measures. The study was conducted in four basic health units of different rural communities in a municipality in northeastern Brazil, from September 2019 to March 2020.

This study implemented a 6 months multicomponent intervention program. This included home visits by community health workers (CHWs), health worker training, and point-of-care monitoring of the BP and HbA1c levels during patients' meetings (including during health fairs and in patients' attendance groups). Furthermore, health education for patients and their families to manage chronic NCDs were also provided.

The group-based self-management education was prioritized because it was more cost-effective (Steinsbekk et al., 2012), and at least two groups of patients were followed-up per month in each unit. Because it was a rural area, the patients' homes were very distant from one another; thus, each shift (4 h) of work by the research team contemplated on average, only three home visits. The health team activities in the waiting room of the health units were limited to the days of care of patients with hypertension and/or diabetes.

Due to the coronavirus disease (COVID-19) pandemic, it was no longer possible to bring patients together in collective activities because they belonged to the risk group of COVID-19. Thus, the study ended 45 days before the forecast, which generated a loss of follow-up.

The research team that implemented the interventions in the four health units comprised of 20 people (8 researchers and 12 undergraduate students), who were trained prior to the beginning of the data collection. Each team member received a tablet containing the Kobo Tool Box® software with socioeconomic, clinical questions and BP and HbA1c measurements.

Medical professionals, nurses, and CHWs also underwent training to better manage the patients with hypertension and diabetes during the follow-up. The training took place separately for each category of health workers within a 6 h workload.

The inclusion criteria were all the patients who were able to be reached during home visits, health fairs, and patients' attendance groups in the 6 month period. Patients should be over 18 years old and who were registered in health units and were diagnosed with hypertension (BP $\geq 140/90$ mmHg) (Williams et al., 2018) and/or uncontrolled diabetes mellitus (HbA1c above the therapeutic targets: $>7.0\%$ for adults and $>8.0\%$ for patients aged ≥ 65 years) (American Diabetes Association, 2020). During the study period, the research team assisted the CHWs and health teams to identify patients with uncontrolled conditions through home visits, health fairs, and patients' attendance groups and served as mediators between the patients and physicians, to arrange follow-up appointments.

For hypertensive patients, three BP measurement were performed—one on each arm—with a repeat measurement on the arm with a higher value using the Omron HEM-7113 automatic BP measuring device. These measurements were obtained while the patients were seated after resting for at least 5 min (Malachias et al., 2016). The mean of the two highest values were calculated.

For diabetic patients, HbA1c levels were measured using the portable Abbott Afinion™ two Analyzer, a point-of-care device that allows for instant evaluation without needing to visit a clinical laboratory. In a study, “the Cost-Effectiveness study of Point-of-Care A1C Tests in a Primary Care Setting,” because the point-of-care testing of HbA1c levels resulted in an increase in the rate of diabetes control, the higher purchase costs of the point-of-care testing compared to that of laboratory tests, were reportedly offset by the savings from the reduction in diabetes-related complications and hospitalizations (Rosa et al., 2021).

BP and HbA1c levels were measured again within 3 months of the intervention, for each patient. The outcomes were controlled hypertension (<140/90 mmHg) and diabetes (HbA1c <7% for adults; <8% for older persons).

Patients received guidelines to promote self-care, attain a healthy lifestyle, adhere to treatment, and on the need for more frequent follow-ups for new clinical measures. Furthermore, patients with altered HbA1c levels and BP were referred for consultation with a family physician, during which adjustments were made to the drug treatment (whenever necessary) along with reinforcement of information on living a healthy lifestyle, treatment adherence, and self-care, based on the study protocol.

Study Site Context

Brazil has a public health model—the SUS—that guarantees health as a right of citizenship and is an organized healthcare network; specifically, it is configured in the articulated actions of services with different functions to meet the healthcare needs of the population. The main gateway to this healthcare network should be the primary care setting, where most health issues that people face should be addressed. Each basic health unit has a coverage area where residents are registered (Giovannella and Mendonça, 2012). There are still many organizational failures of the SUS that generate dissatisfaction within the population due to the difficulty of carrying out tests, long waiting times before access to specialists, and availability of medicines (Mendes et al., 2012).

The municipality under study has 17 Family Health Units in the rural area, of which 4 units were chosen by convenience. These units, according to the Municipal Health Department data, are reference centers for approximately 18,376 people and have 2,788 hypertensive patients and 565 with diabetes. Each health unit is composed of one each of a physician, nurse, nursing assistant and/or technician, dentist, and oral health assistant or technician, and 6 to 11 CHWs.

Statistical Analysis

Data analysis was performed using Stata version 15.0 (Stata Corporation, College Station, United States).

TABLE 1 | Sociodemographic characteristics and presence of disease of the study population.

Variables	N	%
Sex		
Male	208	32.6
Female	430	67.4
Age (years)		
<40	42	6.6
40 to 59	246	38.5
60 to 79	301	47.2
≥80	49	7.7
Skin color		
White	125	19.6
Black	163	25.5
Brown	317	49.7
Other	33	5.2
Literacy		
Illiterate	227	36.3
Literate	399	63.7
Marital status		
Single/divorced/widowed	226	35.4
Married/lives with partner	412	64.6
Working status		
None	181	28.4
Work	98	15.3
Retired	359	56.3
Monthly per capita income in dollar ^a		
<\$ 53.19	180	29.3
≥\$ 53.19	435	70.7
Diagnosis of hypertension and diabetes		
Hypertension only	372	58.3
Diabetes only	32	5.0
Hypertension and diabetes	234	36.7

^aUS\$ 1 = R\$ 5.64 on October 27, 2020.

NCDs, non-communicable diseases.

Sociodemographic and disease variables were described as absolute and relative frequency. Pearson's Chi-square test was applied to assess the association between sociodemographic variables and the presence of controlled diseases (hypertension and diabetes), with a significance level set at $p < 0.05$. Differences between the mean BP and HbA1c before and after the interventions were assessed using the Kruskal-Wallis non-parametric test; because the Shapiro-Wilk test demonstrated that there was no normality in the numerical variables.

Ethical Aspects

The study was approved by the Ethics Committee on Research in Human Beings of the Multidisciplinary Institute in Health—Campus Anísio Teixeira (Opinion number: 3.357.963).

Informed consent was waived from the patients because the research could not practicably be conducted without a waiver and involved no more than minimal risk.

RESULTS

The baseline study comprised 638 patients who were diagnosed with uncontrolled hypertension ($n = 556$) and/or diabetes ($n = 191$) (Table 1).

TABLE 2 | Results before and after the intervention for the 276 hypertensive and 71 diabetic patients.

Mean	Baseline	95% confidence interval	After intervention	95% confidence interval	Reduction	p-value
SBP (mmHg)	162.2	160.1–164.4	148.8	146.2–151.6	13.4	0.021
DBP (mmHg)	90.0	88.4–91.5	84.2	82.6–85.8	5.8	<0.001
HbA1c (%)	10.02	9.7–10.4	9.47	9.1–9.80	0.55	0.185

DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 3 | Assessment of hypertension and diabetes control by sociodemographic characteristics.

Variables	Hypertension					Diabetes				
	Not controlled		Controlled		p value	Not controlled		Controlled		p value
	N	%	N	%		N	%	N	%	
Sex					0.737					0.001
Male	57	62.6	34	37.4		8	53.3	7	46.7	
Female	112	60.5	73	39.5		51	91.1	5	8.9	
Age (years)					0.387					0.577
<40	4	36.4	7	63.6		6	100.0	0	0.0	
40 to 59	64	62.7	38	37.3		24	85.7	4	14.3	
60 to 79	82	61.6	51	38.4		26	78.8	7	21.2	
≥80	19	63.3	11	36.7		3	75.0	1	25.0	
Skin color					0.267					0.142
White	33	66.0	17	34.0		10	83.3	2	16.7	
Black	55	67.9	26	32.1		17	85.0	3	15.0	
Brown	69	55.6	55	44.4		30	85.7	5	14.3	
Other	11	55.0	9	45.0		1	33.3	2	66.7	
Literacy					0.441					0.287
Illiterate	64	59.3	44	40.7		16	76.2	5	23.8	
Literate	101	63.9	57	36.1		39	86.7	6	13.3	
Marital status					0.710					0.524
Single/divorced/widowed	56	59.6	38	40.4		20	87.0	3	13.0	
Married/lives with partner	112	61.9	69	38.1		38	80.8	9	19.2	
Working status					0.196					0.737
None	42	53.2	37	46.8		21	87.5	3	12.5	
Work	24	68.6	11	31.4		7	77.8	2	22.2	
Retired	102	63.3	59	36.7		30	81.1	7	18.9	
Monthly per capita income in dollar*					0.017					0.062
<\$ 53.19	38	50.0	38	50.0		20	95.2	1	4.8	
≥\$ 53.19	125	65.8	65	34.2		36	76.6	11	23.4	
Diagnosis of hypertension and diabetes					0.815					0.374
Hypertension only	106	60.6	69	39.4		—	—	—	—	
Diabetes only	—	—	—	—		11	91.7	1	9.3	
Hypertension and diabetes	62	62.0	38	38.0		47	81.0	11	19.0	

Follow-up was completed for 276 (49.6%) hypertensive patients and 71 (37.2%) diabetic patients. The study was interrupted due to the COVID-19 pandemic that led to a greater loss of intense follow-up of diabetes patients, as HbA1c had to be measured every 3 months.

Following intervention, the systolic BP (SBP) of patients had a mean reduction of 13.4 mmHg ($p = 0.021$) and the diastolic BP (DBP) had a mean reduction of 5.8 mmHg ($p < 0.001$). Regarding HbA1c levels of diabetic patients, the mean reduction was 0.55% ($p = 0.185$) (Table 2).

BP was controlled (<140/90 mmHg) in 107 (38.8%) patients; while the SBP decreased by ≥ 10 mmHg in 156 (56.5%) patients and DBP decreased by ≥ 5 mmHg in 141 patients (51.1%). HbA1c

levels were controlled (<7.0% for adults or <8.0% for older persons) in 12 (16.9%) patients, and there was a reduction of $\geq 1\%$ in HbA1c levels in 27 (38.0%) patients.

As shown in Table 3, a per capita income $< \$ 53.19$ was associated with greater hypertension control ($p = 0.017$) and being male was associated with a higher diabetes control ($p = 0.001$).

DISCUSSION

Our study showed a significant reduction in the mean BP, but not in HbA1c level, in patients who completed the follow-up. Several

studies indicate that considerable decreases in morbidity and premature mortality correlate with reductions in BP among hypertensive patients (Williams et al., 2018) and with glycemic control in diabetes patients (Schnell et al., 2017).

However, the achievement of BP and HbA1c control remains low worldwide (Schnell et al., 2017; Williams et al., 2018). Our BP control results were superior to those of another intervention study conducted in a specialized outpatient clinic in Brazil, where BP control was achieved in 30% of the patients (Coelho et al., 2005). Another study conducted by our team in urban areas of two Brazilian cities found that hypertensive patients had better BP control at the end of the intervention than at baseline. Therefore, at 1 year of follow-up in the two cities, mean reductions of 4.2 mmHg ($p < 0.001$) and 1.9 mmHg ($p < 0.01$) in SBP and DBP occurred, respectively ($p < 0.05$) (Flor et al., 2020).

A decrease of 10 mmHg in SBP or 5 mmHg in DBP was associated with significant reductions in all major cardiovascular events (approximately 20%) and all-cause mortality from 10 to 15% (Williams et al., 2018). In our study, 56.5 and 51.1% of the patients achieved these reductions in SBP and DBP, respectively.

Considering the socioeconomic characteristics of the population in our study, an association was found between having lower income and hypertension control in patients ($p = 0.017$). This result suggests that the interventions had a higher impact on this population group because it led to a reduction in health inequalities more often faced by this group of people.

Regarding diabetic patients, being male was associated with a greater control of diabetes ($p = 0.001$). This result suggests that the active search of patients by the work team, the timely interventions, and the offer of point-of-care measurement of HbA1c were more important for this group of patients, since men seek less health services than women (Lima et al., 2011).

In our study the mean reduction in HbA1c levels following the intervention was not significant. This result may be related to the early interruption of follow-up of these patients due to the COVID-19 pandemic in Brazil. Nevertheless, some patients achieved the control of HbA1c levels, and a larger number achieved a reduction of at least 1% in HbA1c levels. This reduction is important because it is associated with significant decreases in microvascular complications and mortality (Krishnamurti and Steffes, 2001).

The American Diabetes Association (ADA) recommends that HbA1c tests be performed twice a year for patients who are within the metabolic control goal and every 3 months for patients with change in treatment and/or out-of-goal test results (American Diabetes Association, 2020). However, most people with diabetes do not undergo HbA1c monitoring as recommended by the ADA (Egbunike and Gerard, 2013). In addition to the lack of testing following HbA1c test requests, there is an additional challenge whereby the test results are withheld until the patient clinically consults with the health professionals, which leads to delays in the administration of therapeutic strategies (Egbunike and Gerard, 2013).

In the study conducted by our team in two Brazilian cities, HbA1c levels were reduced by 0.6% ($p < 0.001$) and 0.9% ($p < 0.001$), respectively. Furthermore, approximately 10.3 and 25.0% more patients achieved diabetes control than those at baseline in each of the cities (Flor et al., 2020). A study in South Africa showed that after 2 years of providing HbA1c point-of-care testing at a primary care clinic site, a 1.3% reduction in the mean HbA1c ($p < 0.01$) level was achieved (Motta et al., 2017). In our population, following intervention, approximately 17% of the diabetic patients achieved disease control compared to that at the baseline, and 38% achieved a reduction of at least 1% in HbA1c.

In our study, the positive results may also be related to the benefits of using a point-of-care device to measure HbA1c levels. This allowed examinations to be performed at the time of care with the immediate result of the measurement availed; hence, essential interventions for effective control, such as treatment changes and emphasis on lifestyle changes, could be performed instantly (American Diabetes Association, 2020). Furthermore, a study showed that although the unit cost of the HbA1c measurement per point-of-care device was higher than that measured in a laboratory, its use was associated with cost reduction in medical care (Schnell et al., 2017).

However, with this being a quasi-experimental study, it is important to note that this type of design has some intrinsic limitations, including 1) the absence of random samples and 2) the absence of a comparator group in relation to the group of differentiated participants with interventions. Another limitation of this study was the short time of intervention and loss of follow-up; therefore, studies with longer follow-up periods may show more robust results.

Nevertheless, even though the randomized trial is the gold standard in the evaluation of community intervention trials, practical and ethical issues argue in favor of the almost experimental study model. This is because the interventions needed to be applied to as many patients as possible by the work team, in a community in need.

The innovative process of this study facilitated access to multifaceted interventions by patients from rural communities that effectively improved their BP and HbA1c levels. Despite the short duration of the study, the interventions can be sustainable on the long term, as they were designed to support family health teams in identifying patients with uncontrolled hypertension and diabetes, in addition to promoting lifestyle changes, adherence to treatment, self-care, and optimization of therapy. Therefore, we strongly encourage that other multicomponent intervention studies with longer durations be conducted in patients with diseases such as NCDs, to aid health professionals in improving the care of these populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee on Research in Human Beings of the Multidisciplinary Institute of Health–Campus Anísio Teixeira (identification by Opinion number: 3.357.963). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Design and planning: DS, DR, CK, JM, MO, SM, TC, and VC. Implementation of the interventions: JM, MO, TC, and VC. Analysis and interpretation of the results: JM, MO, TC, and VC. Drafting of the manuscript: DS, DR, CK, JM, MO, SM, TC, and VC. All authors approved the final version for submission.

REFERENCES

- American Diabetes Association (2020). Standards of medical care in diabetes-2020 abridged for primary care providers. *Clin. Diabetes* 38, 10–38. doi:10.2337/cd20-as01
- Coelho, E. B., Moysés Neto, M., Palhares, R., Cardoso, M. Cd. M., Geleilete, T. J. M., and Nobre, F. (2005). Relationship between attendance to outpatient consultations and blood pressure control in hypertensive patients. *Arq. Bras. Cardiol.* 85, 157–161. doi:10.1590/s0066-782x2005001600002
- Costa, A. F., Flor, L. S., Campos, M. R., Oliveira, A. F. D., Costa, M. D. F. D. S., Silva, R. S. D., et al. (2017). Burden of type 2 diabetes mellitus in Brazil. *Cad. de Saúde Pública*, 33. e00197915. doi:10.1590/0102-311x00197915
- Crhisten, R. S. (2016). *Succession, masculinization, aging and education in family farming. What is the influence of these factors on the rural exodus?* Francisco Beltrão, Brazil: Instituto de Formação do Cooperativismo Solidário-Instituto Infocofs, 1–15.
- Egbunike, V., and Gerard, S. (2013). The impact of point-of-care A1C testing on provider compliance and A1C levels in a primary setting. *Diabetes Educ.* 39, 66–73. doi:10.1177/0145721712465340
- Flor, L. S., Wilson, S., Bhatt, P., Bryant, M., Burnett, A., Camarda, J. N., et al. (2020). Community-based interventions for detection and management of diabetes and hypertension in underserved communities: a mixed-methods evaluation in Brazil, India, South Africa and the United States. *BMJ Glob. Health* 5, e001959. doi:10.1136/bmjgh-2019-001959
- Giovannella, L., and Mendonça, M. H. M. (2012). “Atenção Primária à Saúde,” in *Políticas e sistemas de saúde no Brasil [Health policies and systems in Brazil]* 1. Editor Fiocruz. 2nd Edn (Rio de Janeiro, Brazil: CEBES), 493–546.
- He, J., Irazola, V., Mills, K. T., Poggio, R., Beratarrechea, A., Dolan, J., et al. (2017). Effect of a community health worker-led multicomponent intervention on blood pressure control in low-income patients in Argentina. *JAMA* 318, 1016–1025. doi:10.1001/jama.2017.11358
- Krishnamurti, U., and Steffes, M. W. (2001). Glycohemoglobin: a primary predictor of the development or reversal of complications of diabetes mellitus. *Clin. Chem.* 47, 1157–1165. doi:10.1093/clinchem/47.7.1157
- Lima, L. M. D., Schwartz, E., Muniz, R. M., Zillmer, J. G. V., and Ludtke, I. (2011). Profile of HiperDia system users from three primary healthcare units in southern Brazil. *Rev. Gaúcha Enferm.* 32, 323–329. doi:10.1590/s1983-14472011000200016
- Mendes, A. D. C. G., Miranda, G. M. D., Figueiredo, K. E. G., Duarte, P. O., and Furtado, B. M. A. S. M. (2012). [Access to primary healthcare services: still a way to go]. *Ciênc. Saúde Colet.* 17, 2903–2912. doi:10.1590/s1413-81232012001100007
- Motta, L. A., Shephard, M. D. S., Brink, J., Lawson, S., and Rheeder, P. (2017). Point-of-care testing improves diabetes management in a primary care clinic in South Africa. *Prim. Care Diabetes* 11, 248–253. doi:10.1016/j.pcd.2016.09.008

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- Nascimento, B. R., Brant, L. C. C., Yadgir, S., Oliveira, G. M. M., Roth, G., Glenn, S. D., et al. (2020). Trends in prevalence, mortality, and morbidity associated with high systolic blood pressure in Brazil from 1990 to 2017: estimates from the “Global Burden of Disease 2017” (GBD 2017) study. *Popul. Health Metrics* 18, 1–22. doi:10.1186/s12963-020-00218-z
- Pessoa, V. M., Almeida, M. M., and Carneiro, F. F. (2018). Como garantir o direito à saúde para as populações do campo, da floresta e das águas no Brasil?. *Saúde debate* 42, 302–314. doi:10.1590/0103-11042018s120
- Philip, P. M., Kannan, S., and Parambil, N. A. (2018). Community-based interventions for health promotion and disease prevention in noncommunicable diseases: a narrative review. *J. Educ. Health Promot.* 7, 141. doi:10.4103/jehp.jehp_145_18
- Rosa, L. S., Mistro, S., Oliveira, M. G., Kochergin, C. N., Cortes, M. L., Medeiros, D. Sd., et al. (2021). Cost-effectiveness of point-of-care A1C tests in a primary care setting. *Front. Pharmacol.* 11, 2147. doi:10.3389/fphar.2020.588309
- Schnell, O., Crocker, J. B., and Weng, J. (2017). Impact of HbA1c testing at point of care on diabetes management. *J. Diabetes Sci. Technol.* 11, 611–617. doi:10.1177/1932296816678263
- Silva-Tinoco, R., Cuatecontzi-Xochitiotzi, T., De la Torre-Saldaña, V., León-García, E., Serna-Alvarado, J., Guzmán-Olvera, E., et al. (2020). Role of social and other determinants of health in the effect of a multicomponent integrated care strategy on type 2 diabetes mellitus. *Int. J. Equity Health* 19, 75. doi:10.1186/s12939-020-01188-2
- Malachias, M. V. B., Gomes, M. A. M., Nobre, F., Alessi, A., Feitosa, A. D., and Coelho, E. B. (2016). VII diretriz Brasileira de Hipertensão. [VII Brazilian guideline for hypertension]. *Arq. Bras. Cardio.* 107, 7–13. doi:10.5935/abc.20160152
- Steinsbekk, A., Rygg, L., Lisulo, M., Rise, M. B., and Fretheim, A. (2012). Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. *BMC Health Serv. Res.* 12, 213. doi:10.1186/1472-6963-12-213
- Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., et al. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* 39, 3021–3104. doi:10.1093/eurheartj/ehy339

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Efficacy of Antiangiogenic Drugs in the Treatment of Diabetic Macular Edema: A Bayesian Network Analysis

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Aims: To compare the efficacy of five kinds of antiangiogenic drugs in the treatment of diabetic macular edema

Methods: A comprehensive search of seven databases without language restrictions includes PubMed, EMBASE, Web of Science, CBM, the Cochrane Library, CNKI, and WanFang data. All literature used was published before October 2020. Eligible randomized trials were screened for inclusion in this study, and Bayesian framework was used to perform a network meta-analysis (NMA). Data on the mean change of best-corrected visual acuity (BCVA), central macular thickness (CMT) and intraocular pressure (IOP) at 6 months were extracted.

Results: 25 randomized controlled trials (RCTs) that covered 2214 eyes, which received treatment of more than 3 months durations were included. In the pooled pair-wise meta-analysis, there was no statistically significant difference between all treatments. The same result was observed in the network meta-analysis with 0–37.82% Global I-squared. For BCVA at 6 months, conbercept and ranibizumab may be favorable than bevacizumab, aflibercept, triamcinolone acetonide and sham injections according to the ranking probabilities. As for CMT at 6 months, ranibizumab may be the most effective compared to bevacizumab, aflibercept and triamcinolone acetonide. In terms of IOP at 6 months, ranibizumab have better effect than bevacizumab, triamcinolone acetonide and sham injections. The results of sensitivity analysis also confirm it.

Conclusion: The analysis confirms that ranibizumab may be the most favorable for BCVA improvement and have a stronger efficacy in decreasing CMT and IOP than other drugs when taking all the indicators into consideration. This conclusion may provide clinical evidence to guide treatment decisions. However, more high-quality randomized controlled trials will be necessary to further confirm this.

Keywords: antiangiogenic drugs, diabetic macular edema, network meta-analysis, best-corrected visual acuity, central macular thickness, intraocular pressure

INTRODUCTION

Diabetic macular edema is one of the most common and serious complications of diabetes (Sayin et al., 2015). It is due to the unstable state of long-term high blood glucose levels that causes damage to the retinal vasculature, resulting in enhanced permeability of the retinal blood vessels and accumulation of fluid in the macular area, causing diabetic macular edema (Shin et al., 2014). Once diabetic macular edema occurs, it can significantly reduce vision. Data shows that about one-third of people with diabetes will develop retinopathy, and about 2.6% of blind syndromes worldwide can be contributed to diabetes (Leasher et al., 2016). With the development of a large number of randomized clinical trials, intravitreal injection has gradually replaced the method of grid laser photocoagulation, and has significantly improved the treatment efficacy of macular edema. Diabetic macular edema treatment guidelines issued by European Retina Specialist Association (EURETINA) in 2017 pointed out that anti-vascular growth factor is a safe and effective first-line treatment for diabetic macular edema (Schmidt-Erfurth et al., 2017).

There are many types of antiangiogenic drugs, the effectiveness of various drugs is different, and there is a lack of direct comparison evidence for these drugs, making it difficult to evaluate the effectiveness of multiple drugs. Moreover, there are few studies comparing the efficacy of drugs alone, and the number of included literatures is not enough. This is the first study which has estimated and compared the effectiveness of all triple antiangiogenic therapy that has been studied in randomized trials. Compared to same type meta-analysis, this study included a full range of antiangiogenic drugs and compared the differences in efficacy between single drugs. In addition, this study is of a higher standard, due to accurate experimental types of randomized trials, identifying interventions outside of laser interference, unity of follow-up time and outcome indicators. We aimed to evaluate the efficacy of five kinds of antiangiogenic drugs in the treatment of diabetic macular edema. This method can provide clinical evidence to guide treatment decisions.

MATERIALS AND METHODS

The study was conducted in accordance with the guidelines of the Cochrane Multiple Interventions Methods Group (Chaimani et al., 2017).

Search Strategy

PubMed, EMBASE, Web of Science, CBM, the Cochrane Library, CNKI, and WanFang data were used to identify relevant studies published before October 2020. The search terms (diabetic macular edema) and (ranibizumab or bevacizumab or aflibercept or conbercept or pegaptanib or triamcinolone acetate or dexamethasone or fluocinolone) and (randomized controlled trial or RCT or random) were used. All available literatures were considered for review. Manual search was also performed to ensure complete retrieval using references of key articles.

Study Selection and Data Extraction

All investigators independently assessed all trials for eligibility and extracted data. After the initial extraction was completed, the results were checked by each investigator. In the case of disagreements, consensus was reached through discussion. The full text of all the articles were obtained and the same eligibility criteria was used to determine which, if any, to exclude at this stage. The follow-up time of each randomized trial, the average age and sex ratio of patients, grouping, intervention measures, and outcome indicators were recorded. Each reviewer independently read each article, assessed the completeness of the data extraction, and confirmed the quality rating.

Eligibility Criteria

The included literature needs to meet the following criteria: 1) Meets the relevant diagnostic criteria of type I or II diabetes complicated with diabetic macular edema; 2) Interventions can only be antiangiogenic drugs, including ranibizumab or bevacizumab or aflibercept or conbercept or triamcinolone acetate or pegaptanib or dexamethasone or fluocinolone; 3) Outcome measures included BCVA or CMT or IOP more than 3 months; 4) Study design must be randomized controlled trials; 5) Only included patients who had not received laser treatment for at least 3 months before trials. Trials that included other drugs, trials that had incomplete or incalculable data, trials that did not have baseline data and trials that had left and right eyes compared to each other were excluded.

Risk of Bias Within Individual Studies

Four independent reviewers (MR W, WT Z, R Z and YF W) reviewed all the included studies. Any disagreements were discussed and rechecked together. The Cochrane Collaboration using the Cochrane risk of bias tool of Review Manager were used for assessing risk of bias method in randomized controlled trials. After all the outcomes were evaluated, a summary of confidence examining the effectiveness of a comparison between ranibizumab and other drugs was created using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Nikolakopoulou et al., 2020).

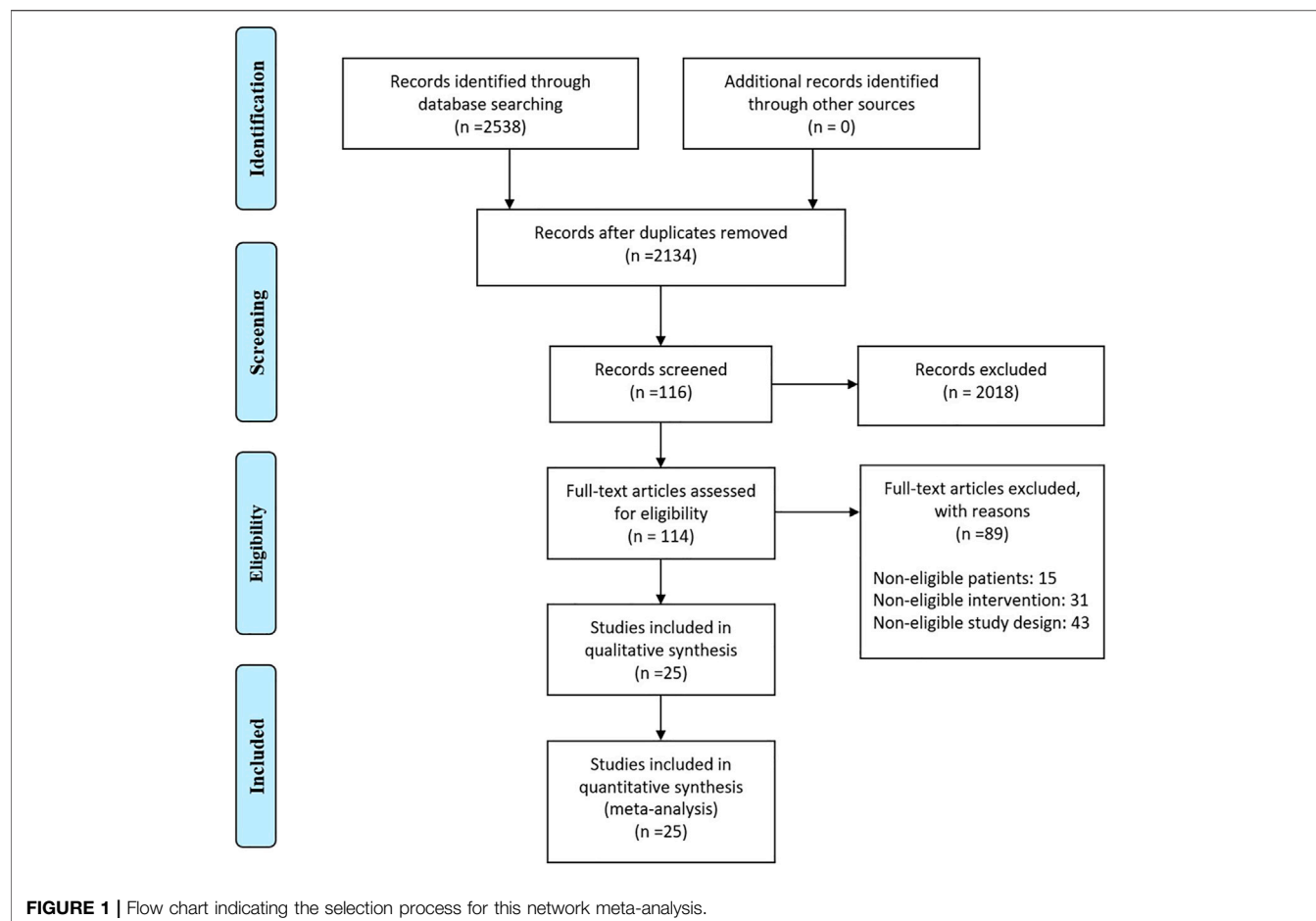
Clinical Endpoints

BCVA, CMT at 6 months were set as primary visual outcomes. In addition, IOP at 6 months was also used as important outcome indicator.

Statistical Analysis

In order to make the results more reliable and reduce the heterogeneity between data, the mean changes before and after treatment were calculated. This was an intention-to-treat analysis based on random effect model. Summarized effect size was calculated as mean differences (MD). First, a direct meta-analysis of trials that compared different treatments was done. Then, the Bayesian network meta-analysis was conducted to compare between different treatment that no head-to-head trials.

Pairwise meta-analyses were conducted beforehand for every treatment comparison. Heterogeneity across individual studies was assessed by the Cochran Q test (Chi-squared) and Higgins



I-squared inconsistency statistic. If there was no significant heterogeneity ($p > 0.05$, I-squared $< 50\%$), a fixed effects model was used. Otherwise, a random effects model was used. Given the low heterogeneity detected across all direct meta-analyses, fixed-effects estimates were reported.

This Bayesian network meta-analysis was done by R with gemtc package. Within the Bayesian hierarchical model frameworks, the number of chains was 3; thinning interval, 10; tuning iterations, 10,000; simulation iterations, 60,000; and initial values scaling, 2.5. Moreover, all the treatments were ranked based on the analysis of ranking probabilities.

Furthermore, the analysis at 6 months is star-shaped and does not contain a closed loop, so local inconsistency of the network cannot be assessed. Global inconsistency was judged by using the value of deviance information criterion (DIC) between the consistency and inconsistency model. If the DIC difference was within five, the data was generally considered consistent. To demonstrate the robustness of the results, a sensitivity analysis was performed. According to the follow-up time, the efficacy evaluation was brought forward to 3 months and later to 12 months, to see whether the conclusion was consistent with the follow-up time of 6 months. Inconsistency as well as statistical disagreement of direct and indirect evidence was assessed by using node-split method in sensitivity analysis. Moreover, a $p >$

0.05 was considered as no significant inconsistency. All data was analyzed by using R 3.6.3.

RESULT

Study Screening

Figure 1 shows the detailed steps of the literature selection process. Through searching the literature databases, 2538 relevant literatures were found, and 2424 duplications and unrelated literatures were excluded. Then, literatures were further selected by reading the full text, excluding substandard samples, substandard interventions and substandard research design, and finally included 25 articles.

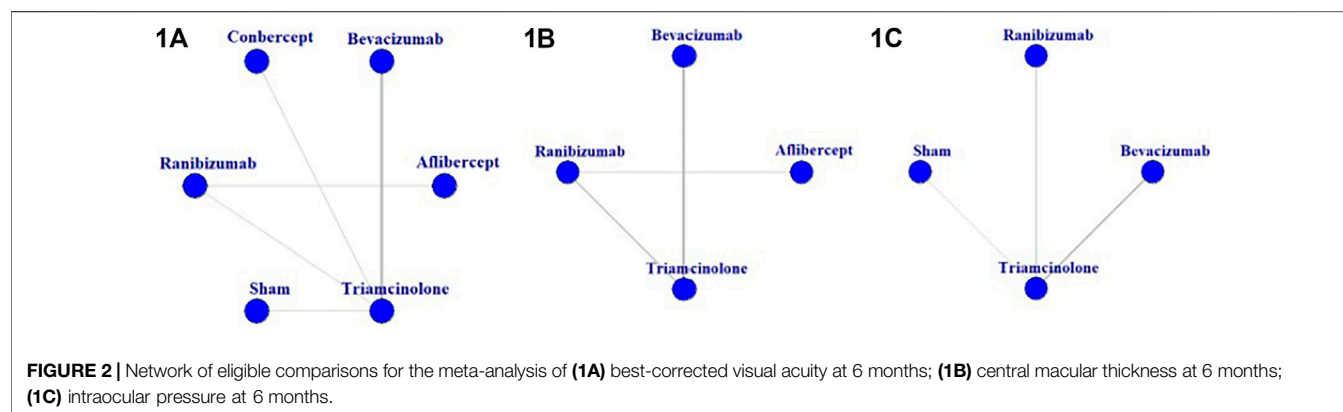
Study Characteristics and Network Geometry

In total, 25 trials were included in the network meta-analysis, the basic characteristics of them were presented in **Table 1**. A network of eligible comparisons for the multiple-treatment meta-analysis was constructed (**Figure 2**). Five treatments were analyzed: ranibizumab, bevacizumab, aflibercept, conbercept, triamcinolone acetonide. Most trials (22 of 25) were

TABLE 1 | The basic characteristics of the included literature.

Study id	Follow-up	Gender (male/female)	Mean age	Experimental group		Control group	
				No. of eyes	Intervention	No. of eyes	Intervention
Jonas et al. (2006)	24 weeks	NA	65.7 ± 7.5/68.8 ± 9.9	29	20 mg IVT	12	Sham injections
Genentech, Inc. (2007)	48 weeks	212/165	62.1 ± 9.6	T1:125 T2:125	T1:0.3 mg IVB T2: 0.5 mg IVB	127	Sham injections
Paccola et al. (2007)	24 weeks	15/11	67.08 ± 4.67/ 65.58 ± 8.44	13	4 mg IVT	13	1.5 mg IVB
Wang et al. (2009)	48 weeks	7/17	52.4/51.6	12	4 mg IVT	12	Sham injections
Ma (2010)	24 weeks	22/33	60.34 ± 7.2	30	4 mg IVT	30	1.25 mg IVB
Massin et al. (2010)	48 weeks	81/70	63.6 ± 9.95	51	0.3 mg IVR	49	Sham injections
Marey and Ellakwa (2011)	12 weeks	53/37	57.64 ± 7.23	30	4 mg IVT	30	1.25 mg IVB
Lim et al. (2012)	48 weeks	50/55	60.4 ± 7.4	38	1.25 mg IVB	37	2 mg IVT
Wan et al. (2013)	12 weeks	24/30	55.8	30	0.5 mg IVR	30	4 mg IVT
Ekinci et al. (2014)	48 weeks	32/68	68 ± 9/65 ± 14	50	1.25 mg IVB	50	0.05 mg IVR
Sonoda et al. (2014)	12 weeks	34/17	59.2 ± 12.5/62.9 ± 11.4	25	4 mg IVT	26	1.25 mg IVB
Yan et al. (2016)	12 weeks	44/36	63.4 ± 9.6	40	0.5 mg IVR	40	4 mg IVT
Pan (2016)	24 weeks	44/34	66.5 ± 4.4/66.2 ± 4.2	39	0.05 ml IVR	39	0.05 mg IVT
Xue et al. (2016)	12 weeks	49/31	51.2 ± 3.7/51.9 ± 3.6	40	0.05 ml IVR	40	0.05 mg IVT
Zhang et al. (2016a)	24 weeks	33/27	62.4 ± 3.4/63.1 ± 2.9	30	0.05 ml IVR	30	0.05 mg IVT
Zhou (2016)	12 weeks	NA	NA	20	0.05 ml IVR	21	4 mg IVT
Neto et al. (2017)	24 weeks	43/34	NA	39	1.25 mg IVB	38	4 mg IVT
Fouda and Bahgat (2017)	48 weeks	NA	55.05 ± 4.7/56.64 ± 5.8	35	2 mg IVZ	35	0.5 mg IVR
Baghi et al. (2017)	12 weeks	51/72	63 ± 7	T1:42 T2:42	T1:2.5 mg IVZ T2: 1.25 mg IVZ	39	1.25 mg IVB
Li et al. (2018)	48 weeks	55/47	58.0 ± 6.6/58.2 ± 6.7	51	0.05 ml IVR	51	0.05 mg IVT
Jabbarpoor et al. (2018)	48 weeks	51/72	63 ± 7	T1:42 T2:42	T1:2.5 mg IVZ T2: 1.25 mg IVZ	39	1.25 mg IVB
Schlingemann et al. (2019)	24 weeks	101/65	63.9 ± 11.6/64.9 ± 11.6	84	1.25 mg IVB	82	0.5 mg IVR
Ji et al. (2019)	24 weeks	65/55	45.39 ± 4.22/ 45.87 ± 5.19	60	0.5 mg IVC	60	0.5 mg IVT
Ren et al. (2019)	12 weeks	37/41	57	30	0.5 mg IVR	30	2 mg IVT
Rodrigues et al. (2020)	24 weeks	39/26	60.7 ± 6.6/62.8 ± 8.2	32	1.25 mg IVB	28	1.20 mg IVT

Abbreviations: IVT, intravitreal triamcinolone acetate; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVZ, intravitreal aflibercept; IVC, intravitreal conbercept; T, experimental group; C, control group; NA, no available.

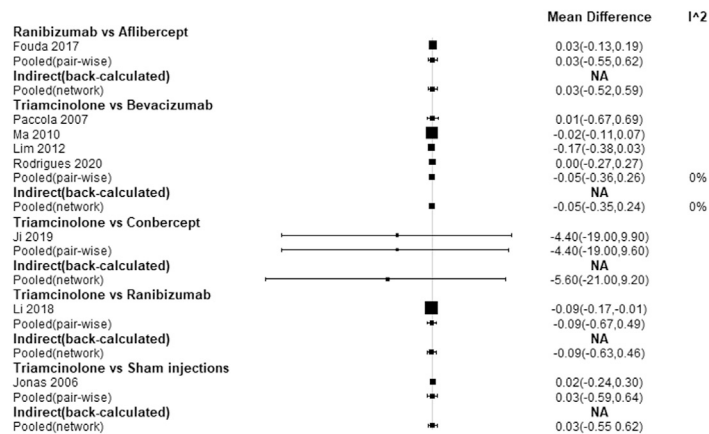


two-grouped studies (Jonas et al., 2006; Paccola et al., 2007; Wang et al., 2009; Ma, 2010; Massin et al., 2010; Marey and Ellakwa, 2011; Lim et al., 2012; Wan et al., 2013; Ekinci et al., 2014; Sonoda et al., 2014; Pan, 2016; Xue et al., 2016; Yan et al., 2016; Zhang et al., 2016b; Zhou, 2016; Fouda and Bahgat, 2017; Neto et al., 2017; Li et al., 2018; Ji et al., 2019; Ren et al., 2019; Schlingemann et al., 2019; Rodrigues et al., 2020) and the rest were three-grouped studies

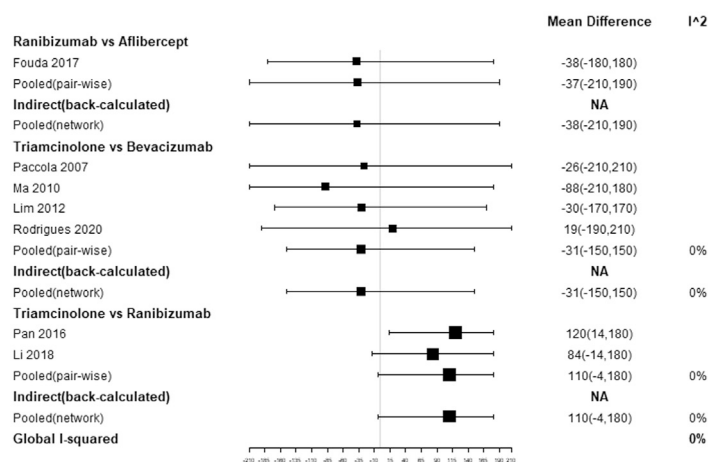
(Genentech, Inc., 2007; Baghi et al., 2017; Jabbarpoor et al., 2018). Overall, 2214 eyes were randomly assigned to one or two of the five antiangiogenic treatments or to the sham injection and were included in the network meta-analysis.

The mean duration of the studies was 6 months (nine studies lasted 3 months, eleven lasted 6 months, and ten lasted 12 months or more), and the mean sample size was 43 eyes per group

Best-corrected visual acuity at 6 months



Central macular thickness at 6 months



Intraocular pressure at 6 months

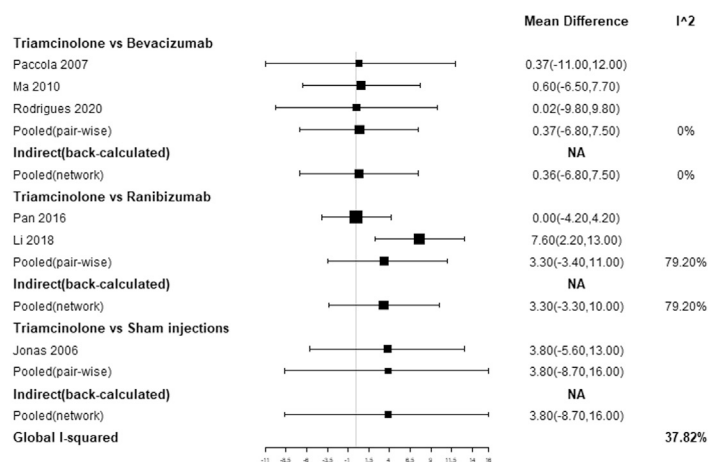


FIGURE 3 | Pair-wise meta-analysis and network meta-analysis of different pharmacological interventions on effect of diabetic macular edema at 6 months.

(minimum/maximum 12/127). In the sample included in the study, the gender ratio was balanced (males accounted for 55.0%) with an average age of about 60.62 years. In terms of clinical

characteristics, most included studies recruited patients classified as having type I or II diabetes complicated with diabetic macular edema. The overall quality of studies was rated as good, despite

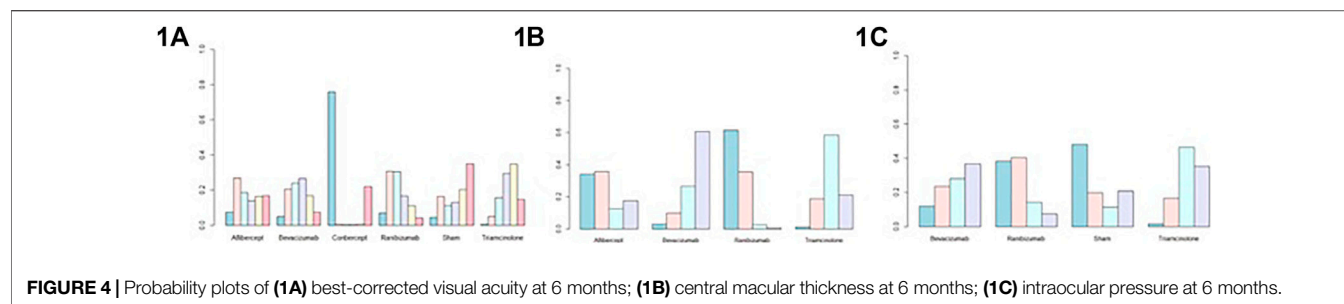


FIGURE 4 | Probability plots of **(1A)** best-corrected visual acuity at 6 months; **(1B)** central macular thickness at 6 months; **(1C)** intraocular pressure at 6 months.

some studies not disclosing details regarding randomize and allocation concealment.

Risk of Bias and Quality Assessment

The quality of the studies included in this network meta-analysis is shown in **Supplementary Figure S1**. In relation to the random sequence generation, allocation concealment, blinding of participants and personnel and outcome assessment, one trial was rated as “high risk of bias” (1 of 25 trials), whereas for attrition bias and reporting bias, the majority of trials were rated as “low risk of bias”, because they reported the complete outcome data (24 and 25 trials respectively). Those rated at “unclear risk of bias” had issues relating to random sequence generation, and allocation concealment (13 and 21 trials, respectively) and masking of participants and personnel (16 trials/64.0%).

The results of the GRADE evaluation of interventions for ranibizumab were presented in **Supplementary Table S1**. All the reasons for downgrading were labeled. Due to the network analysis at 6 months is star-shaped and does not contain a closed loop, local inconsistency of the network cannot be assessed. Therefore, the level of evidence was all downgraded.

Pair-Wise Meta-Analysis

In pooled pair-wise meta-analysis, there was no statistically significant difference between ranibizumab, bevacizumab, aflibercept, conbercept, triamcinolone acetamide and sham injections in BCVA at 6 months. As for CMT at 6 months, ranibizumab, bevacizumab, aflibercept and triamcinolone acetamide also did not show a statistically significant difference. In terms of IOP at 6 months, the same conclusion was observed in ranibizumab, bevacizumab, triamcinolone acetamide and sham injections.

NETWORK META-ANALYSIS

Best-Corrected Visual Acuity at 6 Months

Figure 3 and **Supplementary Table S2** shows the BCVA comparison results at 6 months. Non-significant results were found when comparing between all treatments. As for ranking the results, the efficacy of antiangiogenic drugs in order of most to least are as follows: conbercept, ranibizumab, aflibercept, triamcinolone acetamide, bevacizumab and sham injections (**Figure 4**).

Central Macular Thickness at 6 Months

Figure 3 and **Supplementary Table S2** show the CMT comparison results at 6 months. The NMA comparison using Bayesian framework indicated that ranibizumab, bevacizumab, aflibercept and triamcinolone acetamide also did not show statistically significant difference. According to ranking probabilities, ranibizumab may decrease CMT more significantly than aflibercept, bevacizumab and triamcinolone acetamide, with aflibercept being probably the second most effective (**Figure 4**).

Intraocular Pressure at 6 Months

IOP comparison results at 6 months are shown in **Figure 3** and **Supplementary Table S2**. There were no significant differences between pairs of treatment between ranibizumab, bevacizumab, sham injections and triamcinolone acetamide. As for ranking the results, ranibizumab may decrease IOP more significantly than bevacizumab, sham injections and triamcinolone acetamide (**Figure 4**). Meanwhile, bevacizumab may be the second most effective.

Inconsistency Analysis

Global inconsistency of the network meta-analysis is summarized under consistency and inconsistency assumption (**Supplementary Table S3**). The difference of DIC between two models was no more than five, which means the results are generally considered consistent.

Sensitivity Analysis

To demonstrate the robustness of our results, a sensitivity analysis was conducted by dividing different follow-up periods. After 3 months, both pooled pair-wise meta-analysis and network meta-analysis showed no statistically significant difference between all treatments (**Supplementary Figure S2**), with ranibizumab being the most favorable for BCVA improvement, decreasing CMT and IOP according to the ranking probabilities (**Supplementary Figure S3**). After 12 months, the same conclusion was observed in both pooled pair-wise meta-analysis and network meta-analysis (**Supplementary Figure S4**), with ranibizumab being the most favorable for BCVA improvement and decreasing CMT (**Supplementary Figure S3**). After sensitivity analysis, the main result revealed no significant change in NMA results, indicating the robustness and reliability of the statistical analysis.

DISCUSSION

This is the first study which has estimated and compared the effectiveness of all triple antiangiogenic therapy that has been studied in randomized trials. Compared to previous meta-analysis, this study included a full range of antiangiogenic drugs and compared the differences from three perspectives between single drugs. In addition, this study has a higher standard, due to accurate experimental types of randomized trials, identifying interventions outside of laser interference, unity of follow-up time and inclusion of trials published in non-English publications. A sufficient number of literatures, a total of 25 articles, was selected and included in this study.

According to the statistical results, it is shown that no matter which outcome indicator is compared or which follow-up period is observed, ranibizumab may have the best curative effect. A randomized controlled trial showed that the relative effect of intravitreal aflibercept, bevacizumab, or ranibizumab depended on baseline visual acuity, and that these drugs are equally effective in patients who initially had mild visual impairment (Wells et al., 2015), which is consistent with the comparison of the network meta-analysis. From a head-to-head trial, ranibizumab improves vision quickly and steadily compared with placebo and reduced the risk of long-term visual loss (Quan et al., 2012). Another study confirmed that ranibizumab significantly improved vision and is well tolerated by patients.

A recent review (Zhang et al., 2016a) published in 2016 that compared 21 trials (4703 eyes), suggested that intravitreal aflibercept is most favorable, with both BCVA improvement and CMT reduction within 12 months compared with other current therapies in the management of diabetic macular edema. In addition, another study (Pham et al., 2019) evaluated head-to-head randomized controlled trials comparing aflibercept, bevacizumab, and ranibizumab (or any combination of head-to-head comparisons) in adult patients with diabetic macular edema. The study found that patients with diabetic macular edema treated with aflibercept experienced significantly higher vision gain at 12 months than patients receiving ranibizumab or bevacizumab. This is slightly different from the conclusion reached in this study, which indicated aflibercept is second only to ranibizumab in both BCVA improvement and CMT reduction according to the ranking probabilities.

With respect to the efficacy of the various drugs, short-term and long-term efficacy were compared, and data from three periods (3, 6, and 12 months). As for the safety of antiangiogenic drugs in the treatment of diabetic macular edema, IOP was chosen to quantitatively evaluate this. Because the amount of data available regarding IOP at 12 months is limited, only data from 3 to 6 months were compared. There was no statistical difference in the efficacy of all drugs at 6 months.

This study has limitations to some extent, because the present literature is not comprehensive enough, random test sample size is not big enough, and it incorporated literature of variable quality. In addition, the research results were impacted by using selected trials from different regions, ages of the patients, and levels of medical treatment. These factors may have a potential impact on the results, although it was found that the heterogeneity of the study is not high. Moreover, measurements that are not easily affected by patients' baseline conditions, including changes in visual acuity, central macular thickness and intraocular pressure before and after treatment, thus the statistical analysis and conclusions are relatively reliable. 3, 6, and 12 months after the operation were chosen as times of result analysis. This choice was guided by the availability of various trial data, which also helped to compare the short-term and long-term effects of using the drugs.

This systematic review and network meta-analysis determined the efficacy of different anti-angiogenic drugs on diabetic macular edema. The analysis confirms that ranibizumab may be most favorable for BCVA improvement and have a stronger efficacy in decreasing CMT and IOP than using other drugs when taking all the indicators into consideration. This conclusion may help doctors evaluate the balance of pros and cons of various drugs and adjust their treatment accordingly.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Conception and design: QL and MW; Collection and assembly of data: XZ and YL; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors; Accountable for all aspects of the work: All authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.637667/full#supplementary-material>.

REFERENCES

- Baghi, A., Jabbarpoor Bonyadi, M. H., Ramezani, A., Azarmina, M., Moradian, S., Dehghan, M. H., et al. (2017). Two doses of intravitreal ziv-aflibercept versus bevacizumab in treatment of diabetic macular edema: a three-armed, double-blind randomized trial. *Ophthalmol. Retina* 1 (2), 103–110. doi:10.1016/j.oret.2016.08.007
- Chaimani, A., Caldwell, D. M., Li, T., Higgins, J. P. T., and Salanti, G. (2017). Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. *J. Clin. Epidemiol.* 83, 65–74. doi:10.1016/j.jclinepi.2016.11.015
- Ekin, M., Ceylan, E., Çakıcı, Ö., Tanyıldız, B., Olcaysu, O., and Çağatay, H. H. (2014). Treatment of macular edema in diabetic retinopathy: comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. *Expert Rev. Ophthalmol.* 9 (2), 139–143. doi:10.1586/17469899.2014.900439
- Fouda, S. M., and Bahgat, A. M. (2017). Intravitreal aflibercept versus intravitreal ranibizumab for the treatment of diabetic macular edema. *Clin. Ophthalmol.* 11, 567–571. doi:10.2147/OPTH.S131381
- Genentech, Inc. (2007). A study of ranibizumab injection in subjects with clinically significant macular edema (ME) with center involvement secondary to diabetes mellitus (RISE). Available at: <https://clinicaltrials.gov/show/NCT00473330> (Accessed May 15, 2007).
- Jabbarpoor, B. M., Baghi, A., Ramezani, A., Yaseri, M., and Soheilani, M. (2018). One-year results of a trial comparing 2 doses of intravitreal ziv-aflibercept versus bevacizumab for treatment of diabetic macular edema. *Ophthalmol. Retina* 2 (5), 428–440. doi:10.1016/j.oret.2017.09.010
- Ji, X. Y., Sun, H. L., Li, C. W., and Chen, X. Y. (2019). Comparison of different drugs in the treatment of retinopathy caused by type 2 diabetes. *J. Pract. Med.* 35 (4), 598–601. doi:10.3969/j.issn.1006-5725.2019.04.022
- Jonas, J. B., Kamppe, B. A., Harder, B., Vossmerbaeumer, U., Sauder, G., and Spandau, U. H. M. (2006). Intravitreal triamcinolone acetonide for diabetic macular edema: a prospective, randomized study. *J. Ocul. Pharmacol. Ther.* 22 (3), 200–207. doi:10.1089/jop.2006.22.200
- Leasher, J. L., Bourne, R. R. A., Flaxman, S. R., Jonas, J. B., Keeffe, J., Naidoo, K., et al. (2016). Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. *Diabetes Care* 39 (9), 1643–1649. doi:10.2337/dc15-2171
- Li, Y. X., Hu, J., and Zhang, W. (2018). Effect of rezumab and triamcinolone acetonide on the treatment effect of diabetic macular edema. *Contemp. Med.* 24 (14), 19–21. doi:10.3969/j.issn.1009-4393.2018.14.007
- Lim, J. W., Lee, H. K., and Shin, M. C. (2012). Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial. *Ophthalmologica* 227 (2), 100–106. doi:10.1159/000331935
- Ma, J. (2010). Intravitreal triamcinolone acetonide versus bevacizumab for the treatment of diabetic macular edema. Available at: <http://www.hebmu.edu.cn/>.
- Marey, H., and Ellakwa, A. F. (2011). Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin. Ophthalmol.* 5 (1), 1011–1016. doi:10.2147/OPTH.S22103
- Massin, P., Bandello, F., Garweg, J. G., Hansen, L. L., Harding, S. P., Larsen, M., et al. (2010). Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes care* 33 (11), 2399–2405. doi:10.2337/dc10-0493
- Neto, H. O., Regatieri, C. V., Nobrega, M. J., Muccioli, C., Casella, A. M., Andrade, R. E., et al. (2017). Multicenter, randomized clinical trial to assess the effectiveness of intravitreal injections of bevacizumab, triamcinolone, or their combination in the treatment of diabetic macular edema. *Ophthalmic Surg. Lasers Imaging Retina* 48 (9), 734–740. doi:10.3928/23258160-20170829-08
- Nikolakopoulou, A., Higgins, J. P. T., Papakonstantinou, T., Chaimani, A., Del Giovane, C., Egger, M., et al. (2020). CINEMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med.* 17 (4), e1003082. doi:10.1371/journal.pmed.1003082
- Paccola, L., Costa, R. A., Folgosa, M. S., Barbosa, J. C., Scott, I. U., and Jorge, R. (2007). Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). *Br. J. Ophthalmol.* 92 (1), 76–80. doi:10.1136/bjo.2007.129122
- Pan, Z. J. (2016). The effect of intravitreal injection of ranibizumab and triamcinolone acetonide on diabetic macular edema. *Mod. Diagn. Treat.* 27 (12), 2214–2215.
- Pham, B., Thomas, S. M., Lillie, E., Lee, T., Hamid, J., and Richter, T., et al. (2019). Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis. *BMJ Open* 9 (5), e022031. doi:10.1136/bmjopen-2018-022031
- Quan, D. N., David, M. B., Dennis, M. M., David, S. B., Sunil, P., and Leonard, F., et al. (2012). Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 119 (4), 789–801. doi:10.1016/j.ophtha.2011.12.039
- Ren, Z., Zhang, W., Huang, W., Zeng, J., Zhao, X., and Zhang, X. (2019). Clinical efficacy and safety of intra-vitreous injection of Lucentis combined with triamcinolone acetonide in treatment of diffuse diabetic macular edema. *Chin. J. Clinicians* 13 (6), 409–418. doi:10.3877/cma.j.issn.1674-0785.2019.06.002
- Rodrigues, M. W., Cardillo, J. A., Messias, A., Siqueira, R. C., Scott, I. U., and Jorge, R. (2020). Bevacizumab versus triamcinolone for persistent diabetic macular edema: a randomized clinical trial. *Graefes Arch. Clin. Exp. Ophthalmol.* 258 (3), 479–490. doi:10.1007/s00417-019-04564-z
- Sayin, N., Kara, N., and Pekel, G. (2015). Ocular complications of diabetes mellitus. *WJD* 6 (1), 92–108. doi:10.4239/wjd.v6.i1.92
- Schlingemann, R. O., Vader, M., Schauwvlieghe, A., Dijkman, G., Hooymans, J., Los, L., et al. (2019). Comparing the efficacy of bevacizumab to ranibizumab in patients with diabetic macular oedema: the brdme study. *Eur. J. Ophthalmol.* 29 (3), NP18–NP9. doi:10.1016/j.oret.2020.02.008
- Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B. S., et al. (2017). Guidelines for the management of diabetic macular edema by the European society of Retina specialists (EURETINA). *Ophthalmologica* 237 (4), 185–222. doi:10.1159/000458539
- Shin, E. S., Sorenson, C. M., and Sheibani, N. (2014). Diabetes and retinal vascular dysfunction. *J. Ophthalmic Vis. Res.* 9 (3), 362–373. doi:10.1371/journal.pone.0103148
- Sonoda, S., Sakamoto, T., Yamashita, T., Otsuka, H., Shirasawa, M., Kakiuchi, N., et al. (2014). Effect of intravitreal triamcinolone acetonide or bevacizumab on choroidal thickness in eyes with diabetic macular edema. *Invest. Ophthalmol. Vis. Sci.* 55 (6), 3979–3985. doi:10.1167/iovs.14-14188
- Wan, L., Wang, R., and Zhong, J. (2013). Investigation on lucentis inhibition to macular edema in diabetic retinopathy. *J. Chin. Ophthalmol. Otorhinolaryngol.* 3 (4), 204–207. doi:10.3969/j.issn.1674-9006.2013.04.010
- Wang, X. J., Kuang, G. Y., Chen, Y. B., Zhai, N., Wang, W., Qin, W., et al. (2009). Intravitreal injection of triamcinolone acetonide in the treatment of diabetic retinopathy and macular edema. *Youjiang Med. J.* 37 (04), 425–426.
- Wells, J. A., Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Aiello, L. P., et al. (2015). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N. Engl. J. Med.* 372 (13), 1193–1203. doi:10.1056/NEJMoa1414264
- Xue, S., Chen, P., Liu, W., and Yuan, J. (2016). Intravitreal injection of ranibizumab versus triamcinolone acetonide for diabetic macular edema. *Int. Med. Health Guidance News* 22 (20), 3149–3151. doi:10.3760/cma.j.issn.1007-1245.2016.20.033
- Yan, J., Jiang, W. H., and Peng, X. F. (2016). Observation of clinical effect of lucentis in treatment of diabetic macular edema. *China Med. Pharm.* 6 (5), 109–111.
- Zhang, L., Wang, W., Gao, Y., Lan, J., and Xie, L. (2016a). The efficacy and safety of current treatments in diabetic macular edema: a systematic review and network meta-analysis. *PLoS One* 11 (7), e0159553. doi:10.1371/journal.pone.0159553
- Zhang, Z. G., Ma, W. X., and Zhang, W. G. (2016b). Clinical effect of treating diabetic macular edema by vitreous cavity injection of ranibizumab and triamcinolone acetonide. *World Latest Med. Inf.* 16 (94), 11. doi:10.3969/j.issn.1671-3141.2016.94.007
- Zhou, R. L. (2016). A comparative observation of 41 cases of diabetic macular edema treated with ranibizumab and triamcinolone acetonide. *Shaanxi Med. J.* 45 (1), 91–92. doi:10.3969/j.issn.1000-7377.2016.01.038

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Strategies to Approach Medicines Litigation: An Action Research Study in Brazil

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Background: In the last decades, litigation has been increasingly used to access medicines in Brazil. This phenomenon has led to the development of diverse strategies to reduce its negative impact on the organization of pharmaceutical services. In spite of that, managers still face difficulties dealing with lawsuits.

Objective: This study aims to report the planning and implementation of strategies to approach medicines litigation in a municipality located in the southeast region of Brazil.

Methods: Mixed methods were employed through an action research cycle. A network coordination team included researchers from university and municipal managers. The scenario analysis comprised the characterization of pharmaceutical services and the profile of medicines lawsuits. Afterward, strategies were planned to deal with the central problem identified. The action plan involved educational outreach visits and distribution of printed materials for health professionals, evaluated through opinion survey. Group conversations were conducted with the users of the public health system, followed by thematic analysis of reports.

Results: The characterization of pharmaceutical services in the municipality revealed that treatments supplied were in accordance with the National Medicines Policy. In addition, a sector was implemented to attend demands for non-incorporated medicines. In spite of the services available, the characterization of lawsuits indicated that the main claimants were users of the public health system, requiring non-incorporated medicines, with therapeutic alternatives available. Thus, educational outreach visits were held in 14 health units (23 physicians in total). Everyone who answered the evaluation declared that they were very satisfied with the approach. Group conversations with the users of the health system reached 227 participants in total. In regard to users' perception about pharmaceutical services, thematic analysis of reports identified three main categories including aspects related to medicines provided, users assisted, and quality of service.

Conclusion: The study described the first cycle of an action research project to develop strategies to approach medicines litigation at the municipal level. The application of educational outreach visits for health professionals and group conversations with

health system users is a promising approach to improve access to information about pharmaceutical services in Brazil.

Keywords: pharmaceutical services, health's judicialization, right to health, action research, essential medicines, educational outreach visits, group conversations

INTRODUCTION

The lawsuits for access to medicines impact the structure, financing, and organization of healthcare services as they neglect the priorities established through public policies and force reallocation of financial and human resources with the potential to widen inequality (Wang, 2015). Brazil has faced a marked increase in the expenditure on claims ordered by litigation since 2005 (Cubillos et al., 2012). Data from the Ministry of Health estimated that from 2009 to 2016, the amount allocated to deal with lawsuits rose approximately 13 times, reaching more than US\$ 293 million (Ayres et al., 2018).

Therefore, efforts have been made to mitigate the negative impacts on the public health system by different institutions involved with the phenomenon. In response to litigation, health system managers had to remodel and structure new services to address the increasing demand of lawsuits to access medicines (Catanheide et al., 2016).

In Brazil, the institutional response of the judicial branch included the Recommendation 31/2010 (*Conselho Nacional de Justiça*, 2010) issued by the National Council of Justice, which advises courts to implement actions to support judges. These included the requirement of detailed medical reports to support decision-making, encouraging judicial workers to visit health units, and the establishment of interinstitutional agreements to provide health workers support in assessing the clinical issues presented by the claimants. In conjunction, the aim of these measures was to raise the courts' awareness about healthcare policies giving a broader perspective of the system in order to enable better decisions.

From the legislative branch, the Federal Law 12.401/2011 (Brasil, 2011a) clarifies the definition of the right to health in the Constitution stating that integral access to medicines in the public health system encompasses the provision of treatments according to the funded lists and the clinical protocols and therapeutic guidelines issued by the Ministry of Health. However, previous studies suggest that part of the lawsuits could be prevented if the regulations of the public health system were adhered to (Carvalho and Leite, 2014; Lopes et al., 2014; Catanheide et al., 2016; Freitas et al., 2020).

Despite the current pharmaceutical policy and the strategies implemented by the legislation, medicines litigation is still a challenging topic for the various actors involved (Carvalho and Leite, 2014; Biehl et al., 2019; Vargas-Pelaez et al., 2019). It is believed that through action research in which actors are involved cooperatively, it could contribute to the planning and implementation of strategies in the local context for a better approach to medicines litigation in a municipality located in southeastern Brazil.

METHODS

Design and Setting

This study used mixed methods with an action research design. This approach combines action and reflection, and it is recommended to identify deficiencies in the health services with a key aspect of allowing the emancipation of subjects, through their involvement in research and shared construction of knowledge (Thiollent, 2011).

The study site was a municipality in the southeastern region of Brazil, located in the state of Rio de Janeiro with a population of 230,000 inhabitants (IBGE, 2016). The health secretary and the pharmaceutical services (PS) department of the municipality, as well as many others in Brazil, faced a large number of litigation cases in health, especially related to medicines. To deal with this reality, these sectors contacted a local university to establish a university–community partnership to come up with strategies to improve this scenario.

The Network Coordination Team and the Research Plan

The network coordination team was composed of seven pharmacists: three researchers from the university and four municipal managers. The former with experience in public health and direct involvement in outreach projects, while the city managers have had hands-on experience working for at least 5 years in the PS department.

The network coordination team initiated the diagnosis (scenario analysis) by identifying the central problem, followed by a planning phase of the strategy to be implemented. Finally, the action research cycle involved the application of the developed strategy, its evaluation by health professionals, and reflection by the team.

Scenario Analysis

The identification of the central problem related to medicines litigation involved two main actions: an analysis of the organization of PS and the profile of litigated medicines in the municipality. To understand how PS was structured, the research group analyzed the municipality's electronic address to check the legal documents available and current actions developed by the PS sector. The identified actions were classified according to the categories presented by Yamauti et al. (2020).

To characterize the profile of medicines litigation, data were collected in the public pharmacy responsible for dispensing non-incorporated medicines to users of the municipal health system. All information collected were in accordance with the Brazilian Law of Access to Information (Law 12.527/2011) (Brasil, 2011b), which guarantees privacy of user identification. For this data

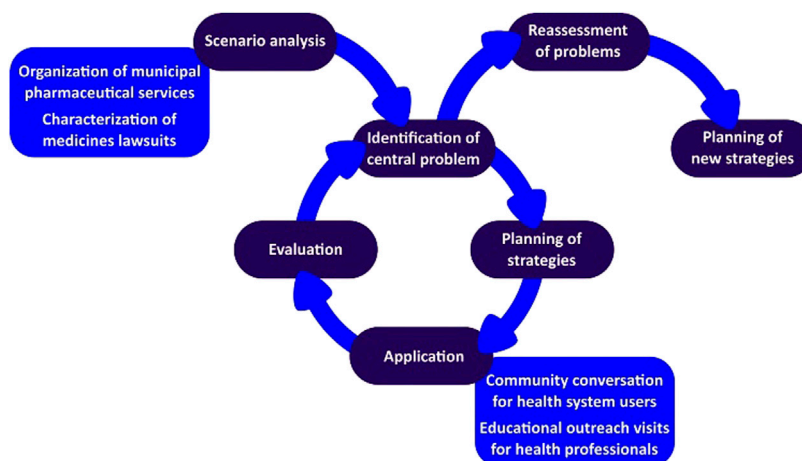


FIGURE 1 | Action research cycle.

collection, the eligibility criteria were: inclusion of all lawsuits against the public health system that were in force in March 2018 requiring at least one item registered as a medicine. In all lawsuits described, claimants were fully attended with all medicines litigated, even if they were not regularly funded in the public health system.

The following variables were collected: lawsuit register number, date of request, age of the patient, gender, prescriber(s) registration number, medical specialty(s), the type of service that provided the prescription, legal representation of the plaintiff, lawyer's registration number, presence of prescription and medical report in the lawsuit, medicine(s), dosage form, and clinical indication. Descriptive analysis of the data was performed by determining the absolute and relative frequencies (qualitative variables), means, medians, and standard deviation (quantitative variables).

The requested medicines were classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the presence in one of the official lists of medicines funded by the municipality's health system, namely, Brazilian National List of Essential Medicines (RENAME, in Portuguese), 2017 edition (Ministério da Saúde, 2017); medicines offered by the State Secretary of Health (Secretaria Estadual de Saúde do Rio de Janeiro, 2018); and the Municipal List of Essential Medicines (REMUME, in Portuguese) (Prefeitura Municipal de Macaé, 2017). Additionally, medicines not listed in Brazilian lists were compared to the Model List of Essential Medicines (MLEM) from the World Health Organization (World Health Organization, 2017).

In order to better understand the reasons for the prescription of non-incorporated medicines, therapeutic alternatives were evaluated according to their availability in at least one of the lists. This analysis was according to the Manual of Indicators of Evaluation and Monitoring of Medicines Lawsuits, which suggests considering medicines in the same pharmacological subgroup at the ATC system as an alternative (Pepe et al., 2011).

Planning Phase and Application of the Strategy

The planning phase was guided by the central problem identification related to medicines litigation, and possible gaps in the PS organization were listed for which hypotheses were proposed to help the development of an action plan. The defined action plan involved educational interventions, both for health professionals and users of the municipal public health system (Figure 1).

For health professionals, planned educational visits based on the principles of educational outreach, also known as academic detailing, and the development of printed educational materials were adopted. Academic detailing consists of educational encounters led by a trained facilitator held at the health unit aiming to stimulate behavioral changes, including the prescriptions practices (Kunstler et al., 2019). Undergraduate pharmacy students were recruited to carry out the visits, having received training promoted by the network coordination team. It should also be noted that students were always accompanied by graduated professionals. All health professionals who provided medical care at specialized centers responsible for medicine prescription to users identified as relevant to the central problem in question and who agreed to participate in the educational visit were considered eligible for this. Thus, for this activity, the sample was for convenience, from contact with 19 specialized health centers.

For the health system users, group conversations were held at Family Health Strategies (ESF, in Portuguese), which are Brazilian health units responsible for primary health care. The group conversations aimed to discuss PS organization in the SUS, especially how to access medicines in the public health system of the municipality. For the activity, a semi-structured script was proposed (Supplementary Appendix 1), and two students previously trained for this activity conducted it. One was the mediator, who facilitated the discussions, encouraging the free expression of ideas, and the other one the observer, who

registered doubts and opinions presented. Based on these notes, a report of the group conversation was prepared using a standardized document with fields to include date, location, team that was present in the activity, moderator, observer, number of participants, general characteristics (gender and age group), duration, and one field for detailed description of the activity. The sample of this activity was also for convenience, and all ESF in the city, 44 in total, were invited, in those which contact and acceptance were possible, the activity was carried out.

Evaluation

For the educational outreach visits, at the end of the visits, the professionals were invited to fill out an evaluation form, which included six questions addressing 1) clarity of the proposal's presentation, 2) duration of the visit, 3) appropriateness of the material, 4) clarification of doubts, 5) posture of the student, and 6) verbal expression. A 5-point Likert scale was used, ranging from very dissatisfied to very satisfied. The evaluation form also included three open questions that allowed the health professional to report suggestions or additional comments (**Supplementary Appendix 1**).

In regard to group conversations, each report produced by the observer was reviewed and, if necessary, complemented by the other team participants who were present at the conversation. Thematic analysis of these reports was led with an inductive approach (Braun and Clarke, 2006). The first author, who had participated in all group conversations, conducted coding and identification of themes. Then, the results were discussed and reviewed by the second author.

Ethical Aspects

This study is approved by the Research Ethics Committee of the Federal University of Rio de Janeiro—Campus Macaé (Protocol number: 4.187.153)—and respected the ethical protocols recommended in Resolution no 466/2012 (Brasil, 2012) of the National Health Council, which includes the Regulatory Guidelines for Research involving human beings.

RESULTS

Organization of Pharmaceutical Services

In Brazil, medicines funded by SUS are divided into three groups, called components, namely, basic, specialized, and strategic. The first encompasses medicines employed at primary health care, mainly acquired by the municipal government; the second includes high-cost medication, managed by each state government; and the strategic component, which comprises treatments for diseases with potential endemic impact and under federal responsibility (Ministério da Saúde, 2019).

According to the National Medicines Policy, RENAME is the main reference for medicines selection in the public system. Municipalities are responsible for electing medicines according to the epidemiology of diseases affecting their citizens, resulting in the REMUME. At the time of the research, the REMUME had been updated in 2017, including 211 medicines for primary health care (Prefeitura Municipal de Macaé, 2017), 80.6% of it

corresponded to products included in the national list. In addition, 77.2% of REMUME were listed on MLEM (World Health Organization, 2017).

PS also provided access to medicines from the strategic and specialized components. For the latter, the municipality had one public pharmacy dispensing high-cost treatments, managed by the state government (Secretaria Estadual de Saúde do Rio de Janeiro, 2019). Therefore, the structure of PS was organized to provide treatments consistent with the regulations of the public health system.

Not only did the municipal PS provide assistance for users claiming listed medicines but a special sector was also implemented to evaluate demands for non-incorporated products, called pharmaceutical support service. The sector was responsible for registering and evaluating requirements from administrative proceedings, in addition to attending cases of medicines lawsuits (compliance with court orders) (Prefeitura Municipal de Macaé, 2016). In regard to strategies to approach medicines litigation, it was observed that the PS department had implemented actions related to the organization of assistance, administrative proceedings, and compliance with court orders (Yamauti et al., 2020), as described in **Figure 2**.

Problems Related to Medicines Litigation

In spite of the local organization of PS available at the public health system, lawsuits continue to be employed as a strategy to access pharmacological treatments in the municipality. The study identified and analyzed 82 lawsuits requiring medicines, which were litigated from 2005 to 2018. The full description of demands can be found in **Supplementary Appendix 1**.

In relation to the legal representation, 81.8% ($n = 63$) of the lawsuits were from the public sector, represented by the municipal public defender's office and 18.2% were from private lawyers. Since the public defender's office represents citizens of low income or high social vulnerability, the main litigants in the present study were from the lower social class.

In addition, litigants were mainly assisted by the public health system. In regard to the type of the service, 82.9% ($n = 68$) of lawsuits included prescription from public health units, 11.0% ($n = 9$) from private health units, and 6.1% ($n = 5$) from both.

The endocrine, nutritional, and metabolic diseases (ICD-10: Chapter IV) were the most frequent conditions requesting treatments, with higher frequency for diabetes mellitus (21, 25.6%), followed by the disorders of other endocrine glands (4, 4.9%). The second and third most frequent conditions were the mental and behavioral disorders (10, 12.2%) and the diseases of the nervous system (8, 9.8%), respectively.

The characterization of medicines required in the lawsuits according to the ATC classification system can be found in **Supplementary Appendix 1**. The lawsuits demanded 227 medicines, ranging from one to 15 medicines/patient (mean 2.77, SD = 2.57 medicines/patient), corresponding to 132 substances and 150 dosage forms. Insulins and analogues represented 26.0% of the pharmaceutical products litigated. By the time of this investigation, these medicines were not incorporated in SUS. The first evaluation conducted by the

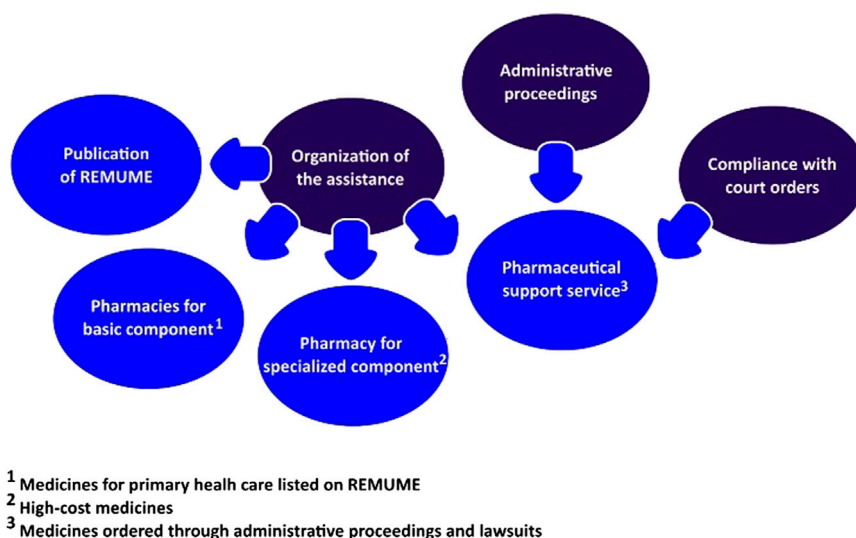


FIGURE 2 | Strategies implemented by the Municipal Secretary of Health to deal with medicines litigation.

Ministry of Health concluded that there was no robust evidence that they were more effective than human insulin for the control of diabetes (CONITEC, 2017). However, long and fast-acting insulins were included in the latest version of RENAME and will be supplied for the treatment of diabetes mellitus type 1 (Ministério da Saúde, 2019).

Medicines litigation demanded mainly products outside lists of funding in SUS. Only seven lawsuits (8.5%) demanded just incorporated medicines, prescribed in accordance with the clinical criteria established by the Clinical Protocols and Therapeutic Guidelines (national documents that regulate the access of high-cost medicines). Among all medicines claimed, 60.7% were not incorporated in RENAME. In regard to presence in the local lists, only 13.3% of medicines were supplied by the State Secretary of Health and 20% were listed on the REMUME.

The majority of lawsuits disregarded the existence of therapeutic alternatives in SUS. Among the 91 non-incorporated medicines, it was possible to identify therapeutic alternatives for 72 of them (85.7%), and only four (4.4%) were considered essential according to the WHO MLEM. For diabetes mellitus, metformin, glibenclamide, and gliclazide were listed at REMUME as blood glucose-lowering drugs (ATC A10A), while human insulin and NPH (ATC A10A) were the insulins available in SUS. In regard to nervous system agents, five lawsuits demanded three antipsychotics (ATC N05A: aripiprazole, levomepromazine, and paliperidone) with nine therapeutic alternatives (chlorpromazine chloride, haloperidol, haloperidol decanoate, lithium carbonate, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone). In addition, for the four antiepileptics (ATC N03A) litigated, 11 medicines were listed in RENAME (**Supplementary Appendix 1**). Nevertheless, based on the information available in most of the lawsuits, it was not possible to recognize if the listed medicines had been used previously by the litigant.

Defining the Central Problem

In this context, medicines litigation predominantly demanded medicines unavailable in the public health system. Therefore, the network coordination team elected as the central problem for the first cycle of this action research the prescription of non-incorporated medicines with therapeutic alternatives in the public health system.

Since medicines litigation is a complex phenomenon, secondary influencing factors were also listed and will be addressed in future stages of action research: 1) the appropriateness of medicines offered in SUS and 2) quality of PS offered at the municipality. These issues were not initially considered a priority for the following reasons: listed medicines were in accordance with the National Medicines Policy, and the results do not suggest that the majority of litigation had been a result of problems related to the management of PS, which could be observed if lawsuits claimed mainly incorporated products.

Planning and Application

Based on the central problem, the network coordination team proposed two hypotheses: 1) knowledge gap about medicines incorporated in SUS and 2) distrust in the available treatments. Since communication is a key issue on both hypotheses, strategies to improve access to information about the organization of PS, especially about incorporated medicines, were considered a priority. In order to strengthen primary health care, the network coordination team agreed to focus on wide dissemination of REMUME.

Educational visits to discuss about REMUME were led between August 2018 and December 2019 in 14 health units where 24 medical specialties offered care for SUS. In total, 23 physicians participated in the visits, in which 80 brochures and 70 posters were distributed for consultation of REMUME. Among the 23 visited health professionals, 11 filled in the evaluation form. Everyone declared that they were very satisfied with the

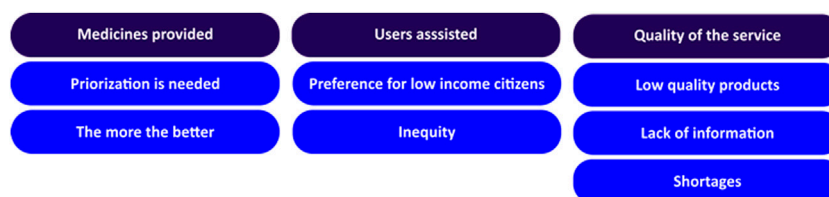


FIGURE 3 | Categories identified through thematic analysis of reports of group conversations.

printed materials, two suggested that the same approach should be employed to the medicines of the specialized component of PS, and two mentioned the relevance of the initiative for the population.

Group conversations with users of the public health system were conducted in 21 ESF. The discussions lasted from 20 to 60 min, varying from five to 23 participants, including 227 in total. In regard to participants' perception about PS in the public health system, thematic analysis of reports identified three main categories, including aspects related to medicines provided, users assisted, and quality of service (**Figure 3**).

It was observed that participants of group conversations had different perspectives about medicines supplied in the public health system. Some argued that all medicines should be available, while others recognized the need of a prioritization process.

"The SUS, yes, it should give the treatment, the medicines that people need, because there are many medicines that we don't have the money to buy."

"I don't think that (the government) would have a budget for everything, so they would have to focus on the specific ones."

Demand on the prescriptions and cost (higher priority for the most expensive) were two criteria mentioned independently by participants during discussions to determine the importance of a specific medicine.

"I think the government should give the most expensive medicines, because we can buy a dipyrone."

"It (the government) must supply the most used medicines that are prescribed by physicians"

Under the category of users assisted, participants claimed that low-income citizens should be preferably supported.

"They should analyze the person's financial situation to provide medicine."

"We must think of people who are unable to buy the medicines they need."

In spite of that, equity was an issue raised during discussions. It was mentioned that non-incorporated medicines were prescribed

only to people who could buy it because even if they were accessible by administrative proceedings or lawsuits, there is a risk of shortages in the public health system.

"Special medicines are only taken by people who are rich. For poor people, physicians only prescribe the cheap insulin"

In regard to quality of the service, a divergence in terms of satisfaction with PS in the municipality was also observed. While some declared that shortages were frequent, others affirmed that they had integral access to their treatments.

"Whenever I go to the pharmacy, I can never get my medicines."

"When (medicine) is lacking in one day, the supply is soonly restarted."

The lack of information also emerged during discussions, either of the specialized component and the "Programa Farmácia Popular" (in Portuguese). The latter was created by the Brazilian government to complement access to medicines through provision of free or cofinancing items in private pharmacies affiliated to the program.

"It was good, the Farmácia Popular I had already seen, but I didn't know I could get medicines for free."

"My husband uses atorvastatin and I buy it every month, I didn't know it was available on the public system."

In addition, participants were frequently unsure about the quality of medicines provided. Some of them believe that products supplied in the public health system have lower quality and even reported that some physicians recommended them to buy, instead of taking it in the public pharmacy. Similarly, generic medicines were also perceived as less effective than brand products.

"Some physicians ask us to buy, because the medicines given by SUS do not work."

"It is not possible to have this huge difference in price and have the same effect (generic medicines)."

DISCUSSION

The misconceptions about the right to health definition in the Brazilian Constitution result in judicial decisions that privilege individual claims, obligating managers to provide all medicines required (Wang, 2015). As a consequence, lawsuits can generate inequities since the distribution of resources will be related to the user's litigation capacity. Thus, the present study described the first cycle of an action research project to develop strategies to approach medicines litigation at the municipal level.

Essential medicines lists are worldwide used as a key strategy to enable universal health coverage; however, funded products may vary significantly between countries (Persaud et al., 2019). In Brazil, the incorporation of medicines in the public system has evolved with the creation of CONITEC (National Council for Incorporation of Technologies in the National Health System) in 2011. Since then, the number of medicines provided in the public health system has been increasing (Yamauti et al., 2017), yet this was not associated with a reduction in litigation (Chieffi et al., 2017; Oliveira et al., 2020).

It is claimed that despite the adequacy of the National Medicines Policy, the perception that needs to access medicines in Brazil are not being fulfilled leads to the increasing use of lawsuits to provide treatments (Catanheide et al., 2016). Nevertheless, it could be argued that there is a gap between legislation and services.

Federal Law 12.401/2011 (Brasil, 2011a) established that the provision of medicines in SUS must follow the official medicines lists and Clinical Protocols and Therapeutic Guidelines. Thus, the litigation of non-incorporated medicines described here corroborates with previous investigations reporting that judicial decisions are not based on the current regulation of PS in the public health system (Lopes et al., 2014; Lopes et al., 2019), and most of the lawsuits could be avoided if the essential medicines lists were followed (Catanheide et al., 2016). In addition, our study revealed that medicines claimed in lawsuits were not considered essentials according to the WHO MLEM. It is reported that the main litigated products had not been incorporated in SUS because of lack of efficacy or cost-effectiveness (Chieffi et al., 2017). For universal health coverage to be possible, public policies must be adequately implemented. Litigation may be justified in some cases but should not be a rule as it is observed in Brazil.

The reasons for lack of adherence to medicines lists are multifactorial. It is reported that the prescription of non-incorporated medicines can be attributed to ineffective distribution of the lists, inadequate sensitization, lack of enforcement mechanisms, and influence of the pharmaceutical industry (Ofori-Asenso et al., 2016; Campos Neto et al., 2017). In regard to RENAME, a previous study highlighted that efforts for dissemination of the list were never a priority in Brazil; consequently, noncompliance is not an unexpected result that could potentially impair the organization of PS (Osorio-de-Castro et al., 2018).

Surprisingly, while strategies involving training about PS are incipient (Gerlack et al., 2017), the advertisement of medicines is unregulated in SUS. Medicines information from industry freely circulates in the public health system. Only 24.2% of the

municipalities have norms to regulate visits from representatives of laboratories, and 32.8% regulates the distribution of free samples in health units (Costa et al., 2017). As a consequence, health professionals' view about PS may be distorted. A nationwide study evaluating physicians' awareness about essential medicines lists revealed they do not have adequate information and also perceive that the composition of the lists is not adequate for clinical demands (Magarinos-Torres et al., 2014).

In the present study, the implementation of educational visits was well accepted by health professionals, and it was even suggested that it should be expanded to include medicines provided by specialized component, reinforcing the importance of improving access to information about medicines provided in SUS.

In regard to users, the World Health Organization highlights the importance of civil society participation in planning and evaluation of health system services (De Savigny and Adam, 2009). In addition, based on a survey with actors from Latin America and Caribe, strategies that empower the society about the right to health were considered very important to approach medicines litigation (Pinzón-Flórez et al., 2016). For this purpose, educational strategies involving users of the public health system are needed to promote engagement and improve access to PS in SUS. This is especially relevant considering that in judiciary, health professional, and patient organizations' perceptions, medicine selection and clinical guidelines do not meet population needs (Magarinos-Torres et al., 2014; Vargas-Pelaez et al., 2019).

The activities developed on this study revealed interesting aspects related to users' views about medicines availability. Most participants tended to believe that the medical prescriptions should define the supply of medicines in the public health system, and a higher number of products would improve care in SUS. In contrast, there were also complaints about drug shortages, which may sound contradictory since increasing the number of medicines in REMUME will potentially make management of supply chain even more challenging.

This study is a partnership university-community which developed and implemented an innovative approach to address medicines litigation. Considering the context, how to plan and develop strategies to mitigate the threats imposed by lawsuits? The present characterization of litigation is similar to the previous studies conducted in Brazil (Oliveira et al., 2020), while others diverge, for example, by demanding mainly incorporated medicines (Freitas et al., 2020). The lack of a national database of lawsuits hinders a comprehensive overview of the phenomenon and, consequently, the generalization of the results. Nevertheless, the strategies described can guide future policies to approach litigation in different regions of the country.

One plausible explanation presented here is that prescribers demanded medicines outside the funded lists because they are not provided with adequate information about what is offered in the public system. Therefore, educational strategies are key to improve access to medicines. In spite of that, the use of educational visits for dissemination of medicine lists and strategies promoting dialogue with health system users about PS have not been reported previously.

Despite the acceptability of the strategies, equally from health workers' and users' perspectives, some barriers were identified. In

relation to prescribers, it was challenging to schedule educational visits with the health unity manager and adjusting with the number of consultations of each physician. In contrast, with group conversations, the lack of regular educational activities and an adequate place for discussions were the main difficulties faced.

The present study has some limitations. The lack of an electronic database with information related to medicines litigation imposed challenges to data collection. Additionally, most of the lawsuits did not describe properly the reasons for litigation. Thus, it was not possible to identify, for most of the lawsuits, if the litigant had already used listed medicines before demanding non-incorporated products. Furthermore, the strategies did not include actions addressed to the judiciary sector; thus, they are not comprehensive in terms of all actors involved in litigation.

In regard to the central problem, additional influencing factors were raised, but they were not tackled yet. Medicines lists should be submitted to a careful revision to confirm if they meet the needs of the population. Likewise, failures in PS should be assessed in future investigations. The impact of the educational visits on prescribing practices is under evaluation, and the results will be reported in a future study.

It is hoped that this study can open space for new types of actions and discussion for facing medicines litigation. It is not only necessary to understand the profile of lawsuits, but it is also essential to create actions to deal with them. The group understands that empowering the society to enable them to be part of the solution to the infinite needs in the health system is a fundamental part of this process.

The effectiveness of educational interventions with different actors involved in litigation is still an issue to be investigated to support managers to implement actions to deal with this phenomenon. In addition, future studies investigating the cost-effectiveness of educational interventions would advance the comprehension of how these strategies could lead to more rational use of financial resources.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

REFERENCES

- Ayres, F., Lopes, H., Yeung, L., Oliveira, V., Vasconcelos, N., Carlotti, D., et al. (2018). Judicialização da Saúde no Brasil: perfil das demandas, causas e propostas de solução. Available at: <https://www.cnj.jus.br/wp-content/uploads/conteudo/arquivo/2019/03/f74c66d46cfea933bf22005ca50ec915.pdf> (Accessed February 13, 2020).
- Biehl, J., Socal, M. P., Gauri, V., Diniz, D., Medeiros, M., Rondon, G., et al. (2019). Judicialization 2.0: understanding right-to-health litigation in real time. *Glob. Public Health* 14, 190–199. doi:10.1080/17441692.2018.1474483
- Brasil (2011a). “Lei no 12.401, de 28 de abril de 2011,” in *Altera a Lei no 8.080, de 19 de setembro de 1990, para dispor sobre a assistência terapêutica e a incorporação de tecnologia em saúde no âmbito do Sistema Único de Saúde – SUS* (Brasília, Brazil: Diário Oficial da União). Available at: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/lei/l12401.htm#:~:text=Altera%20a%20Lei%20n%C2%BA%208.080,Sistema%20C3%9Anico%20de%20Sa%C3%BAde%20%2D%20SUS.&&text=%E2%80%9CArt.&text=A%20assist%C3%AAncia%20terap%C3%AAutica%20integral%20a,do%20inciso%20I%20do%20art (Accessed February 13, 2020).
- Brasil (2011b). “Lei no 12.527, de 18 de novembro de 2011,” in *Regula o acesso a informações previsto no inciso XXXIII do art. 5º, no inciso II do § 3º do art. 37 e no § 2º do art. 216 da Constituição Federal; altera a Lei no 8.112, de 11 de dezembro de 1990; revoga a Lei no 11.111, de 5 de maio de 2005, e dispositivos da Lei no 8.159, de 8 de janeiro de 1991; e dá outras providências* (Brasília, Brazil: Diário Oficial da União). Available at: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/lei/l12527.htm (Accessed February 12, 2020).
- Brasil (2012). Resolução n 466, de 12 de dezembro de 2012. *Aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos*. Brasília, Brazil: Diário Oficial da União. Available at: https://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html (Accessed February 12, 2020).

ETHICS STATEMENT

The study was reviewed and approved by the Research Ethics Committee of the Federal University of Rio de Janeiro—Campus Macaé (Protocol number: 4.187.153). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FLSM, DMSSS, and LCC contributed to the design of the study and to the analysis of results. FLSM and DMSSS collected data and conducted planning and implementation of the strategies. All authors contributed to the manuscript and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.612426/full#supplementary-material>.

- Braun, V., and Clarke, V. (2006). Using thematic analysis in psychology. *Qual. Res. Psychol.* 3, 77–101. doi:10.1191/1478088706qp0630a
- Campos Neto, O. H., Gonçalves, L. A. O., and Andrade, E. I. G. (2017). A judicialização da Saúde na percepção de médicos prescritores. *Interface* 22, 165–176. doi:10.1590/1807-57622016.0314
- Carvalho, M. N. d., and Leite, S. N. (2014). Itinerário dos usuários de medicamentos via judicial no estado do Amazonas, Brasil. *Interface* 18, 737–748. doi:10.1590/1807-57622013.0930
- Catanheide, I. D., Lisboa, E. S., and Souza, L. E. P. F. d. (2016). Características da judicialização do acesso a medicamentos no Brasil: uma revisão sistemática. *Physis* 26, 1335–1356. doi:10.1590/s0103-73312016000400014
- Chieffi, A. L., Barradas, R. C. B., and Golbaum, M. (2017). Legal access to medications: a threat to Brazil's public health system? *BMC Health Serv. Res.* 17, 499. doi:10.1186/s12913-017-2430-x
- CONITEC (2017). Relatório de Recomendação nº 245. Insulinas análogas de ação rápida para Diabetes Mellitus Tipo 1. Available at: http://conitec.gov.br/images/Relatorios/2017/Relatorio_Insulinas_DiabetesTipo1_final.pdf (Accessed May 29, 2019).
- Conselho Nacional de Justiça (2010). “Recomendação no 31 de 30 de março de 2010,” in *Recomenda aos tribunais a adoção de medidas visando melhor subsidiar os magistrados e demais operadores do direito, para assegurar maior eficiência na solução de demandas judiciais envolvendo a assistência à saúde* (Brasília, Brazil: Diário da Justiça Eletrônico). Available at: <https://atos.cnj.jus.br/atos/detalhar/atos-normativos?documento=877#:~:text=Recomenda%20aos%20Tribunais%20a%20ado%20C3%A7%C3%A3o,envolvendo%20a%20assist%C3%Aancia%20C3%A0%20sa%C3%BAde> (Accessed February 12, 2020).
- Costa, E. A., Araújo, P. S., Pereira, M. T., Souto, A. C., Souza, G. S., Guerra, A. A., et al. (2017). Technical issues and conservation conditions of medicines in the primary health care of the Brazilian Unified Health System. *Rev. Saude Publica* 51, 12s. doi:10.11606/S1518-8787.2017051007106
- Cubillos, L., Escobar, M., Pavlovic, S., and Iunes, R. (2012). Universal health coverage and litigation in Latin America. *J. Health Organ. Manag.* 26, 390–406. doi:10.1108/14777261211239034
- De Savigny, D., and Adam, T. (2009). *Systems thinking for health systems strengthening*. Geneva, Switzerland: Alliance for Health Policy and Systems Research, World Health Organization.
- Freitas, B. C. d., Fonseca, E. P. d., and Queluz, D. d. P. (2020). A Judicialização da saúde nos sistemas público e privado de saúde: uma revisão sistemática. *Interface* 24, e190345. doi:10.1590/interface.190345
- Gerlack, L. F., Karnikowski, M. G. O., Areda, C. A., Galato, D., Oliveira, A. G., Álvares, J., et al. (2017). Management of pharmaceutical services in the Brazilian primary health care. *Rev. Saude Publica* 51, 15s. doi:10.11606/S1518-8787.2017051007063
- IBGE (2016). *Pesquisa nacional por amostra de domicílios: síntese de indicadores 2015*. Rio de Janeiro, Brazil: IBGE.
- Kunstler, B. E., Lennox, A., and Bragge, P. (2019). Changing prescribing behaviours with educational outreach: an overview of evidence and practice. *BMC Med. Educ.* 19, 311. doi:10.1186/s12909-019-1735-3
- Lopes, L. C., Silveira, M. S., Camargo, I. A., Barberato-Filho, S., Del Fiol, F. S., and Osorio-de-Castro, C. G. (2014). Biological drugs for the treatment of psoriasis in a public health system. *Rev. Saude Publica* 48, 651–661. doi:10.1590/S0034-8910.2014048005109
- Lopes, L. d. M. N., Coelho, T. L., Diniz, S. D., and Andrade, E. I. G. d. (2019). Integralidade e universalidade da assistência farmacêutica em tempos de judicialização da saúde. *Saude Soc.* 28, 124–131. doi:10.1590/s0104-12902019180642
- Magarinos-Torres, R., Esher, Â., Caetano, R., Pepe, V. L. E., and Osorio-de-Castro, C. G. S. (2014). Adesão às listas de medicamentos essenciais por médicos brasileiros em atuação no sistema único de saúde. *Rev. Bras. Educ. Med.* 38, 323–330. doi:10.1590/S0100-55022014000300006
- Ministério da Saúde (2017). *Relação nacional de Medicamentos Essenciais: RENAME 2017*. Brasília, Brazil: Ministério da Saúde.
- Ministério da Saúde (2019). *Relação nacional de Medicamentos essenciais: RENAME 2020*. Brasília, Brazil: Ministério da Saúde.
- Ofori-Asenso, R., Brhlikova, P., and Pollock, A. M. (2016). Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995–2015). *BMC Public Health* 16, 724. doi:10.1186/s12889-016-3428-8
- Oliveira, Y. M. da C., Braga, B. S. F., Farias, A. D., Pereira, S. P. D., and Ferreira, M. A. F. (2020). Judicialization of medicines: effectiveness of rights or break in public policies? *Rev. Salud Pública* 54, 130. doi:10.11606/s1518-8787.2020054002301
- Osorio-de-Castro, C. G. S., Azeredo, T. B., Pepe, V. L. E., Lopes, L. C., Yamauti, S., Godman, B., et al. (2018). Policy change and the national essential medicines list development process in Brazil between 2000 and 2014: has the essential medicine concept been abandoned? *Basic Clin. Pharmacol. Toxicol.* 122, 402–412. doi:10.1111/bcpt.12932
- Persaud, N., Jiang, M., Shaikh, R., Bali, A., Oronsaye, E., Woods, H., et al. (2019). Comparison of essential medicines lists in 137 countries. *Bull. World Health Organ.* 97, 394–404C. doi:10.2471/BLT.18.222448
- Pinzón-Flórez, C. E., Chapman, E., Cubillos, L., and Reveiz, L. (2016). Prioritization of strategies to approach the judicialization of health in Latin America and the Caribbean. *Rev. Saude Publica* 50, 56. doi:10.1590/S1518-8787.2016050005728
- Prefeitura Municipal de Macaé (2017). Portaria SMS no 01/2017. Institui a Relação Municipal de Medicamentos (Remune Macaé 2017). Available at: http://www.macaerj.gov.br/midia/uploads/REMUME%20MACAE%202017%20publica%C3%A7%C3%A3o%202003_2017%20Portaria%20SMS%2001_2017.pdf (Accessed March 11, 2020).
- Prefeitura Municipal de Macaé (2016). Medicamentos são distribuídos em 13 farmácias populares. Available at: <http://www.macaerj.gov.br/saude/leitura/noticia/medicamentos-sao-distribuidos-em-13-farmacias-populares> (Accessed March 11, 2020).
- Secretaria Estadual de Saúde do Rio de Janeiro (2018). Lista de Medicamentos. Available at: <https://www.saude.rj.gov.br/medicamentos/lista-de-medicamentos> (Accessed June 24, 2018).
- Secretaria Estadual de Saúde do Rio de Janeiro (2019). Resolução SES nº 1939/2019. Estabelece incentivo financeiro para estruturação dos pólos municipais do componente especializado da Assistência Farmacêutica no estado do Rio de Janeiro. Available at: <https://brasilus.com.br/wp-content/uploads/2019/11/res1939.pdf> (Accessed March 11, 2020).
- Thiollent, M. (2011). *Metodologia da pesquisa-ação*. São Paulo, Brazil: Cortez Publishing House.
- Vargas-Pelaez, C. M., Rover, M. R. M., Soares, L., Blatt, C. R., Mantel-Teeuwisse, A. K., Rossi, F. A., et al. (2019). Judicialization of access to medicines in four Latin American countries: a comparative qualitative analysis. *Int. J. Equity Health* 18, 68. doi:10.1186/s12939-019-0960-z
- Pepe, V. L. E., Ventura, M., and Osório-de-Castro, C. (2011). *Manual de indicadores de avaliação e monitoramento das demandas judiciais de medicamentos*. Rio de Janeiro, Brazil: Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública Sérgio Arouca.
- Wang, D. W. L. (2015). Right to health litigation in Brazil: the problem and the institutional responses: figure 1. *Hum. Rights L. Rev.* 15, ngv025. doi:10.1093/hrlr/ngv025
- World Health Organization (2017). *WHO model list of essential medicines*. Geneva, Switzerland: WHO.
- Yamauti, S. M., Barreto, J. O. M., Barberato-Filho, S., and Lopes, L. C. (2020). Strategies implemented by public institutions to approach the judicialization of health care in Brazil: a systematic scoping review. *Front. Pharmacol.* 11, 1128. doi:10.3389/fphar.2020.01128
- Yamauti, S. M., Bonfim, J. R. d. A., Barberato-Filho, S., and Lopes, L. C. (2017). Essencialidade e racionalidade da relação nacional de medicamentos essenciais do Brasil. *Ciênc. Saúde Coletiva* 22, 975–986. doi:10.1590/1413-81232017223.07742016

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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From Precision Metapharmacology to Patient Empowerment: Delivery of Self-Care Practices for Epilepsy, Pain, Depression and Cancer Using Digital Health Technologies

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To improve long-term outcomes of therapies for chronic diseases, health promotion and lifestyle modifications are the most promising and sustainable strategies. In addition, advances in digital technologies provide new opportunities to address limitations of drug-based treatments, such as medication non-adherence, adverse effects, toxicity, drug resistance, drug shortages, affordability, and accessibility. Pharmaceutical drugs and biologics can be combined with digital health technologies, including mobile medical apps (digital therapeutics), which offer additional clinical benefits and cost-effectiveness. Promises of drug+digital combination therapies are recognized by pharmaceutical and digital health companies, opening opportunities for integrating pharmacotherapies with non-pharmacological interventions (metapharmacology). Herein we present unique features of digital health technologies which can deliver personalized self-care modalities such as breathing exercises, mindfulness meditation, yoga, physical activity, adequate sleep, listening to preferred music, forgiveness and gratitude. Clinical studies reveal how aforementioned complimentary practices may support treatments of epilepsy, chronic pain, depression, cancer, and other chronic diseases. This article also describes how digital therapies delivering “medicinal” self-care and other non-pharmacological interventions can also be personalized by accounting for: 1) genetic risks for comorbidities, 2) adverse childhood experiences, 3) increased risks for viral infections such as seasonal influenza, or COVID-19, and 4) just-in-time stressful and traumatic circumstances. Development and implementation of personalized pharmacological-behavioral combination therapies (precision metapharmacology) require aligning priorities of key stakeholders including patients, research communities, healthcare industry, regulatory and funding agencies. In conclusion, digital technologies enable integration of pharmacotherapies with self-care, lifestyle interventions and patient

Abbreviations: ACE, adverse childhood experiences; CBT, cognitive behavioral therapy; HPA, the hypothalamic-pituitary-axis; HRQoL, health-related quality of life; MDD, major depressive disorder; PWE, people with epilepsy; RCT, randomized controlled trial; SaMD, software as a medical device.

empowerment, while concurrently advancing patient-centered care, integrative medicine and digital health ecosystems.

Keywords: mHealth, prescription medications, telemedicine, machine learning, pharmacy care, internet, self-management, software as a medical device

DIGITAL HEALTH TECHNOLOGIES AND PHARMACOTHERAPIES

Despite a significant progress in developing new therapies, there is a growing number of people in the world living with chronic diseases (Disease, 2018). At the same time, emergence of digital health technologies has coincided with growing number of studies illustrating limitations of pharmaceutical drugs and biologics for treating chronic medical conditions (Monnat, 2018; Sverdlov et al., 2018). Challenges of pharmacotherapies for chronic diseases include: 1) medication non-adherence which affects 30–50% of people living with chronic medical conditions (Brown and Bussell, 2011), 2) treatment-resistant populations of people living with epilepsy, chronic pain, depression, and cancer (Kwan et al., 2011; Borsook et al., 2018; Pandarakalam, 2018; Assaraf et al., 2019), 3) adverse effects, tolerability, toxicity, mortality (Monnat, 2018), and 4) affordability, accessibility, and shortages of medications (Kesselheim et al., 2016). All aforementioned problems contribute to decreasing therapy outcomes while increasing healthcare costs.

Digital health technologies (also known as mobile health, or mHealth) use software to deliver diverse clinical functionalities including non-pharmacological interventions for chronic diseases (Rowland et al., 2020). Digital therapeutics are mobile medical apps which intend to treat specific medical conditions and have received regulatory clearance or approval (software as medical device, SaMD) (Patel and Butte, 2020; Shuren et al., 2018; Sverdlov et al., 2018). An increasing number of studies show clinical benefits of mobile and web-based apps, or therapeutic video games, in people with diabetes, substance use, depression, anxiety, schizophrenia and bipolar disorder, chronic pain, epilepsy, cardiovascular diseases, and cancer (Sverdlov et al., 2018; Chung, 2019; Sin et al., 2020). Clinical benefits and cost-effectiveness of digital interventions favor their implementation into health care (Jiang et al., 2019; Nordyke et al., 2019; Dang et al., 2020; Richards et al., 2020).

Digital therapeutics are currently prescribed by health care providers. Marketed digital therapeutics are approved or cleared as SaMD (510k or *de novo* pathways) by the United States Food and Drug Administration (FDA) Center for Devices and Radiological Health. Based on results from pivotal clinical studies (Patel and Butte, 2020). The FDA established the Software Precertification program allowing selected software companies to market lower-risk mobile apps without a regulatory review, or for higher-risk mobile medical apps after abbreviated review process (Alon et al., 2020). In addition, the FDA established Digital Health Center of Excellence, thus further emphasizing growing commitments of regulatory agencies, industry and R&D communities to support advancements in digital health technologies.

Sverdlov and colleagues described a rationale for developing combinations of digital therapeutics and pharmaceutical drugs (Sverdlov et al., 2018). Such drug+digital combinations would exhibit improved efficacy as compared to drug-alone or software-alone interventions. For example, developing drug-device combination products containing digital therapeutics offers promise for people with intractable epilepsy (Afra et al., 2018; Bulaj, 2014). The adjunct digital therapy, reSET®, has been approved in combination with buprenorphine for opioid use disorder (Patel and Butte, 2020). Mobile apps and serious video games can improve medication adherence further supporting benefits of integrating digital technologies with pharmacotherapies (Pouls et al., 2021). Pharmaceutical and biotech industries have recognized opportunities to innovate and improve treatments for chronic diseases, as illustrated by examples of collaborative partnerships between pharma and digital health companies [see **Supplementary Table S1** and the recent commentary (Patel and Butte, 2020)].

Precision metapharmacology can be defined as intervention comprising pharmacological and non-pharmacological treatments, in which non-pharmacological components are tailored for individual patients (**Figure 1**). It is apparent that digital health technologies are empowered to deliver personalized non-pharmacological interventions, while drug+digital combination therapies can be developed using a regulatory pathway of drug-device combination products (in this case a mobile medical app is a medical device, or SaMD) (Afra et al., 2018; Bulaj, 2014). As discussed below, precision metapharmacology has an ability to deliver patient-centered care by integrating pharmacological treatments with behavioral interventions including personalized self-care practices.

SELF-CARE PRACTICES COMPATIBLE WITH DIGITAL HEALTH TECHNOLOGIES

According to the World Health Organization, self-care is “the ability of individuals, families and communities to promote health, prevent disease, maintain health, and to cope with illness with or without the support of a healthcare provider” (who.int). The concept of self-care comprises self-management (the ability to manage symptoms, treatments and lifestyle changes) and self-efficacy (the level of confidence in one’s ability to practice self-care) (Richard and Shea, 2011). Promoting self-care and lifestyle interventions are particularly applicable to chronic medical conditions (Coulter et al., 2015; Riegel et al., 2017). **Table 1** illustrates examples of clinical and physiological effects of self-care practices such as physical exercise, yoga, breathing exercises, mindfulness meditation, music, sleep, gratitude, and forgiveness. Noteworthy, these

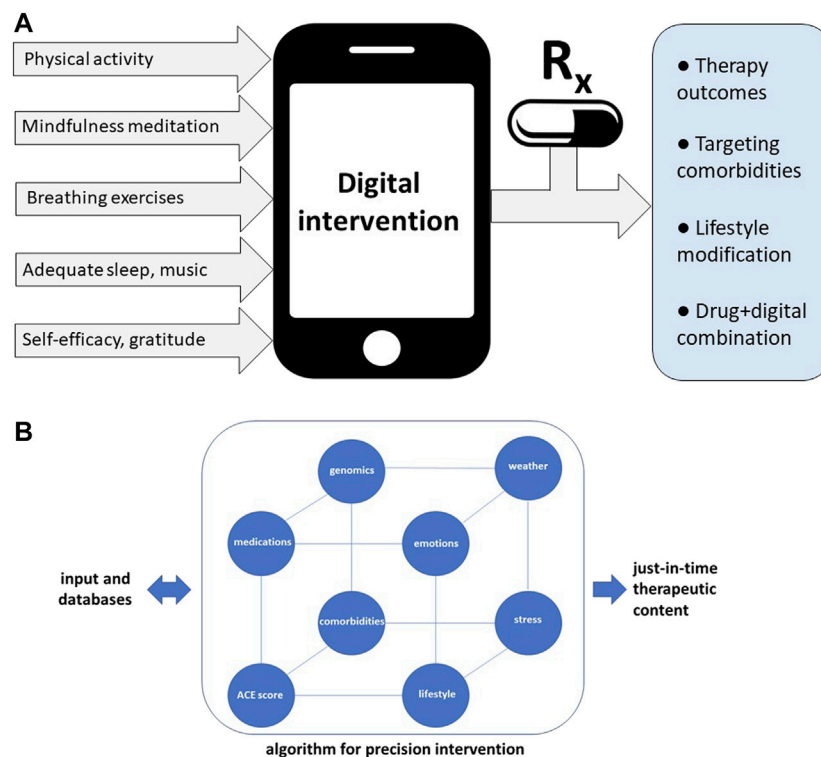


FIGURE 1 | Precision metapharmacology integrates pharmacotherapies with personalized, non-pharmacological interventions for chronic medical conditions including neurological, cardiovascular, metabolic, neurodegenerative, pulmonary, infectious diseases, mental disorders, and cancer. **(A)** Examples of diverse self-care practices delivered by digital health technologies aiming to improve therapy outcomes and lifestyle modifications. Such digital interventions can be offered via digital health ecosystems (Shegog et al., 2020), or combined with pharmacotherapies (drug+digital combination therapies) (Sverdlov et al., 2018). Integration of digital therapeutics (mobile medical apps) with prescription medications is enabled using the regulatory pathway for drug-device combination products (in this case medical device is a mobile medical app, “software as medical device”) (Bulaj, 2014). Expected outcomes of precision metapharmacology also include patient empowerment. **(B)** Examples of diverse factors included in algorithms optimizing delivery of just-in-time digital therapy content. For patients with higher adverse childhood experiences (ACE) scores or genetic risks for comorbidities, digital intervention can include cognitive behavioral therapy (CBT) combined with self-care practices which can mitigate risks for depression or anxiety. Optimization of digital content may include traumatic circumstances related to personal life, emotional state, or extreme atmospheric conditions.

complimentary practices are also considered safe, non-invasive and without serious adverse effects.

Non-pharmacological interventions and self-care practices exert clinical benefits and physiological effects via diverse mechanisms of action. As illustrated in **Table 1**, self-care can modulate the central nervous system and the peripheral nervous system activities. Improving the parasympathetic tone can lead to such clinical outcomes as reduction of inflammation (Bonaz et al., 2018) and epileptic seizures (Sesso and Sicca, 2020; Yuen and Sander, 2017). Interestingly, pleiotropic physiological effects of self-care practices also impact cardiovascular and the immune system functions, further benefitting people who incorporate such “medicinal” self-care practices.

As illustrated in **Figure 1A**, non-pharmacological interventions for chronic medical conditions can be delivered via mobile and web-based apps (Whitehead and Seaton, 2016). Currently, cognitive behavioral therapy (CBT) is a commonly used “active ingredient” in digital therapeutics. Digital health technologies have been shown to deliver diverse modalities including physical exercise, yoga, breathing exercises,

mindfulness meditation, music, nutrition, sleep, social support, and gratitude (examples of mobile and web-based apps delivering these modalities are listed in **Supplementary Table S2**). Notably, digital delivery of such non-pharmacological interventions has already shown clinical benefits for chronic pain (Shebib et al., 2019), depression and anxiety (Pine et al., 2020), cancer (Kim et al., 2018) and epilepsy (Si et al., 2020). Research on mobile and web-based apps support delivery of self-care people with chronic conditions (**Supplementary Table S2**).

PRECISION DIGITAL INTERVENTIONS FOR EPILEPSY, PAIN, DEPRESSION AND CANCER

Precision digital therapies can be defined as software-delivered interventions tailored to individual patient preferences while adjusting the content based on preexisting conditions, adverse experiences and just-in-time circumstances. Noteworthy, software is compatible with just-in-time adaptive

TABLE 1 | Examples of clinically-beneficial self-care modalities and their physiological effects.

Non-pharmacological modality	Examples of clinical benefits	Physiological effects and potential mechanisms of action
Breathing exercises	● Reduction of depressive symptoms in MDD Sharma et al. (2017) ● Improvement of lifespan and HRQoL in people with lung cancer Wu et al. (2017); Liu et al. (2013) ● Reduction of chronic low back pain Anderson and Bliven, (2017) ● Reduction of epileptic seizures Haut et al. (2018) ● Reduction of blood pressure Brandani et al. (2017)	● Modulation of parasympathetic nervous system and cardiac autonomic control Toschi-Dias et al., (2017); Pramanik et al. (2009) ● Increased neuronal oscillations in the brain Bhaskar et al. (2020) ● Reduction of pro-inflammatory cytokines and modulation of immune functions Zope and Zope, (2013); Twai et al. (2016)
Mindfulness/meditation	● Improvements of anxiety, depression and pain Goyal et al. (2014) ● Decrease in pain Hilton et al., (2017); Zeidan and Vago, (2016) ● Improvements in depression and anxiety, seizure frequency and HRQoL in PWE Wood et al. (2017); Tang et al. (2015) ● Improved self-regulation Vago and Silbersweig (2012) ● Improved sleep quality Guerra et al. (2020)	● Activation of anterior cingulate cortex and other brain structures involved in self-regulation of emotions and attention Tang et al. (2015) ● Reduced systolic blood pressure, CRP, TNFα Pascoe et al. (2017)
Physical activity	● Improved cognitive functions Cai et al., (2017) ● Reduction of cancer-related fatigue Jiang et al. (2020) ● Reduction of depressive symptoms Gujral et al. (2017) ● Pain relief in chronic low back pain Chou et al. (2017)	● Modulation of the HPA and autonomous Zschucke et al. (2015); Joyner and Green (2009) ● Modulation of cytokines and immune functions Nieman and Wentz (2019) ● Increase in brain-derived neurotrophic factor (BDNF) Dinoff et al., (2017)
Yoga practice	● Reduction of depressive symptoms Brinsley et al. (2020) ● Improvements in HRQoL, fatigue, immunity markers, and other physical and psychological symptoms in cancer care Agarwal and Maroko-Afek (2018); Danhauer et al. (2019) ● Reduction in pain intensity for low back pain Chou et al. (2017); Nahin et al. (2016) ● Improved HRQoL and reduction of epileptic seizures Panebianco et al. (2017) ● Reduction of migraine headaches Kumar et al. (2020)	● Modulation of the sympathetic nervous system and the HPA axis, reduction of cortisol, fasting blood glucose and cholesterol Pascoe et al. (2017) ● Improvement of cardiovascular biomarkers Mohammad et al. (2019) ● Decrease of pro-inflammatory markers IL-1β, IL-6 and TNFα Falkenberg et al. (2018)
Listening to music	● Reduction of depression levels Leubner and Hinterberger (2017); Tang et al. (2020) ● Lowering BP, decrease of anxiety and depressive symptoms in breast cancer patients Wang et al., (2018) ● Reduction of cancer-related fatigue Qiu et al. (2017) ● Reduction of pain Garza-Villarreal et al. (2017); Lee (2016) ● Reduction of epileptic seizures Yuen and Sander (2017); Rafiee et al. (2020)	● Modulation of parasympathetic nervous system Mojtavavi et al. (2020) ● Modulation of the immune system Chanda and Levitin (2013) ● Modulation of dopaminergic system Salimpoor et al. (2011) ● Modulation of opioid receptors Mallik et al. (2017)
Adequate sleep	● Reduced anxiety Pires et al. (2016) ● Improved all-cause mortality and cardiovascular events Yin et al. (2017) ● Improved memory, cognitive functions and emotional regulation Walker (2009)	● Improves inflammatory homeostasis and immune functions Irwin, (2019); Besedovsky et al. (2019) ● Modulation of the HPA axis and the sympathetic nervous system Irwin, (2019) ● Modulation of synaptic plasticity Raven et al. (2018)
Forgiveness	● Lower level of pain Carson et al. (2005) ● Lower levels of anxiety and depression Friedberg et al. (2009) ● Lowering blood pressure Lawler et al. (2003)	● Activation of lateral prefrontal cortex and other specific brain structures Fourie et al. (2020) ● Modulation of the autonomic nervous system, heart rate and blood pressure Witvliet et al. (2001)
Gratitude	● Improved mental health including symptoms of depression and anxiety Heckendorf et al. (2019); Wong et al. (2018) ● Improved cognitive performance Balconi et al. (2019) ● Improved sleep quality Boggiss et al. (2020)	● Activation of dorsolateral prefrontal cortex Balconi et al. (2019) ● Modulation of cardiovascular stress reactivity Ginty et al., (2020)

interventions (JITAI) enabling changes of the therapy content in response to real-life circumstances (Nahum-Shani et al., 2018; Wang and Miller, 2019). Just-in-time adjustments can address such factors as stressful and traumatic situations, atmospheric conditions, or public health emergencies. **Figure 1B** illustrates diversity of factors which can be incorporated in optimizing digital content for patient-centered care. Developing algorithms which can optimize digital interventions is an exciting new frontier in medicine (Triantafyllidis and Tsanas, 2019).

Adverse childhood experiences (ACE) are associated with compromised health outcomes (Bellis et al., 2019), including mental health (Kim et al., 2019) and stress response dysregulation (Jiang et al., 2019). People with ACE scores 4, or higher, are at increased risks for comorbid conditions including depression, obesity, and cardiovascular diseases (Campbell et al., 2016). ACE scores might also be associated with compromised medication non-adherence and therapy outcomes (Derefinko et al., 2019; Korhonen et al., 2015). Another subset of factors which can affect therapy outcomes comprises atmospheric conditions (air pollution, wildfires, floods, extreme weather like high temperatures) (Stewart et al., 2017), and unpredictable circumstances, such as the COVID-19 pandemic. Aforementioned factors can lead to chronic-stress and inflammation thus further affecting mental and physical health. Clinical applications of genomics enable identification of genetic risks for depression (Wray et al., 2018), metabolic syndrome and cardiovascular complications (Kraja et al., 2014; Warren et al., 2017). Thus, digital content can account for genetic and epigenetic susceptibilities to comorbidities when optimizing non-pharmacological interventions.

Table 1 and **Supplementary Table S3** illustrate how clinical and physiological effects of breathing exercises, mindfulness meditation, physical activity, yoga, music, sleep, forgiveness, and gratitude practice can directly benefit people living epilepsy, pain, depression, and cancer. It is important to emphasize that clinical evidence for efficacy and effectiveness of these non-pharmacological modalities vary, further emphasizing needs for large-scale RCTs. Despite knowledge gaps, we describe examples of self-care modalities which could be offered via digital interventions for specific indications. As emphasized in **Supplementary Table S3**, most modalities are directly applicable as adjunct therapies for epilepsy, pain, depression and cancer, while forgiveness intervention may additionally benefit patients with depression or comorbid depression. Currently, content of mobile apps for people with epilepsy, pain, depression, and cancer is designed for specific indications [e.g., self-management for epilepsy (Si et al., 2020), CBT for depression (Mantani et al., 2017), mindfulness meditation, self-management, physical exercise, education for cancer (Jongierius et al., 2019), a combination of physical therapy, CBT and education for chronic low back pain (Shebib et al., 2019)]. Creating disease-specific digital health ecosystems (Shegog et al., 2020) could expand a repertoire of available self-care modalities for each indication, further supporting more personalized digital interventions.

Epilepsy

Delivery of non-pharmacological interventions and self-care as adjunct digital therapy for people with epilepsy (PWE) was

recently described (Afra et al., 2018; Shegog et al., 2020). “Active ingredients” included listening to specific music compositions which were shown to reduce epileptic seizures (Sesso and Sicca, 2020), and additional self-management practices such as adequate sleep, avoidance of seizure triggers and stress management (Afra et al., 2018). The most recent meta-analysis (Sesso and Sicca, 2020) and RCT (Rafiee et al., 2020) of music-based interventions for reduction of epileptic seizures support this “active ingredient” in digital therapeutics. As further illustrated in **Table 1** and **Supplementary Table S3**, personalized digital therapies for PWE can also include breathing exercises and engagement in physical activities (Häfele et al., 2017; Haut et al., 2018; Vancampfort et al., 2019). Such modalities could be delivered using digital ecosystems, as described for epilepsy self-management (Shegog et al., 2013; Shegog et al., 2020). Since PWE can experience depression or anxiety as comorbidities, additional self-care features could include yoga, mindfulness meditation, or gratitude journaling. The recent RCT on using a mobile app for epilepsy self-management showed reduction of seizures (Si et al., 2020). Opportunities to combine self-care with antiseizure medications to improve seizure control in people with epilepsy were previously discussed (Bulaj, 2014; Bulaj et al., 2016).

Pain

Pharmacologic treatment of chronic pain often provides inadequate relief and causes unwanted adverse effects; therefore, many individuals turn to non-pharmacological interventions. Literature supports the use of diverse self-care practices for chronic pain management since many interventions have been found to be safe, effective and offer the potential to decrease medication use (Nahin et al., 2016; Tick et al., 2018). For example, precision digital therapies for chronic pain can include a personalized combination of several modalities, such as physical exercises, yoga, meditation mindfulness, music and other non-pharmacological modalities. As shown in **Supplementary Table S3**, a patient with chronic pain and comorbid depression can further benefit from forgiveness and gratitude interventions. Noteworthy, a meta-analysis investigated the effects of music on pain and found that musical interventions resulted in statistically significant reductions in opioid and non-opioid intake (Lee, 2016). Positive results from testing mobile apps delivering physical therapies and mindfulness training to treat chronic back pain (Shebib et al., 2019; Huber et al., 2017; Priebe et al., 2020) support development of such precision digital technologies for pain indications.

Depression

Depression is considered an underdiagnosed and undertreated condition, treated predominantly with antidepressants and CBT. Despite established efficacy, many patients continue to experience symptoms with these treatment modalities (Cleare et al., 2015). As a result, self-care practices are increasingly being used as adjunctive treatments (Villaggi et al., 2015; van Grieken et al., 2018; Saeed et al., 2019). Digital health technologies have recently emerged as clinically effective methods to deliver self-care interventions to reduce depressive symptoms (Mantani et al., 2017; Moberg et al., 2019; Richards et al., 2020). Precision digital

interventions for depression can combine CBT with additional self-care modalities such as breathing exercises (Sharma et al., 2016), listening to music (Schriewer and Bulaj, 2016; Leubner and Hinterberger, 2017), engaging in physical activities (Kvam et al., 2016), forgiveness and gratitude (**Supplementary Table S3**). A unique opportunity of digital interventions is their capability to adjust digital content and dosing based on ACE scores, as well as unexpected stressors and adversities (**Figure 1B**). For people with depression who also have higher ACE scores, algorithms can increase a daily dose of recommended physical exercise or specific type of music to enhance modulation of affective states (Fernandez-Sotos et al., 2016). Optimizing digital content can further benefit from integration of daily emotional states and weather forecast, suggesting activities adjusted for just-in-time and real-life circumstances (**Figure 1B**). For example, based on unfavorable weather for outdoor physical activities, precision digital intervention may instead engage a patient with indoor activities, such as breathing exercises, listening to music and gratitude journaling (**Table 1**).

Cancer

Integrative cancer care during and after chemotherapy and surgeries includes support for mental and physical health. Diverse non-pharmacological modalities can not only improve fatigue, sleep and HRQoL, but can also strengthen the immune system (**Table 1**). Digital health technologies for people with cancer include mobile apps for pain relief (Yang et al., 2019), self-management (Fjell et al., 2020; Kim et al., 2018), or videogames designed to promote physical exercise and mental empowerment in pediatric oncology patients (Bruggers et al., 2018; Govender et al., 2015). Personalized digital interventions for oncology patients can provide diverse self-care modalities such as physical exercises, yoga, mindfulness meditations, and breathing exercises (**Supplementary Table S3**). Since some of these modalities can improve immune system functions [e.g., listening to music or 30-min walking can increase activities of natural killer (NK) cells and lymphocytes (Chanda and Levitin, 2013; Fancourt et al., 2014; Pauwels et al., 2014; Nieman and Wentz, 2019)], such self-care practices can further support anticancer therapies. Potential benefits of these interventions also include reduced symptom distress, decreased unplanned hospitalizations, and improved medication adherence, quality of life and survival (Aapro et al., 2020).

The Immune System

As highlighted by the COVID-19 coronavirus pandemic, all chronically-ill patients could benefit from improved innate and adaptive immune responses to viral infections. It is timely to emphasize that several self-care modalities, such as adequate sleep, moderate-intensity exercises, breathing exercises and listening music can modulate the immune functions (**Table 1** and **Supplementary Table S3**). For example, sleep has been linked to susceptibility to viral and bacterial infections and responses to vaccinations (Irwin, 2015; Irwin, 2019). When combined with nutritional interventions (Iddir et al., 2020), such self-care practices have a potential for mitigating viral infections (e.g., seasonal influenza) while also improving immune responses to vaccinations.

Given shortcomings of medication therapies for management of chronic diseases, it is becoming apparent that adjunctive treatment modalities are needed to help patients achieve optimal care outcomes and that care needs to be individualized to account for patient-specific factors and conditions. Precision digital interventions can be adjusted for stressful or traumatic events (personal and family accidents, wildfires) which could trigger additional anxiety and/or depression (Graham et al., 2019). Since atmospheric conditions can impact people with epilepsy (Xu et al., 2016; Brás et al., 2018; Chang et al., 2019), cardiovascular diseases (Stewart et al., 2017), arthritis (Savage et al., 2015), or seasonal affective disorders (Wirz-Justice, 2018), digital therapy can include algorithms which take into account weather forecast. These examples illustrate a unique potential of digital health technologies to optimize interventions based on predictability of seasonal factors and weather forecast. This article specifically highlights the benefits of precision, digital self-care interventions; however, it should be noted that many other digital technology tools exist that provide disease education, symptom tracking, remote provider management, monitoring digital biomarkers, and more.

PRECISION METAPHARMACOLOGY: OPPORTUNITIES AND LIMITATIONS

Pharmaceutical industry recognizes opportunities to integrate pharmacotherapies with digital health technologies (Hird et al., 2016; Sverdlov et al., 2018) (see also **Supplementary Table S1**). Precision metapharmacology offers benefits for both patients and the health care systems. This concept is supported by recent developments including: 1) emerging reports on cost-effectiveness and clinical benefits of precision digital care (Jiang et al., 2019; Richards et al., 2020), 2) creating mobile apps for personalized self-management interventions through machine learning algorithms, e.g., (Mork et al., 2018; Sandal et al., 2019; Triantafyllidis and Tsanas, 2019; Miura et al., 2020; Sandal et al., 2020), 3) provider health systems starting to invest in digital health technologies (Safavi et al., 2020), 4) increasing number of studies reporting clinical benefits of “medicinal” self-care practices (**Table 1**), 5) increasing awareness about limitations of pharmacotherapies for chronic diseases such as medication non-adherence and tolerability/toxicity, and 6) regulatory approvals of mobile medical apps and advances to create drug+digital combination therapies (Bulaj, 2014; Afra et al., 2018; Sverdlov et al., 2018; Patel and Butte, 2020). Development of quantum computing (Arute et al., 2019) may facilitate applications of deep learning algorithms to optimize digital content using big data, internet-of-things (IoT) and biofeedback analyses coupled to just-in-time circumstances (such as atmospheric conditions) (Cianconi et al., 2020; Morganstein and Ursano, 2020).

While apparent opportunities for integrating digital health technologies with pharmacotherapies include improving therapy outcomes (Armitage et al., 2020) and medication adherence (via medication reminders) (Perez-Jover et al., 2019; Pouls et al., 2021), two underappreciated aspects are: 1) patient empowerment and engagement in the therapy (Bruggers et al.,

2012; Risling et al., 2017), and 2) health promotion, lifestyle modifications and disease prevention (Naslund et al., 2017; Bonn et al., 2019; Debon et al., 2019). These two aspects can improve public health by decreasing chronic disease burden (Diseases and Injuries, 2020). Targeting lifestyle modifications may also reduce transgenerational transmission of ACE scores and risks for developing chronic medical conditions, further benefiting public health (Oral et al., 2016; Plass-Christl et al., 2017). Another benefit of empowering patients with personalized digital interventions is reducing workload in health care thus mitigating high burnout rates among physicians, physician assistants, nurses and pharmacists (Bridgeman et al., 2018).

Challenges and limitations of developing and implementation of precision digital interventions and metapharmacology have been discussed elsewhere (Hird et al., 2016; Sverdlov et al., 2018; Chung, 2019; Germine et al., 2019; AMCP Partnership Forum, 2020). In summary, these include: 1) cybersecurity and privacy concerns, 2) mismatch between rapid pace for consumer electronics and slower pace of developing therapeutic interventions, 3) regulatory pathways to approve drug+digital combination therapies, 4) patient adherence to digital interventions, 5) implementation and reimbursement, and 6) the lack of data on effectiveness and cost-effectiveness of combining pharmacotherapies with digital interventions. Cybersecurity risks for mobile apps connected to the internet and networks are addressed by data encryption, authentication, code integrity, identification of vulnerabilities, and abilities to detect cybersecurity events. Another real-life challenge is patient adherence to digital interventions which may vary depending on type of delivered modalities (Baumel et al., 2019), and can be improved by personalization and gamification (Litvin et al., 2020; Wei et al., 2020). While digital interventions are considered as non-invasive and relatively low-risk for patients, the safety of mobile medical apps has not been systemically studied. Implementation, adoption and scalability of digital therapeutics can vary from country to country, and depends on reimbursement policies (Powell et al., 2019; Gordon et al., 2020) and support from patients and health care providers (Sverdlov et al., 2018; AMCP Partnership Forum, 2020; Dang et al., 2020; Patel and Butte, 2020).

Given cross-disciplinary aspects of precision metapharmacology, advancing such technologies require aligning priorities of key stakeholders including research communities, patients, healthcare providers and healthcare industry, as well as regulatory and funding agencies (Varsi et al., 2019). To overcome aforementioned challenges, there are multiple incentives for key stakeholders. For patients, self-care and empowerment delivered via digital technologies offer means to improve therapy outcomes and HRQoL. Notably, since aforementioned self-care practices are complimentary, long-term implementation of these non-pharmacological interventions is not associated with more out-of-pocket expenses. For pharmaceutical and biotech industry, drug+digital combination therapies may offer strengthening intellectual property protections via copyrights of digital content and software (Bulaj, 2014). For health care insurance companies and health care systems, digital interventions offer cost savings (Jiang et al., 2019; Richards et al., 2020). For research communities, precision metapharmacology encourages preclinical and clinical discoveries on improving pharmacotherapies by

combining them with non-pharmacological interventions (Metcalf et al., 2019). For governments and funding agencies, developing and delivery of lifestyle interventions offer means to reduce burden of chronic diseases and to improve public health. In summary, advancing precision metapharmacology offers win-win opportunities for health care stakeholders.

CONCLUSION

Digital health technologies offer new opportunities to integrate health promotion, self-care and lifestyle interventions, while simultaneously mitigating limitations of pharmacotherapies such as medication non-adherence, tolerability, or drug resistance. While we illustrate examples of integrating self-care with pharmacotherapies for epilepsy, pain, depression, and cancer, this strategy applies to diverse chronic conditions including cardiovascular, metabolic, neurodegenerative, pulmonary, infectious diseases and mental disorders. Looking forward and beyond next decade, precision metapharmacology has a potential to treat multiple chronic diseases at both individual and global levels while empowering patients and health care providers. In conclusion, delivery of personalized self-care practices using digital health technologies will innovate precision medicine and patient-centered care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

EB, GB, JC, and ME searched and analyzed literature, and wrote the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.612602/full#supplementary-material>.

REFERENCES

- Aapro, M., Bossi, P., Dasari, A., Fallowfield, L., Gascón, P., Geller, M., et al. (2020). Digital health for optimal supportive care in oncology: benefits, limits, and future perspectives. *Support Care Cancer* 28 (10), 4589–4612. doi:10.1007/s00520-020-05539-1
- Afra, P., Bruggers, C. S., Sweney, M., Fagatele, L., Alavi, F., Greenwald, M., et al. (2018). Mobile software as a medical device (SaMD) for the treatment of epilepsy: development of digital therapeutics comprising behavioral and music-based interventions for neurological disorders. *Front. Hum. Neurosci.* 12, 171. doi:10.3389/fnhum.2018.00171
- Agarwal, R. P., and Maroko-Afek, A. (2018). Yoga into cancer care: a review of the evidence-based research. *Int. J. Yoga* 11 (1), 3–29. doi:10.4103/ijoy.IJOY_42_17
- Alon, N., Stern, A. D., and Torous, J. (2020). Assessing the Food and drug administration's risk-based framework for software precertification with top health apps in the United States: quality improvement study. *JMIR Mhealth Uhealth* 8 (10), e20482. doi:10.2196/20482
- AMCP Partnership Forum (2020). Digital therapeutics-what are They and where Do They Fit in pharmacy and medical benefits? *J. Manag. Care Spec. Pharm.* 26 (5), 674–681. doi:10.18553/jmcp.2020.19418
- Anderson, B. E., and Bliven, K. C. H. (2017). The use of breathing exercises in the treatment of chronic, nonspecific low back pain. *J. Sport Rehabil.* 26 (5), 452–458. doi:10.1123/jsr.2015-0199
- Armitage, L. C., Kassavou, A., and Sutton, S. (2020). Do mobile device apps designed to support medication adherence demonstrate efficacy? A systematic review of randomised controlled trials, with meta-analysis. *BMJ Open* 10 (1), e032045. doi:10.1136/bmjopen-2019-032045
- Arute, F., Arya, K., Babbush, R., Bacon, D., Bardin, J. C., Barends, R., et al. (2019). Quantum supremacy using a programmable superconducting processor. *Nature* 574 (7779), 505–510. doi:10.1038/s41586-019-1666-5
- Assaraf, Y. G., Brozovic, A., Gonçalves, A. C., Jurkovicova, D., Linē, A., Machuqueiro, M., et al. (2019). The multi-factorial nature of clinical multidrug resistance in cancer. *Drug Resist. Updates* 46, 100645. doi:10.1016/j.drug.2019.100645
- Balconi, M., Fronda, G., and Vanutelli, M. E. (2019). A gift for gratitude and cooperative behavior: brain and cognitive effects. *Soc. Cogn. Affect Neurosci.* 14 (12), 1317–1327. doi:10.1093/scan/nsaa003
- Baumel, A., Muench, F., Edan, S., and Kane, J. M. (2019). Objective user engagement with mental health apps: systematic search and panel-based usage analysis. *J. Med. Internet Res.* 21 (9), e14567. doi:10.2196/14567
- Bellis, M. A., Hughes, K., Ford, K., Ramos Rodriguez, G., Sethi, D., and Passmore, J. (2019). Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: a systematic review and meta-analysis. *The Lancet Public Health* 4 (10), e517–e528. doi:10.1016/s2468-2667(19)30145-8
- Besedovsky, L., Lange, T., and Haack, M. (2019). The sleep-immune crosstalk in health and disease. *Physiol. Rev.* 99 (3), 1325–1380. doi:10.1152/physrev.00010.2018
- Bhaskar, L., Tripathi, V., Kharya, C., Kotabagi, V., Bhatia, M., and Kochupillai, V. (2020). High-Frequency cerebral activation and interhemispheric synchronization following sudarshan kriya yoga as global brain rhythms: the state effects. *Int. J. Yoga* 13 (2), 130–136. doi:10.4103/ijoy.IJOY_25_19
- Boggiss, A. L., Consedine, N. S., Brenton-Peters, J. M., Hofman, P. L., and Serlachius, A. S. (2020). A systematic review of gratitude interventions: effects on physical health and health behaviors. *J. Psychosomatic Res.* 135, 110165. doi:10.1016/j.jpsychores.2020.110165
- Bonaz, B., Bazin, T., and Pellissier, S. (2018). The vagus nerve at the interface of the microbiota-gut-brain Axis. *Front. Neurosci.* 12, 49. doi:10.3389/fnins.2018.00049
- Bonn, S. E., Lof, M., Ostenson, C. G., and Trolle Lagerros, Y. (2019). App-technology to improve lifestyle behaviors among working adults - the Health Integrator study, a randomized controlled trial. *BMC Public Health* 19 (1), 273. doi:10.1186/s12889-019-6595-6
- Borsook, D., Youssef, A. M., Simons, L., Elman, I., and Eccleston, C. (2018). When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain* 159 (12), 2421–2436. doi:10.1097/j.pain.0000000000001401
- Brandani, J. Z., Mizuno, J., Ciolac, E. G., and Monteiro, H. L. (2017). The hypotensive effect of Yoga's breathing exercises: a systematic review. *Complement. Ther. Clin. Pract.* 28, 38–46. doi:10.1016/j.ctcp.2017.05.002
- Brás, P. C., Barros, A., Vaz, S., Sequeira, J., Melancia, D., Fernandes, A., et al. (2018). Influence of weather on seizure frequency - clinical experience in the emergency room of a tertiary hospital. *Epilepsy Behav.* 86, 25–30. doi:10.1016/j.yebeh.2018.07.010
- Bridgeman, P. J., Bridgeman, M. B., and Barone, J. (2018). Burnout syndrome among healthcare professionals. *Am. J. Health Syst. Pharm.* 75 (3), 147–152. doi:10.2146/ajhp170460
- Brinsley, J., Schuch, F., Lederman, O., Girard, D., Smout, M., Immink, M. A., et al. (2020). Effects of yoga on depressive symptoms in people with mental disorders: a systematic review and meta-analysis. *Br. J. Sports Med.* doi:10.1136/bjsports-2019-101242
- Brown, M. T., and Bussell, J. K. (2011). Medication adherence: WHO cares? *Mayo Clinic Proc.* 86 (4), 304–314. doi:10.4065/mcp.2010.0575
- Bruggers, C. S., Baranowski, S., Besiser, M., Leonard, R., Long, D., Schulte, E., et al. (2018). A prototype exercise-empowerment mobile video game for children with cancer, and its usability assessment: developing digital empowerment interventions for pediatric diseases. *Front. Pediatr.* 6, 69. doi:10.3389/fped.2018.00069
- Bruggers, C. S., Altizer, R. A., Kessler, R. R., Caldwell, C. B., Coppersmith, K., Warner, L., et al. (2012). Patient-empowerment interactive technologies. *Sci. Translational Med.* 4 (152), 152ps16. doi:10.1126/scitranslmed.3004009
- Bulaj, G., Ahern, M., Kuhn, A., Judkins, Z., Bowen, R., and Chen, Y. (2016). Incorporating natural products, pharmaceutical drugs, self-care and digital/mobile health technologies into molecular-behavioral combination therapies for chronic diseases. *Curr. Clin. Pharmacol.* 11 (2), 128–145. doi:10.2174/1574884711666160603012237
- Bulaj, G. (2014). Combining non-pharmacological treatments with pharmacotherapies for neurological disorders: a unique interface of the brain, drug-device, and intellectual property. *Front. Neurol.* 5, 126. doi:10.3389/fneur.2014.00126
- Cai, H., Li, G., Hua, S., Liu, Y., and Chen, L. (2017). Effect of exercise on cognitive function in chronic disease patients: a meta-analysis and systematic review of randomized controlled trials. *Clin. Interv. Aging* 12, 773–783. doi:10.2147/cia.s135700
- Campbell, J. A., Walker, R. J., and Egede, L. E. (2016). Associations between adverse childhood experiences, high-risk behaviors, and morbidity in adulthood. *Am. J. Prev. Med.* 50 (3), 344–352. doi:10.1016/j.amepre.2015.07.022
- Carson, J. W., Keefe, F. J., Goli, V., Fras, A. M., Lynch, T. R., Thorp, S. R., et al. (2005). Forgiveness and chronic low back pain: a preliminary study examining the relationship of forgiveness to pain, anger, and psychological distress. *The J. Pain* 6 (2), 84–91. doi:10.1016/j.jpain.2004.10.012
- Chanda, M. L., and Levitin, D. J. (2013). The neurochemistry of music. *Trends Cogn. Sci.* 17 (4), 179–193. doi:10.1016/j.tics.2013.02.007
- Chang, K.-C., Wu, T.-H., Fann, J. C.-Y., Chen, S. L. S., Yen, A. M.-F., Chiu, S. Y.-H., et al. (2019). Low ambient temperature as the only meteorological risk factor of seizure occurrence: a multivariate study. *Epilepsy Behav.* 100 (Pt A), 106283. doi:10.1016/j.yebeh.2019.04.036
- Chou, R., Deyo, R., Friedly, J., Skelly, A., Hashimoto, R., Weimer, M., et al. (2017). Nonpharmacologic therapies for low back pain: a systematic review for an American college of physicians clinical practice guideline. *Ann. Intern. Med.* 166 (7), 493–505. doi:10.7326/m16-2459
- Chung, J.-Y. (2019). Digital therapeutics and clinical pharmacology. *Transl. Clin. Pharmacol.* 27 (1), 6–11. doi:10.12793/tcp.2019.27.1.6
- Cianconi, P., Betro, S., and Janiri, L. (2020). The impact of climate change on mental health: a systematic descriptive review. *Front. Psychiatry* 11, 74. doi:10.3389/fpsy.2020.00074
- Cleare, A., Pariente, C., Young, A., Anderson, I., Christmas, D., Cowen, P., et al. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J. Psychopharmacol.* 29 (5), 459–525. doi:10.1177/0269881115581093
- Coulter, A., Entwistle, V. A., Eccles, A., Ryan, S., Shepperd, S., and Perera, R. (2015). Personalised care planning for adults with chronic or long-term health conditions. *Cochrane Database Syst. Rev.* 2015 (3), CD010523. doi:10.1002/14651858.CD010523.pub2

- Dang, A., Arora, D., and Rane, P. (2020). Role of digital therapeutics and the changing future of healthcare. *J. Fam. Med Prim Care* 9 (5), 2207–2213. doi:10.4103/jfmpc.jfmpc_105_20
- Danhauer, S. C., Addington, E. L., Cohen, L., Sohl, S. J., Van Puymbroeck, M., Albinati, N. K., et al. (2019). Yoga for symptom management in oncology: a review of the evidence base and future directions for research. *Cancer* 125 (12), 1979–1989. doi:10.1002/cncr.31979
- Debon, R., Coleone, J. D., Bellei, E. A., and De Marchi, A. C. B. (2019). Mobile health applications for chronic diseases: a systematic review of features for lifestyle improvement. *Diabetes Metab. Syndr. Clin. Res. Rev.* 13 (4), 2507–2512. doi:10.1016/j.dsx.2019.07.016
- Derefinko, K. J., Salgado García, F. I., Talley, K. M., Bursac, Z., Johnson, K. C., Murphy, J. G., et al. (2019). Adverse childhood experiences predict opioid relapse during treatment among rural adults. *Addict. Behaviors* 96, 171–174. doi:10.1016/j.addbeh.2019.05.008
- Dinoff, A., Herrmann, N., Swardfager, W., and Lanctôt, K. L. (2017). The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. *Eur. J. Neurosci.* 46 (1), 1635–1646. doi:10.1111/ejn.13603
- Disease, G. B. D. (2018). Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392 (10159), 1789–1858. doi:10.1016/S0140-6736(18)32279-7
- Diseases, G. B. D., and Injuries, C. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 396 (10258), 1204–1222. doi:10.1016/S0140-6736(20)30925-9
- Falkenberg, R. I., Eising, C., and Peters, M. L. (2018). Yoga and immune system functioning: a systematic review of randomized controlled trials. *J. Behav. Med.* 41 (4), 467–482. doi:10.1007/s10865-018-9914-y
- Fancourt, D., Ockelford, A., and Belai, A. (2014). The psychoneuroimmunological effects of music: a systematic review and a new model. *Brain Behav. Immun.* 36, 15–26. doi:10.1016/j.bbi.2013.10.014
- Fernandez-Sotos, A., Fernandez-Caballero, A., and Latorre, J. M. (2016). Influence of tempo and rhythmic unit in musical emotion regulation. *Front. Comput. Neurosci.* 10, 80. doi:10.3389/fncom.2016.00080
- Fjell, M., Langius-Eklöf, A., Nilsson, M., Wengström, Y., and Sundberg, K. (2020). Reduced symptom burden with the support of an interactive app during neoadjuvant chemotherapy for breast cancer - a randomized controlled trial. *The Breast* 51, 85–93. doi:10.1016/j.breast.2020.03.004
- Fourie, M. M., Hortensius, R., and Decety, J. (2020). Parsing the components of forgiveness: psychological and neural mechanisms. *Neurosci. Biobehavioral Rev.* 112, 437–451. doi:10.1016/j.neubiorev.2020.02.020
- Friedberg, J. P., Suchday, S., and Srinivas, V. S. (2009). Relationship between forgiveness and psychological and physiological indices in cardiac patients. *Int. J. Behav. Med.* 16 (3), 205–211. doi:10.1007/s12529-008-9016-2
- Garza-Villarreal, E. A., Pando, V., Vuust, P., and Parsons, C. (2017). Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician* 20 (7), 597–610. doi:10.36076/ppj.2017.7.597
- Germine, L., Reinecke, K., and Chaytor, N. S. (2019). Digital neuropsychology: challenges and opportunities at the intersection of science and software. *The Clin. Neuropsychologist* 33 (2), 271–286. doi:10.1080/13854046.2018.1535662
- Ginty, A. T., Tyra, A. T., Young, D. A., John-Henderson, N. A., Gallagher, S., and Tsang, J.-A. C. (2020). State gratitude is associated with lower cardiovascular responses to acute psychological stress: a replication and extension. *Int. J. Psychophysiology* 158, 238–247. doi:10.1016/j.ijpsycho.2020.10.005
- Gordon, W. J., Landman, A., Zhang, H., and Bates, D. W. (2020). Beyond validation: getting health apps into clinical practice. *Npj Digit Med.* 3, 14. doi:10.1038/s41746-019-0212-z
- Govender, M., Bowen, R. C., German, M. L., Bulaj, G., and Bruggers, C. S. (2015). Clinical and neurobiological perspectives of empowering pediatric cancer patients using videogames. *Games Health J.* 4 (5), 362–374. doi:10.1089/g4h.2015.0014
- Goyal, M., Singh, S., Sibinga, E. M. S., Gould, N. F., Rowland-Seymour, A., Sharma, R., et al. (2014). Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern. Med.* 174 (3), 357–368. doi:10.1001/jamainternmed.2013.13018
- Graham, H., White, P., Cotton, J., and McManus, S. (2019). Flood- and weather-damaged homes and mental health: an analysis using england's mental health survey. *Int. J. Environ. Res. Public Health* 16 (18), 3256. doi:10.3390/ijerph16183256
- Guerra, P. C., Santaella, D. F., D'Almeida, V., Santos-Silva, R., Tufik, S., and Len, C. A. (2020). Yogic meditation improves objective and subjective sleep quality of healthcare professionals. *Complement. Therapies Clin. Pract.* 40, 101204. doi:10.1016/j.ctcp.2020.101204
- Gujral, S., Aizenstein, H., Reynolds, C. F., 3rd, Butters, M. A., and Erickson, K. I. (2017). Exercise effects on depression: possible neural mechanisms. *Gen. Hosp. Psychiatry* 49, 2–10. doi:10.1016/j.genhosppsych.2017.04.012
- Häfele, C. A., Freitas, M. P., da Silva, M. C., and Rombaldi, A. J. (2017). Are physical activity levels associated with better health outcomes in people with epilepsy? *Epilepsy Behav.* 72, 28–34. doi:10.1016/j.yebeh.2017.04.038
- Haut, S. R., Lipton, R. B., Cornes, S., Dwivedi, A. K., Wasson, R., Cotton, S., et al. (2018). Behavioral interventions as a treatment for epilepsy: A multicenter randomized controlled trial. *Neurology* 90 (11), e963–e970. doi:10.1212/wnl.0000000000005109
- Heckendorf, H., Lehr, D., Ebert, D. D., and Freund, H. (2019). Efficacy of an internet and app-based gratitude intervention in reducing repetitive negative thinking and mechanisms of change in the intervention's effect on anxiety and depression: results from a randomized controlled trial. *Behav. Res. Ther.* 119, 103415. doi:10.1016/j.brat.2019.103415
- Hilton, L., Hempel, S., Ewing, B. A., Apaydin, E., Xenakis, L., Newberry, S., et al. (2017). Mindfulness meditation for chronic pain: systematic review and meta-analysis. *Ann. Behav. Med.* 51 (2), 199–213. doi:10.1007/s12160-016-9844-2
- Hird, N., Ghosh, S., and Kitano, H. (2016). Digital health revolution: perfect storm or perfect opportunity for pharmaceutical R&D? *Drug Discov. Today* 21 (6), 900–911. doi:10.1016/j.drudis.2016.01.010
- Huber, S., Priebe, J. A., Baumann, K.-M., Plidschun, A., Schiessl, C., and Tölle, T. R. (2017). Treatment of low back pain with a digital multidisciplinary pain treatment app: short-term results. *JMIR Rehabil. Assist. Technol.* 4 (2), e11. doi:10.2196/rehab.9032
- Iddir, M., Brito, A., Dingee, G., Fernandez Del Campo, S. S., Samouda, H., La Frano, M. R., et al. (2020). Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. *Nutrients* 12 (6), 1562. doi:10.3390/nu12061562
- Irwin, M. R. (2019). Sleep and inflammation: partners in sickness and in health. *Nat. Rev. Immunol.* 19 (11), 702–715. doi:10.1038/s41577-019-0190-z
- Irwin, M. R. (2015). Why sleep is important for health: a psychoneuroimmunology perspective. *Annu. Rev. Psychol.* 66, 143–172. doi:10.1146/annurev-psych-010213-115205
- Jiang, M., Ma, Y., Yun, B., Wang, Q., Huang, C., and Han, L. (2020). Exercise for fatigue in breast cancer patients: an umbrella review of systematic reviews. *Int. J. Nurs. Sci.* 7 (2), 248–254. doi:10.1016/j.ijnss.2020.03.001
- Jiang, S., Postovit, L., Cattaneo, A., Binder, E. B., and Aitchison, K. J. (2019). Epigenetic modifications in stress response genes associated with childhood trauma. *Front. Psychiatry* 10, 808. doi:10.3389/fpsy.2019.00808
- Jiang, X., Ming, W. K., and You, J. H. (2019). The cost-effectiveness of digital health interventions on the management of cardiovascular diseases: systematic review. *J. Med. Internet Res.* 21 (6), e13166. doi:10.2196/13166
- Jongerus, C., Russo, S., Mazzocco, K., and Pravettoni, G. (2019). Research-tested mobile apps for breast cancer care: systematic review. *JMIR Mhealth Uhealth* 7 (2), e10930. doi:10.2196/10930
- Joyner, M. J., and Green, D. J. (2009). Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J. Physiol.* 587 (Pt 23), 5551–5558. doi:10.1113/jphysiol.2009.179432
- Kesselheim, A. S., Avorn, J., and Sarpatwari, A. (2016). The high cost of prescription drugs in the United States: Origins and Prospects for Reform. *JAMA* 316 (8), 858–871. doi:10.1001/jama.2016.11237
- Kim, H. J., Kim, S. M., Shin, H., Jang, J.-S., Kim, Y. I., and Han, D. H. (2018). A mobile game for patients with breast cancer for chemotherapy self-management and quality-of-life improvement: randomized controlled trial. *J. Med. Internet Res.* 20 (10), e273. doi:10.2196/jmir.9559
- Kim, Y., Kim, K., Chartier, K. G., Wike, T. L., and McDonald, S. E. (2019). Adverse childhood experience patterns, major depressive disorder, and substance use disorder in older adults. *Aging Ment. Health* 25 (3), 484–489. doi:10.1080/13607863.2019.1693974

- Korhonen, M. J., Halonen, J. I., Brookhart, M. A., Kawachi, I., Pentti, J., Karlsson, H., et al. (2015). Childhood adversity as a predictor of non-adherence to statin therapy in adulthood. *PLoS One* 10 (5), e0127638. doi:10.1371/journal.pone.0127638
- Kraja, A. T., Chasman, D. I., North, K. E., Reiner, A. P., Yanek, L. R., Kilpeläinen, T. O., et al. (2014). Pleiotropic genes for metabolic syndrome and inflammation. *Mol. Genet. Metab.* 112 (4), 317–338. doi:10.1016/j.ymgme.2014.04.007
- Kumar, A., Bhatia, R., Sharma, G., Dhanlika, D., Vishnubhatla, S., Singh, R. K., et al. (2020). Effect of yoga as add-on therapy in migraine (CONTAIN): a randomized clinical trial. *Neurology* 94 (21), e2203–e2212. doi:10.1212/wnl.0000000000009473
- Kvam, S., Kleppe, C. L., Nordhus, I. H., and Hovland, A. (2016). Exercise as a treatment for depression: a meta-analysis. *J. Affective Disord.* 202, 67–86. doi:10.1016/j.jad.2016.03.063
- Kwan, P., Schachter, S. C., and Brodie, M. J. (2011). Drug-resistant epilepsy. *N. Engl. J. Med.* 365 (10), 919–926. doi:10.1056/nejmra1004418
- Lawler, K. A., Younger, J. W., Piferi, R. L., Billington, E., Jobe, R., Edmondson, K., et al. (2003). A change of heart: cardiovascular correlates of forgiveness in response to interpersonal conflict. *J. Behav. Med.* 26 (5), 373–393. doi:10.1023/a:1025771716686
- Lee, J. H. (2016). The effects of music on pain: a meta-analysis. *Jmther* 53 (4), 430–477. doi:10.1093/jmt/thw012
- Leubner, D., and Hinterberger, T. (2017). Reviewing the effectiveness of music interventions in treating depression. *Front. Psychol.* 8, 1109. doi:10.3389/fpsyg.2017.01109
- Litvin, S., Saunders, R., Maier, M. A., and Luttke, S. (2020). Gamification as an approach to improve resilience and reduce attrition in mobile mental health interventions: a randomized controlled trial. *PLoS One* 15 (9), e0237220. doi:10.1371/journal.pone.0237220
- Liu, W., Pan, Y.-L., Gao, C.-X., Shang, Z., Ning, L.-J., and Liu, X. (2013). Breathing exercises improve post-operative pulmonary function and quality of life in patients with lung cancer: a meta-analysis. *Exp. Ther. Med.* 5 (4), 1194–1200. doi:10.3892/etm.2013.926
- Mallik, A., Chanda, M. L., and Levitin, D. J. (2017). Anhedonia to music and mu-opioids: evidence from the administration of naltrexone. *Sci. Rep.* 7, 41952. doi:10.1038/srep41952
- Mantani, A., Kato, T., Furukawa, T. A., Horikoshi, M., Imai, H., Hiroe, T., et al. (2017). Smartphone cognitive behavioral therapy as an adjunct to pharmacotherapy for refractory depression: randomized controlled trial. *J. Med. Internet Res.* 19 (11), e373. doi:10.2196/jmir.8602
- Metcalfe, C. S., Huntsman, M., Garcia, G., Kochanski, A. K., Chikinda, M., Watanabe, E., et al. (2019). Music-Enhanced analgesia and antiepileptic activities in animal models of pain and epilepsy: toward preclinical studies supporting development of digital therapeutics and their combinations with pharmaceutical drugs. *Front. Neurol.* 10, 277. doi:10.3389/fneur.2019.00277
- Miura, K., Goto, S., Katsumata, Y., Ikura, H., Shiraishi, Y., Sato, K., et al. (2020). Feasibility of the deep learning method for estimating the ventilatory threshold with electrocardiography data. *Npj Digit Med.* 3 (1), 141. doi:10.1038/s41746-020-00348-6
- Moberg, C., Niles, A., and Beermann, D. (2019). Guided self-help works: randomized waitlist controlled trial of pacifica, a mobile app integrating cognitive behavioral therapy and mindfulness for stress, anxiety, and depression. *J. Med. Internet Res.* 21 (6), e12556. doi:10.2196/12556
- Mohammad, A., Thakur, P., Kumar, R., Kaur, S., Saini, R. V., and Saini, A. K. (2019). Biological markers for the effects of yoga as a complementary and alternative medicine. *J. Complement. Integr. Med.* 16 (1), 1–15. doi:10.1515/jcim-2018-0094
- Mojtabavi, H., Saghazadeh, A., Valenti, V. E., and Rezaei, N. (2020). Can music influence cardiac autonomic system? A systematic review and narrative synthesis to evaluate its impact on heart rate variability. *Complement. Therapies Clin. Pract.* 39, 101162. doi:10.1016/j.ctcp.2020.101162
- Monnat, S. M. (2018). Factors associated with county-level differences in U.S. Drug-related mortality rates. *Am. J. Prev. Med.* 54 (5), 611–619. doi:10.1016/j.amepre.2018.01.040
- Morganstein, J. C., and Ursano, R. J. (2020). Ecological disasters and mental health: causes, consequences, and interventions. *Front. Psychiatry* 11, 1. doi:10.3389/fpsyg.2020.00001
- Mork, P. J., Bach, K., and self, B. C. (2018). A decision support system to enhance self-management of low back pain: protocol for the selfBACK project. *JMIR Res. Protoc.* 7 (7), e167. doi:10.2196/resprot.9379
- Nahin, R. L., Boineau, R., Khalsa, P. S., Stussman, B. J., and Weber, W. J. (2016). Evidence-based evaluation of complementary health approaches for pain management in the United States. *Mayo Clinic Proc.* 91 (9), 1292–1306. doi:10.1016/j.mayocp.2016.06.007
- Nahum-Shani, I., Smith, S. N., Spring, B. J., Collins, L. M., Witkiewitz, K., Tewari, A., et al. (2018). Just-in-Time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. *Ann. Behav. Med.* 52 (6), 446–462. doi:10.1007/s12160-016-9830-8
- Naslund, J. A., Aschbrenner, K. A., Araya, R., Marsch, L. A., Unützer, J., Patel, V., et al. (2017). Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. *The Lancet Psychiatry* 4 (6), 486–500. doi:10.1016/s2215-0366(17)30096-2
- Nieman, D. C., and Wentz, L. M. (2019). The compelling link between physical activity and the body's defense system. *J. Sport Health Sci.* 8 (3), 201–217. doi:10.1016/j.jshs.2018.09.009
- Nordyke, R. J., Appelbaum, K., and Berman, M. A. (2019). Estimating the impact of novel digital therapeutics in type 2 diabetes and hypertension: health economic analysis. *J. Med. Internet Res.* 21 (10), e15814. doi:10.2196/15814
- Oral, R., Ramirez, M., Coohay, C., Nakada, S., Walz, A., Kuntz, A., et al. (2016). Adverse childhood experiences and trauma informed care: the future of health care. *Pediatr. Res.* 79 (1-2), 227–233. doi:10.1038/pr.2015.197
- Pandarakalam, J. P. (2018). Challenges of treatment-resistant depression. *Psychiat Danub* 30 (3), 273–284. doi:10.24869/psyd.2018.273
- Panebianco, M., Sridharan, K., and Ramaratnam, S. (2017). Yoga for epilepsy. *Cochrane Database Syst. Rev.* 10 (10), CD001524. doi:10.1002/14651858.CD001524.pub3
- Pascoe, M. C., Thompson, D. R., Jenkins, Z. M., and Ski, C. F. (2017). Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. *J. Psychiatr. Res.* 95, 156–178. doi:10.1016/j.jpsychires.2017.08.004
- Pascoe, M. C., Thompson, D. R., and Ski, C. F. (2017). Yoga, mindfulness-based stress reduction and stress-related physiological measures: a meta-analysis. *Psychoneuroendocrinology* 86, 152–168. doi:10.1016/j.psyneuen.2017.08.008
- Patel, N. A., and Butte, A. J. (2020). Characteristics and challenges of the clinical pipeline of digital therapeutics. *Npj Digit Med.* 3 (1), 159. doi:10.1038/s41746-020-00370-8
- Pauwels, E. K. J., Volterrani, D., Mariani, G., and Kostkiewicz, M. (2014). Mozart, music and medicine. *Med. Princ Pract.* 23 (5), 403–412. doi:10.1159/000364873
- Perez-Jover, V., Sala-Gonzalez, M., Guilbert, M., and Mira, J. J. (2019). Mobile apps for increasing treatment adherence: systematic review. *J. Med. Internet Res.* 21 (6), e12505. doi:10.2196/12505
- Pine, R., Fleming, T., McCallum, S., and Sutcliffe, K. (2020). The effects of casual videogames on anxiety, depression, stress, and low mood: a systematic review. *Games Health J.* 9 (4), 255–264. doi:10.1089/g4h.2019.0132
- Pires, G. N., Bezerra, A. G., Tufik, S., and Andersen, M. L. (2016). Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med.* 24, 109–118. doi:10.1016/j.sleep.2016.07.019
- Plass-Christl, A., Haller, A. C., Otto, C., Barkmann, C., Wiegand-Grefe, S., Holling, H., et al. (2017). Parents with mental health problems and their children in a German population based sample: results of the BELLA study. *PLoS One* 12 (7), e0180410. doi:10.1371/journal.pone.0180410
- Pouls, B. P. H., Vriezeekolk, J. E., Bekker, C. L., Linn, A. J., van Onzenoort, H. A. W., Vervloet, M., et al. (2021). Effect of interactive eHealth interventions on improving medication adherence in adults with long-term medication: systematic review. *J. Med. Internet Res.* 23 (1), e18901. doi:10.2196/18901
- Powell, A. C., Bowman, M. B., and Harbin, H. T. (2019). Reimbursement of apps for mental health: findings from interviews. *JMIR Ment. Health* 6 (8), e14724. doi:10.2196/14724
- Pramanik, T., Sharma, H. O., Mishra, S., Mishra, A., Prajapati, R., and Singh, S. (2009). Immediate effect of slow PaceBhastrika pranayama on blood pressure and heart rate. *J. Altern. Complement. Med.* 15 (3), 293–295. doi:10.1089/acm.2008.0440
- Priebe, J. A., Haas, K. K., Moreno Sanchez, L. F., Schoefmann, K., Utpadel-Fischler, D. A., Stockert, P., et al. (2020). Digital treatment of back pain versus standard of care: the cluster-randomized controlled trial, rise-uP. *J Pain Res* Vol. 13, 1823–1838. doi:10.2147/jpr.s260761

- Qiu, J., Jiang, Y. F., Li, F., Tong, Q. H., Rong, H., and Cheng, R. (2017). Effect of combined music and touch intervention on pain response and beta-endorphin and cortisol concentrations in late preterm infants. *BMC Pediatr.* 17 (1), 38. doi:10.1186/s12887-016-0755-y
- Rafee, M., Patel, K., Groppe, D. M., Andrade, D. M., Bercovici, E., Bui, E., et al. (2020). Daily listening to Mozart reduces seizures in individuals with epilepsy: a randomized control study. *Epilepsia Open* 5 (2), 285–294. doi:10.1002/epi4.12400
- Raven, F., Van der Zee, E. A., Meerlo, P., and Havekes, R. (2018). The role of sleep in regulating structural plasticity and synaptic strength: implications for memory and cognitive function. *Sleep Med. Rev.* 39, 3–11. doi:10.1016/j.smrv.2017.05.002
- Richard, A. A., and Shea, K. (2011). Delineation of self-care and associated concepts. *J. Nurs. Scholarsh* 43 (3), 255–264. doi:10.1111/j.1547-5069.2011.01404.x
- Richards, D., Enrique, A., Eilert, N., Franklin, M., Palacios, J., Duffy, D., et al. (2020). A pragmatic randomized waitlist-controlled effectiveness and cost-effectiveness trial of digital interventions for depression and anxiety. *Npj Digit Med.* 3, 85. doi:10.1038/s41746-020-0293-8
- Riegel, B., Moser, D. K., Buck, H. G., Dickson, V. V., Dunbar, S. B., Lee, C. S., et al. (2017). Self-care for the prevention and management of cardiovascular disease and stroke: a scientific statement for healthcare professionals from the American heart association. *J. Am. Heart Assoc.* 6 (9), e006997 doi:10.1161/jaha.117.006997
- Risling, T., Martinez, J., Young, J., and Thorp-Frosie, N. (2017). Evaluating patient empowerment in association with eHealth technology: scoping review. *J. Med. Internet Res.* 19 (9), e329. doi:10.2196/jmir.7809
- Rowland, S. P., Fitzgerald, J. E., Holme, T., Powell, J., and McGregor, A. (2020). What is the clinical value of mHealth for patients?. *Npj Digit Med.* 3, 4. doi:10.1038/s41746-019-0206-x
- Saeed, S. A., Cunningham, K., and Bloch, R. M. (2019). Depression and anxiety disorders: benefits of exercise, yoga, and meditation. *Am. Fam. Physician* 99 (10), 620–627.
- Safavi, K. C., Cohen, A. B., Ting, D. Y., Chaguturu, S., and Rowe, J. S. (2020). Health systems as venture capital investors in digital health: 2011–2019. *Npj Digit Med.* 3, 103. doi:10.1038/s41746-020-00311-5
- Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., and Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat. Neurosci.* 14 (2), 257–262. doi:10.1038/nn.2726
- Sandal, L. F., Overas, C. K., Nordstoga, A. L., Wood, K., Bach, K., Hartvigsen, J., et al. (2020). A digital decision support system (selfBACK) for improved self-management of low back pain: a pilot study with 6-week follow-up. *Pilot Feasibility Stud.* 6, 72. doi:10.1186/s40814-020-00604-2
- Sandal, L. F., Stochkendahl, M. J., Svendsen, M. J., Wood, K., Overas, C. K., Nordstoga, A. L., et al. (2019). An app-delivered self-management program for people with low back pain: protocol for the selfBACK randomized controlled trial. *JMIR Res. Protoc.* 8 (12), e14720. doi:10.2196/14720
- Savage, E. M., McCormick, D., McDonald, S., Moore, O., Stevenson, M., and Cairns, A. P. (2015). Does rheumatoid arthritis disease activity correlate with weather conditions?. *Rheumatol. Int.* 35 (5), 887–890. doi:10.1007/s00296-014-3161-5
- Schriewer, K., and Bulaj, G. (2016). Music streaming services as adjunct therapies for depression, anxiety, and bipolar symptoms: convergence of digital technologies, mobile apps, emotions, and global mental health. *Front. Public Health* 4, 217. doi:10.3389/fpubh.2016.00217
- Sesso, G., and Sicca, F. (2020). Safe and sound: meta-analyzing the Mozart effect on epilepsy. *Clin. Neurophysiol.* 131 (7), 1610–1620. doi:10.1016/j.clinph.2020.03.039
- Sharma, A., Barrett, M. S., Cucchiara, A. J., Gooneratne, N. S., and Thase, M. E. (2016). A breathing-based meditation intervention for patients with major depressive disorder following inadequate response to antidepressants: a randomized pilot study. *J. Clin. Psychiatry* 78 (1), e59–e63. doi:10.4088/JCP.16m10819
- Sharma, A., Barrett, M. S., Cucchiara, A. J., Gooneratne, N. S., and Thase, M. E. (2017). A breathing-based meditation intervention for patients with major depressive disorder following inadequate response to antidepressants: a randomized pilot study. *J. Clin. Psychiatry* 78 (1), e59–e63. doi:10.4088/jcp.16m10819
- Shebib, R., Bailey, J. F., Smittenaar, P., Perez, D. A., Mecklenburg, G., and Hunter, S. (2019). Randomized controlled trial of a 12-week digital care program in improving low back pain. *Npj Digit Med.* 2 1. doi:10.1038/s41746-018-0076-7
- Shegog, R., Bamps, Y. A., Patel, A., Kakacek, J., Escoffery, C., Johnson, E. K., et al. (2013). Managing epilepsy well: emerging e-tools for epilepsy self-management. *Epilepsy Behav.* 29 (1), 133–140. doi:10.1016/j.yebeh.2013.07.002
- Shegog, R., Braverman, L., and Hixson, J. D. (2020). Digital and technological opportunities in epilepsy: toward a digital ecosystem for enhanced epilepsy management. *Epilepsy Behav.* 102, 106663. doi:10.1016/j.yebeh.2019.106663
- Shuren, J., Patel, B., and Gottlieb, S. (2018). FDA regulation of mobile medical apps. *JAMA* 320 (4), 337–338. doi:10.1001/jama.2018.8832
- Si, Y., Xiao, X., Xia, C., Guo, J., Hao, Q., Mo, Q., et al. (2020). Optimising epilepsy management with a smartphone application: a randomised controlled trial. *Med. J. Aust.* 212 (6), 258–262. doi:10.5694/mja2.50520
- Sin, J., Galeazzi, G., McGregor, E., Collom, J., Taylor, A., Barrett, B., et al. (2020). Digital interventions for screening and treating common mental disorders or symptoms of common mental illness in adults: systematic review and meta-analysis. *J. Med. Internet Res.* 22 (9), e20581. doi:10.2196/20581
- Stewart, S., Keates, A. K., Redfern, A., and McMurray, J. J. V. (2017). Seasonal variations in cardiovascular disease. *Nat. Rev. Cardiol.* 14 (11), 654–664. doi:10.1038/nrcardio.2017.76
- Sverdllov, O., van Dam, J., Hannesdottir, K., and Thornton-Wells, T. (2018). Digital therapeutics: an integral component of digital innovation in drug development. *Clin. Pharmacol. Ther.* 104 (1), 72–80. doi:10.1002/cpt.1036
- Tang, Q., Huang, Z., Zhou, H., and Ye, P. (2020). Effects of music therapy on depression: a meta-analysis of randomized controlled trials. *PLoS One* 15 (11), e0240862. doi:10.1371/journal.pone.0240862
- Tang, V., Poon, W. S., and Kwan, P. (2015). Mindfulness-based therapy for drug-resistant epilepsy: an assessor-blinded randomized trial. *Neurology* 85 (13), 1100–1107. doi:10.1212/wnl.0000000000001967
- Tang, Y.-Y., Hölzel, B. K., and Posner, M. I. (2015). The neuroscience of mindfulness meditation. *Nat. Rev. Neurosci.* 16 (4), 213–225. doi:10.1038/nrn3916
- Tick, H., Nielsen, A., Pelletier, K. R., Bonakdar, R., Simmons, S., Glick, R., et al. (2018). Evidence-based nonpharmacologic strategies for comprehensive pain care: The consortium pain task force white paper. *Explore* 14 (3), 177–211. doi:10.1016/j.explore.2018.02.001
- Toschi-Dias, E., Tobaldini, E., Solbiati, M., Costantino, G., Sanlorenzo, R., Doria, S., et al. (2017). Sudarshan Kriya Yoga improves cardiac autonomic control in patients with anxiety-depression disorders. *J. Affective Disord.* 214, 74–80. doi:10.1016/j.jad.2017.03.017
- Triantafyllidis, A. K., and Tsanas, A. (2019). Applications of machine learning in real-life digital health interventions: review of the literature. *J. Med. Internet Res.* 21 (4), e12286. doi:10.2196/12286
- Twal, W. O., Wahlquist, A. E., and Balasubramanian, S. (2016). Yogic breathing when compared to attention control reduces the levels of pro-inflammatory biomarkers in saliva: a pilot randomized controlled trial. *BMC Complement. Altern. Med.* 16, 294. doi:10.1186/s12906-016-1286-7
- Vago, D. R., and Silbersweig, D. A. (2012). Self-awareness, self-regulation, and self-transcendence (S-ART): a framework for understanding the neurobiological mechanisms of mindfulness. *Front. Hum. Neurosci.* 6, 296. doi:10.3389/fnhum.2012.00296
- van Grieken, R. A., van Tricht, M. J., Koeter, M. W. J., van den Brink, W., and Schene, A. H. (2018). The use and helpfulness of self-management strategies for depression: the experiences of patients. *PLoS One* 13 (10), e0206262. doi:10.1371/journal.pone.0206262
- Vancampfort, D., Ward, P. B., and Stubbs, B. (2019). Physical activity and sedentary levels among people living with epilepsy: a systematic review and meta-analysis. *Epilepsy Behav.* 99, 106390. doi:10.1016/j.yebeh.2019.05.052
- Varsi, C., Solberg Nes, L., Kristjansdottir, O. B., Kelders, S. M., Stenberg, U., Zangi, H. A., et al. (2019). Implementation strategies to enhance the implementation of eHealth programs for patients with chronic illnesses: realist systematic review. *J. Med. Internet Res.* 21 (9), e14255. doi:10.2196/14255
- Villaggi, B., Provencher, H., Coulombe, S., Meunier, S., Radziszewski, S., Hudon, C., et al. (2015). Self-management strategies in recovery from mood and anxiety disorders. *Glob. Qual. Nurs. Res.* 2, 2333393615606092. doi:10.1177/2333393615606092

- Walker, M. P. (2009). The role of sleep in cognition and emotion. *Ann. N. Y. Acad. Sci.* 1156, 168–197. doi:10.1111/j.1749-6632.2009.04416.x
- Wang, L., and Miller, L. C. (2019). Just-in-the-Moment adaptive interventions (JITAI): a meta-analytical review. *Health Commun.* 35 (12), 1531–1544. doi:10.1080/10410236.2019.1652388
- Wang, X., Zhang, Y., Fan, Y., Tan, X.-S., and Lei, X. (2018). Effects of music intervention on the physical and mental status of patients with breast cancer: a systematic review and meta-analysis. *Breast Care* 13 (3), 183–190. doi:10.1159/000487073
- Warren, H. R., Evangelou, E., Cabrera, C. P., Gao, H., Ren, M., Mifsud, B., et al. (2017). Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat. Genet.* 49 (3), 403–415. doi:10.1038/ng.3768
- Wei, Y., Zheng, P., Deng, H., Wang, X., Li, X., and Fu, H. (2020). Design features for improving mobile health intervention user engagement: systematic review and thematic analysis. *J. Med. Internet Res.* 22 (12), e21687. doi:10.2196/21687
- Whitehead, L., and Seaton, P. (2016). The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. *J. Med. Internet Res.* 18 (5), e97. doi:10.2196/jmir.4883
- Wirz-Justice, A. (2018). Seasonality in affective disorders. *Gen. Comp. Endocrinol.* 258, 244–249. doi:10.1016/j.ygcen.2017.07.010
- Witvliet, C. v. O., Ludwig, T. E., and Laan, K. L. V. (2001). Granting forgiveness or harboring grudges: implications for emotion, physiology, and health. *Psychol. Sci.* 12 (2), 117–123. doi:10.1111/1467-9280.00320
- Wong, Y. J., Owen, J., Gabana, N. T., Brown, J. W., McInnis, S., Toth, P., et al. (2018). Does gratitude writing improve the mental health of psychotherapy clients? Evidence from a randomized controlled trial. *Psychotherapy Res.* 28 (2), 192–202. doi:10.1080/10503307.2016.1169332
- Wood, K., Lawrence, M., Jani, B., Simpson, R., and Mercer, S. W. (2017). Mindfulness-based interventions in epilepsy: a systematic review. *BMC Neurol.* 17 (1), 52. doi:10.1186/s12883-017-0832-3
- Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., et al. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* 50 (5), 668–681. doi:10.1038/s41588-018-0090-3
- Wu, W. J., Wang, S. H., Ling, W., Geng, L. J., Zhang, X. X., Yu, L., et al. (2017). Morning breathing exercises prolong lifespan by improving hyperventilation in people living with respiratory cancer. *Medicine (Baltimore)* 96 (2), e5838. doi:10.1097/md.00000000000005838
- Xu, C., Fan, Y. N., Kan, H. D., Chen, R. J., Liu, J. H., Li, Y. F., et al. (2016). The novel relationship between urban air pollution and epilepsy: a time series study. *PLoS One* 11 (8), e0161992. doi:10.1371/journal.pone.0161992
- Yang, J., Weng, L., Chen, Z., Cai, H., Lin, X., Hu, Z., et al. (2019). Development and testing of a mobile app for pain management among cancer patients discharged from hospital treatment: randomized controlled trial. *JMIR Mhealth Uhealth* 7 (5), e12542. doi:10.2196/12542
- Yin, J., Jin, X., Shan, Z., Li, S., Huang, H., Li, P., et al. (2017). Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J. Am. Heart Assoc.* 6 (9). doi:10.1161/jaha.117.005947
- Yuen, A. W. C., and Sander, J. W. (2017). Can natural ways to stimulate the vagus nerve improve seizure control?. *Epilepsy Behav.* 67, 105–110. doi:10.1016/j.yebeh.2016.10.039
- Zeidan, F., and Vago, D. R. (2016). Mindfulness meditation-based pain relief: a mechanistic account. *Ann. N.Y. Acad. Sci.* 1373 (1), 114–127. doi:10.1111/nyas.13153
- Zope, S., and Zope, R. (2013). Sudarshan kriya yoga: breathing for health. *Int. J. Yoga* 6 (1), 4–10. doi:10.4103/0973-6131.105935
- Zschucke, E., Renneberg, B., Dimeo, F., Wüstenberg, T., and Ströhle, A. (2015). The stress-buffering effect of acute exercise: evidence for HPA axis negative feedback. *Psychoneuroendocrinology* 51, 414–425. doi:10.1016/j.psyneuen.2014.10.019

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Switching Between Second-Generation Antipsychotics in Patients with Schizophrenia and Schizoaffective Disorder: 10-Year Cohort Study in Brazil

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Objective: Switching between second-generation antipsychotics (SGAs) is a common clinical practice in the treatment of schizophrenia and schizoaffective disorders due to differences in the drugs' tolerability and safety profiles as well as the challenge of obtaining an ideal response. However, the factors associated with SGA switching remain uncertain and related real-world data are scarce. The main objective was to identify the factors associated with the switching of SGAs in patients with schizophrenia or schizoaffective disorder.

Methods: We conducted a retrospective cohort study of outpatients with schizophrenia or schizoaffective disorder, who were aged ≥ 18 years and received a SGA (clozapine, olanzapine, risperidone, quetiapine or ziprasidone) from a Brazilian pharmaceutical assistance program for at least 3 months. We identified SGA users from 2008 to 2017 by using a national administrative database (Ambulatory Information System-SIA/SUS). The factors associated with the switches were evaluated by Cox proportional hazards regression and adjusted for sex and age; the confidence interval was set at 95% (95% CI).

Results: In total, 563,765 patients were included. Female sex, advanced age of ≥ 70 years, residence in the Brazilian northeast region, and the type of antipsychotic used were associated with an increased risk of switching ($p < 0.001$). The incidence of switching ranged from 37.6/100 person-years for clozapine users to 58.2/100 person-years for risperidone users. Compared to the adjusted hazard ratio, for clozapine users, the corresponding ratios for risperidone, ziprasidone, quetiapine and olanzapine were 1.59 (95% CI, 1.57–1.61), 1.41 (95% CI, 1.39–1.44), 1.25 (95% CI, 1.23–1.26) and 1.11 (95% CI, 1.10–1.12) respectively.

Conclusion: The groups most susceptible to SGA switching in real-life setting were older individuals, women, and those living in the Brazilian northeast region. Risperidone was associated with the highest risk of switching and as expected, clozapine was associated with the lowest risk of switching than that associated with the other SGAs.

Keywords: antipsychotics, agents, schizophrenia, schizoaffective disorder, drug substitution, Brazil

INTRODUCTION

Switching of antipsychotics in the treatment of schizophrenia or related psychotic disorders is a common clinical practice and has been recommended to ensure a more appropriate treatment option in the face of issues including efficacy, safety, or tolerability (Faries et al., 2009; Nyhuis et al., 2010). Therapeutic failure, including suboptimal improvement, persistence of negative or positive symptoms, worsening of certain symptoms or level of functioning, poor treatment adherence, and intolerable adverse reactions may determine the switch during treatment (Keks et al., 2019). The most common reasons for switching related to safety and tolerability, depending on the antipsychotic used, include weight gain, metabolic syndrome, sedation, hyperprolactinemia, anticholinergic effects, increased QT, and sexual dysfunction (Stroup and Gray, 2018).

The decision to switch from one antipsychotic to another should be made considering the possible risks associated with the switching process, such as relapses, exacerbation of some symptoms, new adverse effects, withdrawal syndromes, rebound, and serious drug interactions (Bernardo et al., 2011). Patients who switched antipsychotics were more likely to be hospitalized and use acute care services compared to patients continuing with the initial antipsychotic. In addition, switching resulted in poor clinical outcomes and higher total health care costs (Faries et al., 2009).

Antipsychotics switching could be influenced by various factors: in particular, factors related to the patient, illness, environment, antipsychotics availability, acceptability of treatment, and especially related to the medication (e.g., adverse events, drug interactions, therapeutic response) need to be evaluated (Buckley and Correll, 2008). First-generation and second-generation antipsychotics (SGAs) constitute heterogeneous groups of drugs with different receptor binding and affinity profiles, and hence, distinct clinical effects are expected (Ceroveckí et al., 2013). Knowledge about the differences in the pharmacodynamic and pharmacokinetic characteristics of the previous and newer antipsychotics is crucial for adopting a more effective switching strategy, discontinuation strategy (abrupt discontinuation or tapering) for each agent, and optimization of the outcomes (Correll, 2010).

In case of an abrupt switch from an antipsychotic with high cholinergic affinity, such as olanzapine or clozapine, to that with a low affinity, cholinergic rebound syndrome is likely (Ceroveckí et al., 2013). Switching from antipsychotics with high affinity for histaminergic receptors to those with low affinity will result in rebound insomnia (Buckley and Correll, 2008). Similarly, switching from clozapine to any other antipsychotic, can lead to serious withdrawal effects and rebound psychosis (Ganguli, 2002; Keks et al., 2019).

SGAs are considered high-cost medicines and are dispensed and funded by the Brazilian National Health System (SUS) after an analysis of compliance with the National Clinical Guidelines (Brazil, 2013; Brazil, 2014a). The costs of the treatment of schizophrenia are high worldwide, particularly pharmacological therapy (Santos et al., 2017). SGAs are

responsible for the high cost of treatment for schizophrenia through SUS (Lindner et al., 2009). Patients refractory to other antipsychotics tend to undergo antipsychotics switching and have psychotic outbreaks followed by hospitalizations, which result in a significant economic burden in Brazil (Barbosa et al., 2018).

However, despite the burden and risks, few studies have explored the factors associated with switching antipsychotics in the treatment of schizophrenia and other psychotic disorders (Nyhuis et al., 2010; Xu and Krishnaswamy, 2018). Therefore, the aim of this study was to investigate the factors associated with switching of SGAs in patients with schizophrenia or schizoaffective disorder in Brazil.

METHODS

This study followed the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement which reporting items specific to observational studies using routinely collected health data (Benchimol et al., 2015).

Study Design

This was a retrospective cohort study conducted in all patients who were on SGAs for schizophrenia or schizoaffective disorder treatment and received these medicines through a pharmaceutical assistance program from the SUS, from January 2008 to December 2017.

Setting

The cohort was conducted using register-based data from a nationwide administrative database (Ambulatory Information System, SIA/SUS), where information regarding all outpatient care procedures is collected, and processed and which is used for providing high-cost medicines or procedures for specific diseases according to Brazilian guidelines. This database represents over 200 million procedures/month (Brazil, 2008). These individualized secondary data are publicly available (unrestricted access) and were available from 2008.

The public health system in Brazil, SUS, is universal and free for everyone, and assists approximately 75.6% of the population (Brazil, 2014b). The private health system (health plan or direct payment) acts in a complementary way. Regardless of whether the medical prescription is from a private or public sector, the patient has the right to have access to medicines of high unitary value (e.g., SGA) via SUS, since the coverage of health policy is universal. As they are high-cost medicines, this can inflate the family budget and it is likely that some patients are receiving their pharmacotherapy via the SUS and using the private sector for outpatient and hospital treatment, since health plans in Brazil usually do not provide medicines such as SGA.

The patients get access to these medicines via SUS only after an analysis of compliance with Brazilian guidelines for the treatment of schizophrenia and schizoaffective disorders. So, patients with schizophrenia or schizoaffective disorder who seek to obtain these medicines fully funded by SUS should schedule a doctor's

appointment (from the public or private sector), which will make a proper diagnosis and then will fill out a form to request these medications. This form together with supporting documents are analyzed by the manager of pharmaceutical services and if everything is in accordance with the current Brazilian clinical protocol, the medicine is provided. This process guarantees the supply of medicines up to three months (90 days). After 90 days, if there is a need to continue treatment, the whole process is repeated. For this reason, we adopted the 90-days cut-off. All of this information such as sex, age, race, state of residence, diagnosis, prescribed SGA, dose, quantity dispensed by pharmacy, and date of dispensation are available for consultation and analysis at SIA/SUS database.

Currently, the following SGAs are available through the SUS: oral clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Aripiprazole or injectable SGAs are not available through the SUS.

Brazilian guidelines for schizophrenia or schizoaffective disorders treatment recommend SGA monotherapy (Brazil, 2013). There is no order of preference to use SGA, except clozapine. Clozapine is only used in cases in which patients are refractory to at least two other antipsychotics. Both Brazilian guidelines do not make specific recommendations for the elderly.

Participants

The study included all patients aged ≥ 18 years, who were identified from SIA/SUS database, received SGAs (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) for more than 90 days, during January 2008 to December 2017, and diagnosed with one of the following diseases according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): Paranoid schizophrenia (F20.0), Hebephrenic schizophrenia (F20.1), Catatonic schizophrenia (F20.2), Undifferentiated schizophrenia (F20.3), Post-schizophrenic depression (F20.4), Residual schizophrenia (F20.5), Simple schizophrenia (F20.6), Other schizophrenia (F20.8), Schizoaffective disorder, manic type (F25.0), Schizoaffective disorder, depressive type (F25.1), Schizoaffective disorder, depressive type (F25.2).

Variables

All data were extracted from a single database, SIA/SUS, which contained the data related to the demographics and clinical variables. The drugs were identified in the database using the code belonging to the SIA/SUS.

Exposure groups were considered according to the SGA used at the cohort entry: clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

The following baseline demographic variables were considered: sex, age at cohort entry, race (reported by the physician), geographic region of residence at study entry, and year of cohort entry (defined as the year of the first provision of SGAs from January 1, 2008, to December 31, 2017). The baseline clinical variables considered were: SGA used at cohort entry, diagnosis according to ICD-10 at cohort entry and mean treatment duration (entire study period) in months.

Data Source/Measurement

The data on all the patients identified were gathered from the registers of the nationwide database SIA/SUS. The files that make up the database are fragmented by state, year, and month. The records were linked by the National Health Card number for follow-up using deterministic linkage. There was no linkage with another database.

The first date of SGA provision identified in the SIA/SUS database during the period from January 1, 2008, to December 31, 2017, was considered as the cohort entry date. Some patients might already have received SGAs when they entered the cohort.

During the 10-year study period, all patients were followed up until the last patient record in the SIA/SUS or death. Our analysis did not exclude or censor any patient during the period of study.

Outcomes

The primary outcome was defined as the switch between SGAs. The switch was considered when a patient switched from an oral one SGA to another oral SGA. The following were considered as possible factors associated with SGA switching and that were available in the SIA/SUS: i) sex, ii) age, iii) year of cohort entry (2008–2017), iv) geographic region of residence; v) diagnosis according to ICD-10 codes, and vi) SGA used at study entry (clozapine, risperidone, quetiapine, ziprasidone and olanzapine).

Statistical Analysis

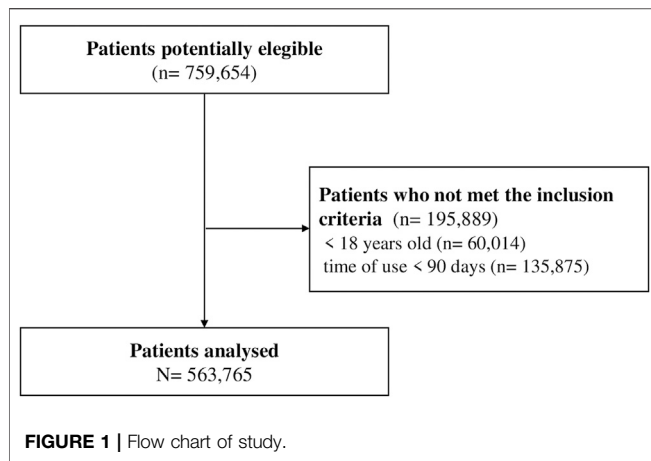
Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables as percentages only for descriptive statistics. Pearson's Chi squared test was performed to analyze correlations between switches and categorical variables. Incidence rates of switches were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratio. Absence of switches was estimated using the Kaplan-Meier method. Log rank test was used to assess the significance of differences between absence of switches curves. Cox regression analysis was performed to analyze the association of age, sex, year of cohort entry, geographic region of residence, diagnosis and SGA used at cohort entry. A multivariable Cox proportional-hazards regression model adjusted by all variables was used to examine the hazard ratios of the included factors.

The same procedure was repeated in the sensitivity analysis with patients who entered at cohort in 2009 to exclude eventual cases of patients who were using SGA before 2008. To assess the consistency of the multivariate model, the proportional-hazards assumption on the basis of Schoenfeld residuals was tested. If the model was not proportional, a comparison was made between the investigated factors using the restricted mean survival time.

All tests were two-tailed. Confidence intervals of 95% and a significance level of $p < 0.05$ were used. All statistical analyses were performed using Stata 14.2.

RESULTS

We identified 759,654 patients with schizophrenia or schizoaffective disorder who were on SGA provided by the



SUS from 2008 to 2017. From among these patients, 25.8% ($n = 195,889$) did not meet the inclusion criteria due to their age or time of use of SGA. A total of 563,765 patients met the inclusion criteria and were included in the cohort, **Figure 1**.

Most of the patients were women (51.6%), the mean patient age at study entry was 46.4 (± 18.6) years, lived in the south of Brazil (60.3%) and the most commonly diagnosed disorder was paranoid schizophrenia (78.2%). The most commonly used SGA at study entry was olanzapine (31.8%), followed by risperidone (29.2%), quetiapine (28.4%), ziprasidone (5.3%), and clozapine (5.2%). The mean follow-up duration was 27 months (IQR: 12.6–57.8), **Table 1**.

There were sex, age, residence region, and treatment length related differences in the frequency of the SGA used. Clozapine, olanzapine, and risperidone were the most often prescribed SGA among men in the entry of the study. The proportion of quetiapine and ziprasidone use among women was higher than that in men.

Quetiapine was more frequently used by elderly individuals aged higher than 60 years, and the frequency of use increased progressively with advancing age (60–69 years: 34.2%; 70–79 years: 48.6%; ≥ 80 years: 62.7%).

The frequency of SGA use differed among the various regions of Brazil. In the southeast region, quetiapine (32.4%) and risperidone (29.8%) were the most used, while in the northeast region, the most commonly used SGAs were olanzapine and risperidone. The median treatment duration varied from approximately 23 (IQR: 11.6–45.3) months for quetiapine to 36 (17.3–81.2) months for clozapine.

Almost all (99.9%) switched the SGA at least once during follow-up. Female sex, advanced age (> 70 years old), residence in the northeast region, study entry from 2009, and a diagnosis of schizoaffective disorders were associated with an increased risk of switching ($p < 0.001$ for each variable, **Table 2**). Compared to the adjusted hazard ratio for clozapine users, the corresponding ratios for risperidone, ziprasidone, quetiapine and olanzapine users were 1.59 (95% CI, 1.57–1.61), 1.41 (95% CI, 1.39–1.44), 1.25 (95% CI, 1.23–1.26), and 1.11 (95% CI, 1.10–1.12).

The incidence of switching was 58.2/100 person-years for risperidone users, followed by 57.6/100 person-year for

quetiapine users, 49.8/100 person-years for ziprasidone users, 43.5/100 person-years for olanzapine users and 37.6/100 person-years for clozapine users. Risperidone was associated with the highest risk of switching, while the corresponding risk associated with clozapine was the lowest.

Figure 2 shows the maintenance of the use of the same SGA during the follow-up period, with time without switching. Patients who used clozapine remained free from switching for a longer duration. In the sensitivity analysis (excluding patients from 2008), we did not identify any important differences in the findings. The result of the tests of proportional-hazards assumption was significant ($p < 0.05$). When repeating the analysis using the restricted mean survival time, the factors associated with switch of SGA were the same.

DISCUSSION

Main Findings

Increased risk of SGA switching was associated with female sex, advanced age, a diagnosis of schizoaffective disorder, and type of SGA used at study entry. Risperidone users were more likely to switch to another SGA, while clozapine users were less likely to switch than other users.

Comparison with Previous Studies

Switching antipsychotics is a common clinical practice in schizophrenia management (Sernyak et al., 2005; Kreyenbuhl et al., 2007; Nyhuis et al., 2010). Our findings confirmed this, and we found that the switches happened at least once in 10 years. The SGAs are similar in terms of effectiveness, except clozapine, but show significant differences in the tolerability profile and adverse reactions, which may explain the switch (Siskind et al., 2016; Preda and Bora, 2019).

Women were more likely to switch SGAs than were men. This finding is consistent with that in other studies (Barbui et al., 2005; Nyhuis et al., 2010) and could be attributed to sex differences and to the fact that women use more health services than do men and, in turn, could detect a suboptimal treatment response or serious adverse event early (Lindamer et al., 2003). There are sex differences in the tolerability and maintenance regimens of antipsychotics in patients with schizophrenia (Seeman, 2004; Barbui et al., 2005; Leotsakou et al., 2008). Women are less tolerant than men to antipsychotics (Barbui et al., 2005). Furthermore, women tend to report adverse effects, such as extrapyramidal and anticholinergic reactions, hyperprolactinemia, and weight gain, more frequently, whereas men report more sexual problems (Barbui et al., 2005; Schwartz et al., 2015; Alberich et al., 2019). Women and men could not be considered a homogenous group in the use of antipsychotics (Seeman, 2004).

Advanced age was another factor associated with switching, which conflicts with other findings, whose age group of switchers was between 42 and 55 years (Kreyenbuhl et al., 2007; Nyhuis et al., 2010). This discrepancy can be attributed to the size of our sample ($n = 563,765$). Our findings come from a large and representative sample (whose results were confirmed by a

TABLE 1 | Demographic and clinic characteristics of study participants according second-generation antipsychotics used.

Variables	Clozapine n = 29,466 (%)	Olanzapine n = 179,486 (%)	Risperidone n = 164,612 (%)	Quetiapine n = 159,989 (%)	Ziprasidone n = 30,212 (%)	Total 563,765
Sex						
Male	18,450 (6.7)	99,416 (36.4)	84,188 (30.8)	58,309 (21.3)	12,516 (4.6)	272,879
Female	11,016 (3.8)	80,070 (27.5)	80,424 (27.6)	101,680 (34.9)	17,696 (6.1)	290,886
Mean age (SD)	38.91 (±13.2)	42.65 (±16.1)	45.82 (±18.4)	54.42 (±20.6)	40.55 (±12.9)	46.61 (±18.6)
Age group at cohort entry (years)						
18–29	8,133 (7.1)	43,640 (37.9)	36,613 (31.8)	20,050 (17.4)	6,709 (5.8)	115,145
30–39	8,610 (7.2)	42,360 (35.7)	33,360 (28.1)	25,998 (21.9)	8,372 (7.0)	118,700
40–49	6,665 (5.9)	38,166 (33.9)	32,372 (28.8)	27,275 (24.3)	7,895 (7.0)	112,373
50–59	3,844 (4.5)	27,716 (32.7)	24,924 (29.5)	23,231 (27.5)	4,894 (5.8)	84,609
60–69	1,454 (3.0)	14,203 (29.2)	14,630 (30.1)	16,602 (34.2)	1,645 (3.4)	48,534
70–79	560 (1.3)	8,447 (19.5)	12,692 (29.3)	21,062 (48.6)	519 (1.2)	43,280
≥ 80	200 (0.5)	4,954 (12.0)	10,021 (24.4)	25,771 (62.7)	178 (0.4)	41,124
Race						
White	3,362 (5.3)	17,286 (27.2)	16,130 (25.4)	24,316 (38.2)	2,478 (3.9)	63,572
Black	208 (3.9)	1,898 (36.2)	1,547 (29.5)	1,345 (25.6)	248 (4.7)	5,246
Pardo	1,877 (5.6)	12,099 (36.1)	8,726 (26.0)	9,562 (28.5)	1,278 (3.8)	33,542
Yellow ^a	628 (5.3)	4,617 (39.1)	2,782 (23.5)	3,370 (28.5)	413 (3.5)	11,810
Indigenous	3 (3.9)	16 (21.0)	30 (39.5)	33 (43.4)	5 (6.6)	76
No information	23,388 (5.2)	143,570 (31.9)	135,397 (30.1)	121,374 (27.0)	25,790 (5.7)	449,519
Year of cohort entry						
2008	9,167 (7.3)	49,423 (39.2)	40,030 (31.8)	16,746 (13.3)	10,622 (8.4)	125,988
2009	1,816 (3.6)	15,753 (31.8)	16,296 (32.9)	12,053 (24.3)	3,659 (7.4)	49,577
2010	2,049 (4.2)	13,148 (26.7)	16,328 (33.2)	14,294 (29.1)	3,331 (6.8)	49,150
2011	2,480 (4.9)	12,284 (24.6)	18,139 (36.4)	13,991 (28.1)	2,983 (5.9)	49,877
2012	1,700 (4.1)	10,610 (25.8)	13,722 (33.3)	13,214 (32.1)	1,915 (4.6)	41,161
2013	1,903 (4.2)	13,084 (29.0)	12,942 (28.7)	15,432 (34.2)	1,745 (3.9)	45,106
2014	1,730 (3.7)	14,125 (30.0)	12,684 (26.9)	17,170 (36.5)	1,280 (2.7)	46,989
2015	3,060 (5.1)	19,525 (32.8)	13,154 (22.1)	21,954 (36.8)	1,883 (3.2)	59,576
2016	3,944 (6.4)	20,298 (32.7)	13,699 (22.1)	21,936 (35.4)	2,142 (3.4)	62,019
2017	1,617 (4.7)	11,236 (32.7)	7,618 (22.2)	13,199 (38.5)	652 (1.9)	34,322
Geographic region of residence at study entry						
South	7,448 (10.7)	22,792 (32.9)	22,139 (32.0)	12,830 (18.5)	3,929 (5.7)	69,138
Northeast	5,060 (5.0)	36,927 (36.7)	29,105 (28.9)	23,354 (23.2)	6,064 (6.0)	100,510
Southeast	13,522 (3.9)	97,447 (28.6)	101,323 (29.8)	110,155 (32.4)	17,834 (5.2)	340,281
North	735 (6.2)	5,079 (43.2)	3,448 (29.3)	2,097 (17.8)	393 (3.3)	11,752
Midwest	2,701 (6.4)	17,241 (40.9)	8,597 (20.4)	11,553 (27.4)	1,992 (4.7)	42,084
Diagnosis at cohort entry (ICD-10 codes)						
Paranoid schizophrenia (F20.0)	223,447 (5.3)	143,816 (32.6)	131,072 (29.7)	118,909 (26.9)	23,514 (5.3)	440,758
Hebephrenic schizophrenia (F20.1)	1,681 (10.6)	5,329 (33.6)	4,098 (25.9)	3,712 (23.4)	1,014 (6.4)	15,834
Catatonic schizophrenia (F20.2)	207 (8.2)	898 (35.6)	696 (27.6)	583 (23.1)	140 (5.5)	2,524
Undifferentiated schizophrenia (F20.3)	806 (5.7)	4,370 (30.9)	3,687 (26.0)	4,452 (31.4)	840 (5.9)	14,155
Post-schizophrenic depression (F20.4)	74 (2.4)	688 (22.3)	657 (21.3)	1,510 (48.9)	159 (5.1)	3,088
Residual schizophrenia (F20.5)	1,397 (7.6)	6,369 (34.6)	4,824 (26.2)	4,320 (23.4)	1,516 (8.2)	18,426
Simple schizophrenia (F20.6)	212 (3.5)	1,786 (29.5)	2,027 (33.5)	1,693 (28.0)	327 (5.4)	6,045
Other schizophrenia (F20.8)	1,487 (2.5)	14,940 (25.7)	16,727 (28.8)	22,329 (38.5)	2,544 (4.4)	58,027
Schizoaffective disorder, manic type (F25.0)	75 (4.2)	480 (27.2)	293 (16.6)	876 (49.7)	39 (2.2)	1,763
Schizoaffective disorder, depressive type (F25.1)	28 (1.6)	419 (24.8)	308 (18.3)	874 (51.8)	57 (3.4)	1,686
Schizoaffective disorder, mixed type (F25.2)	52 (3.5)	391 (26.8)	223 (15.3)	731 (50.1)	62 (4.2)	1,459
Median treatment duration (in months) (IQR)	36.4 (17.3–81.2)	30.9 (14.5–65.7)	26.6 (12.1–56.7)	23.5 (11.6–45.3)	34.6 (15.2–75.0)	27.4 (12.6–57.8)

^aYellow include Asiatic patients and their descendants.

sensitivity analysis adjusted for several confounders), which differ from studies with smaller samples that did not find an association with advanced age. Another study showed that advanced age reduced the likelihood of switching overall which was attributed

to some hypotheses like greater clinical stability or low clinician expectations of potential benefit of antipsychotics switch in older people (Sernyak et al., 2005). But more researches are needed to elucidate it.

TABLE 2 | Factors associated with second generation antipsychotics switch.

Variables	N	Incidence of switches ^a	Hazard Ratio 95% CI not adjusted	p value	Hazard Ratio 95% CI Adjusted ^b	p value	Hazard Ratio 95% CI Sensitivity analysis ^c	p value
Sex								
Males	272,879	0.48	1.00		1.00		1.00	
Females	290,886	0.53	1.10 (1.09–1.11)	<0.001	1.05 (1.05–1.06)	<0.001	1.05 (1.04–1.06)	<0.001
Age group at study entry (years)								
18–29	115,145	0.50	1.00		1.00		1.00	
30–39	118,700	0.48	0.95 (0.94–0.96)	<0.001	0.94 (0.93–0.94)	<0.001	0.93 (0.92–0.94)	<0.001
40–49	112,373	0.46	0.92 (0.91–0.93)	<0.001	0.90 (0.89–0.90)	<0.001	0.89 (0.88–0.90)	<0.001
50–59	84,609	0.48	0.97 (0.96–0.98)	<0.001	0.89 (0.88–0.90)	<0.001	0.87 (0.86–0.88)	<0.001
60–69	48,534	0.52	1.04 (1.03–1.06)	<0.001	0.92 (0.91–0.93)	<0.001	0.89 (0.88–0.90)	<0.001
70–79	43,280	0.59	1.18 (1.17–1.19)	<0.001	1.03 (1.01–1.04)	<0.001	0.98 (0.97–0.99)	0.021
≥ 80	41,124	0.68	1.36 (1.34–1.38)	<0.001	1.14 (1.12–1.15)	<0.001	1.09 (1.08–1.11)	<0.001
Year of cohort entry								
2008	125,988	0.33	1.00		1.00			
2009	49,577	0.41	1.36 (1.34–1.37)	<0.001	1.32 (1.31–1.34)	<0.001	1.00	
2010	49,150	0.44	1.51 (1.49–1.53)	<0.001	1.45 (1.43–1.46)	<0.001	1.17 (1.15–1.18)	<0.001
2011	49,877	0.45	1.58 (1.57–1.60)	<0.001	1.56 (1.54–1.57)	<0.001	1.32 (1.31–1.34)	<0.001
2012	41,161	0.50	1.79 (1.77–1.81)	<0.001	1.74 (1.72–1.76)	<0.001	1.52 (1.50–1.54)	<0.001
2013	45,106	0.54	1.97 (1.95–1.99)	<0.001	1.91 (1.89–1.93)	<0.001	1.72 (1.70–1.75)	<0.001
2014	46,989	0.65	2.41 (2.38–2.43)	<0.001	2.35 (2.32–2.38)	<0.001	2.20 (2.17–2.23)	<0.001
2015	59,576	0.74	2.77 (2.74–2.80)	<0.001	2.80 (2.77–2.83)	<0.001	2.69 (2.66–2.73)	<0.001
2016	62,019	0.95	3.76 (3.72–3.80)	<0.001	3.85 (3.81–3.89)	<0.001	3.84 (3.79–3.90)	<0.001
2017	34,322	1.86	9.59 (9.46–9.72)	<0.001	9.50 (9.37–9.63)	<0.001	9.81 (9.66–9.97)	<0.001
Geographic region of residence at study entry								
South	69,138	0.47	1.00		1.00		1.00	
Northeast	100,510	0.60	1.29 (1.28–1.30)	<0.001	1.31 (1.30–1.33)	<0.001	1.37 (1.36–1.39)	<0.001
Southeast	340,281	0.48	1.06 (1.05–1.07)	<0.001	1.12 (1.11–1.13)	<0.001	1.18 (1.17–1.20)	<0.001
North	11,752	0.53	1.16 (1.14–1.18)	<0.001	1.26 (1.23–1.28)	<0.001	1.33 (1.30–1.36)	<0.001
Midwest	42,084	0.50	1.09 (1.07–1.10)	<0.001	1.12 (1.11–1.13)	<0.001	1.18 (1.16–1.20)	<0.001
Diagnosis at study entry (ICD-10 codes)								
Paranoid schizophrenia (F20.0)	440,758	0.49	1.00		1.00		1.00	
Hebephrenic schizophrenia (F20.1)	15,834	0.47	0.94 (0.92–0.95)	<0.001	0.93 (0.91–0.94)	<0.001	0.92 (0.91–0.94)	<0.001
Catatonic schizophrenia (F20.2)	2,524	0.48	0.97 (0.93–1.00)	0.13	0.99 (0.95–1.03)	0.71	0.97 (0.93–1.02)	0.35
Undifferentiated schizophrenia (F20.3)	14,155	0.52	1.05 (1.03–1.07)	<0.001	0.98 (0.96–0.99)	0.02	0.98 (0.96–0.99)	0.03
Post-schizophrenic depression (F20.4)	3,088	0.50	1.00 (0.97–1.04)	0.64	0.95 (0.92–0.98)	0.01	0.97 (0.94–1.01)	0.24
Residual schizophrenia (F20.5)	18,426	0.44	0.89 (0.88–0.90)	<0.001	0.90 (0.89–0.92)	<0.001	0.90 (0.88–0.91)	<0.001
Simple schizophrenia (F20.6)	6,045	0.54	1.08 (1.05–1.10)	<0.001	0.99 (0.96–1.01)	0.56	0.99 (0.96–1.02)	0.62
Other schizophrenia (F20.8)	58,027	0.55	1.10 (1.09–1.11)	<0.001	1.01 (1.00–1.02)	0.001	1.02 (1.01–1.03)	<0.001
Schizoaffective disorder, manic type (F25.0)	1,763	1.13	2.26 (2.15–2.36)	<0.001	1.09 (1.04–1.14)	<0.001	1.11 (1.05–1.16)	<0.001
Schizoaffective disorder, depressive type (F25.1)	1,686	1.10	2.19 (2.09–2.30)	<0.001	1.10 (1.05–1.16)	<0.001	1.13 (1.07–1.18)	<0.001
Schizoaffective disorder, mixed type (F25.2)	1,459	1.08	2.13 (2.02–2.24)	<0.001	1.11 (1.05–1.17)	<0.001	1.13 (1.07–1.19)	<0.001
SGA used at study entry								
Clozapine	29,466	0.37	1.00		1.00		1.00	
Olanzapine	179,486	0.43	1.15 (1.14–1.17)	<0.001	1.11 (1.10–1.12)	<0.001	1.08 (1.06–1.10)	<0.001
Risperidone	164,612	0.58	1.58 (1.56–1.60)	<0.001	1.59 (1.57–1.61)	<0.001	1.52 (1.50–1.54)	<0.001
Quetiapine	159,989	0.57	1.56 (1.54–1.58)	<0.001	1.25 (1.23–1.26)	<0.001	1.17 (1.15–1.19)	<0.001
Ziprasidone	30,212	0.47	1.29 (1.27–1.31)	<0.001	1.41 (1.39–1.44)	<0.001	1.36 (1.33–1.39)	<0.001

^aIncidence/100 patients-years.^bAdjusted by all variables.^cAdjusted by all variables without 2008 year.

Residents of the northeast region of Brazil were more likely to switch SGAs, which may reflect of socioeconomic factors. The northeast region is one of the poorest regions in Brazil, with high rates of unemployment, illiteracy, and poor basic sanitation. It succeeds the southeastern part in the number of schizophrenia cases in Brazil and is considered a vulnerable region in terms of the development of this disease, and treatment gaps and non-adherence (Dornelas et al., 2019). Although the country offers

universal coverage, there is a shortage of doctors and specialized health professionals in certain regions, (Oliveira et al., 2017), as well as a lack of availability of medicines, with the northeast and northern regions being the most affected. Inadequate availability of psychiatrists and nurses in mental health facilities are considered a significant predictor of treatment gap (Lora et al., 2012).

The subtypes of schizophrenia are generally not studied separately and studies involving patients with schizophrenia

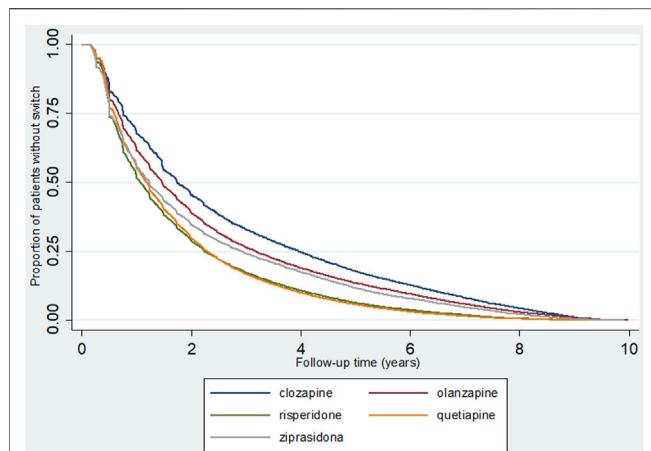


FIGURE 2 | Maintenance of the use of the same antipsychotic (without switch) during the study period, Kaplan-Meier curve.

also include patients with schizoaffective disorder (Brazil, 2014a; Leposavic et al., 2015; Mattila et al., 2015). Although it did not seem predictor of treatment response (Mattila et al., 2015), a diagnosis of schizoaffective disorders, compared to that of paranoid schizophrenia, was likely to be associated with SGA switching, as found in our study. Although relevant data are scarce and evidences pertaining to schizophrenia also includes evidence pertaining to schizoaffective disorders, the effectiveness and tolerability profile of SGAs may differ across these conditions (Murru et al., 2016).

The use of risperidone was associated with a higher risk to switching in our cohort. Despite widespread use, low price, and no clear differences in effectiveness compared to those of other SGAs risperidone produces more movement disorders and prolactin increase than do other SGAs (Komossa et al., 2011). In a study conducted among schizophrenia outpatients, in 37 countries ($n = 17,000$ patients) in which the switches from risperidone to olanzapine and vice versa were compared, patients who switched from risperidone to olanzapine exhibited more favorable outcomes and remained on the medication longer (Hong et al., 2012). In another systematic review (15 studies, $n = 7760$ patients), a comparison between SGAs showed that risperidone was slightly less acceptable than olanzapine (Komossa et al., 2011).

Patients using clozapine switched less than did patients using other SGAs. Meta-analyses have shown that clozapine is more effective than other SGAs, being superior for positive symptoms in the short and long term (Asenjo Lobos et al., 2010; Siskind et al., 2016). Regarding negative symptoms, clozapine was superior only in the short term (Siskind et al., 2016). A cohort study conducted in Sweden among patients ($n = 26,046$) diagnosed with schizophrenia and using antipsychotics showed that clozapine users were most likely to refill prescriptions and had lower rates of re-hospitalization and death by suicide (Ringback Weitof et al., 2014). Other studies also highlighted that the adherence rate was significantly higher in patients treated with clozapine (Cooper et al., 2007; Ascher-Svanum et al., 2008).

These significant clinical benefits may have contributed to clozapine users switching less than other SGA users in our cohort.

However, clozapine is used less frequently and later in treatment. Studies have shown that there are long delays in starting treatment with clozapine in resistant patients (Wheeler, 2008; Howes et al., 2012; Alessi-Severini et al., 2013). Guidelines for schizophrenia treatment do not recommend clozapine as the first option (Brazil, 2013; Kuipers, 2014; Remington et al., 2017; Preda and Bora, 2019). It is offered only to patients who have not responded adequately to adequate doses of at least two different antipsychotics. This is probably due to the risk of inducing agranulocytosis (almost 1%), which can be fatal, and the need for closer monitoring (Preda and Bora, 2019; Van Zuuren, 2019). Other concerns include the risk of cardiovascular diseases. To ensure a balance between effectiveness and safety and considering real-world information about the use of clozapine in outpatients, guidelines could be reviewed and different recommendations could be made.

Strengths and Limitations of the Study

This is the first national cohort study that assessed the factors associated with switching of SGAs dispensed by the Brazilian public sector over 10 years. The use of a nationwide pharmaceutical database allowed us to investigate a large quantity of data on the use of antipsychotics in real-life and to obtain a representative and very large patient population with schizophrenia. Our clear and comprehensive methodology led to robust findings to the public health which could direct future researches.

There are some limitations of this study. First, despite the reliability of the data, the diagnoses were not validated. Second, SIA/SUS is an administrative database that does not consider dispensation from private pharmacies, which could lead to an underestimation of the use of these antipsychotics. Nevertheless, APAC/SIA covers more than 70% of the Brazilian population (more than 148 million inhabitants). Third, as an administrative database, it is not intended for research purposes and may have system data feed errors. However, we carefully checked data inconsistencies to avoid this type of bias and excluded patients who received antipsychotics only once or for less than 90 days. Fourth, detailed clinical data, comorbidities, use of concomitant drugs, as well as the reasons that determined the switches are unavailable because the original purpose of this database is to register the consumption, the charge, and the payment of dispensing high-cost medicines.

CONCLUSION

This nationwide cohort study elucidated the factors associated with SGAs switching in a real-world setting. The choice of the prescribed antipsychotic can determine the trend for switching and affect the long and short-term outcomes for patients with life-long disorders. The findings of our study have implications for future research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study used only secondary no identifiable data from unrestricted access, obtained from the national administrative database, therefore ethical review and approval as well written informed consent were not required for the study on human participants in accordance with the local legislation and institutional requirements.

REFERENCES

- Alberich, S., Fernández-Sevillano, J., González-Ortega, I., Usall, J., Sáenz, M., González-Fraile, E., et al. (2019). A Systematic Review of Sex-Based Differences in Effectiveness and Adverse Effects of Clozapine. *Psychiatry Res.* 280, 112506. doi:10.1016/j.psychres.2019.112506
- Alessi-Severini, S., Le Dorze, J. A., Nguyen, D., Honcharik, P., and Eleff, M. (2013). Clozapine Prescribing in a Canadian Outpatient Population. *PLoS One* 8, e83539. doi:10.1371/journal.pone.0083539
- Ascher-Svanum, H., Zhu, B., Faries, D. E., Lacro, J. P., Dolder, C. R., and Peng, X. (2008). Adherence and Persistence to Typical and Atypical Antipsychotics in the Naturalistic Treatment of Patients with Schizophrenia. *Patient Prefer. Adherence* 2, 67–77. doi:10.2147/ppa.s2940
- Asenjo Lobos, C., Komossa, K., Rummel-Kluge, C., Hunger, H., Schmid, F., Schwarz, S., et al. (2010). Clozapine versus Other Atypical Antipsychotics for Schizophrenia. *Cochrane Database Syst. Rev.* 11, Cd006633. doi:10.1002/14651858.cd006633.pub2
- Barbosa, W. B., Costa, J. d. O., De Lemos, L. L. P., Gomes, R. M., De Oliveira, H. N., Ruas, C. M., et al. (2018). Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil. *Appl. Health Econ. Health Pol.* 16, 697–709. doi:10.1007/s40258-018-0408-4
- Barbui, C., Nosè, M., Bindman, J., Schene, A., Becker, T., Mazzi, M. A., et al. (2005). Sex Differences in the Subjective Tolerability of Antipsychotic Drugs. *J. Clin. Psychopharmacol.* 25, 521–526. doi:10.1097/01.jcp.0000185423.15891.02
- Benchimol, E. I., Smeeth, L., Guttman, A., Harron, K., Moher, D., Petersen, I., et al. (2015). RECORD Working Committee. The REporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement. *PLoS Med.* 12 (10), e1001885. doi:10.1371/journal.pmed.1001885
- Bernardo, M., Vieta, E., Saiz Ruiz, J., Rico-Villademoros, F., Álamo, C., and Bobes, J. (2011). Recommendations for Switching Antipsychotics. A Position Statement of the Spanish Society of Psychiatry and the Spanish Society of Biological Psychiatry. *Revista de Psiquiatría y Salud Ment. (English Edition)* 4, 150–168. doi:10.1016/j.rpsmen.2011.07.001
- Brazil (2008). *Rede Interagencial de Informação para a Saúde. Indicadores básicos para a saúde no Brasil: conceitos e aplicações/Rede Interagencial de Informação para a Saúde. Brasília: Organização Pan-Americana de Saúde.* 349.
- Brazil (2013). Protocolo clínico e diretrizes terapêuticas Esquizofrenia. Available at: <http://portal.arquivos.saude.gov.br/images/pdf/2014/abril/02/pcdt-esquizofrenia-livro-2013.pdf> (Accessed Nov 12, 2019).
- Brazil (2014a). Protocolo clínico e diretrizes clínicas. Transtorno Esquizoafetivo. Available at: <http://conitec.gov.br/images/Protocolos/TranstornoEsquizoafetivo.pdf> (Accessed Nov 12, 2019).
- Brazil (2014b). Financiamento da Saúde: à espera de resgate. Revista de audiências públicas. Available at: www.senado.gov.br/noticias/jornal/emdiscussao/Upload/201401-fevereiro/pdf/em_discussao%21-fevereiro_2014_internet.pdf (Accessed March 10, 2021).
- Buckley, P. F., and Correll, C. U. (2008). Strategies for Dosing and Switching Antipsychotics for Optimal Clinical Management. *J. Clin. Psychiatry* 69 (Suppl. 1), 4–17.

AUTHOR CONTRIBUTIONS

IF and LL were responsible for the study concept and design. MS and IF extracted the data and performed the statistical analysis. IF and LL drafted the manuscript. All authors were responsible for critical revision of the manuscript and have accepted the final version.

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- Cerovecki, A., Musil, R., Klimke, A., Seemüller, F., Haen, E., Schennach, R., et al. (2013). Withdrawal Symptoms and Rebound Syndromes Associated with Switching and Discontinuing Atypical Antipsychotics: Theoretical Background and Practical Recommendations. *CNS Drugs* 27, 545–572. doi:10.1007/s40263-013-0079-5
- Cooper, D., Moisan, J., and Grégoire, J.-P. (2007). Adherence to Atypical Antipsychotic Treatment Among Newly Treated Patients. *J. Clin. Psychiatry* 68, 818–825. doi:10.4088/jcp.v68n0601
- Correll, C. U. (2010). From Receptor Pharmacology to Improved Outcomes: Individualising the Selection, Dosing, and Switching of Antipsychotics. *Eur. Psychiatr.* 25 (Suppl. 2), S12–S21. doi:10.1016/s0924-9338(10)71701-6
- Dornelas, L. T. S. D., Dornelas, C. R. S., De Melo, G. F., Souza, N. B., and Faria, T. A. V. (2019). Fatores socioeconômicos e esquizofrenia nas regiões brasileiras. *Revista Científica Online* 11, 8p.
- Faries, D. E., Ascher-Svanum, H., Nyhuis, A. W., and Kinon, B. J. (2009). Clinical and Economic Ramifications of Switching Antipsychotics in the Treatment of Schizophrenia. *BMC Psychiatry* 9, 54. doi:10.1186/1471-244x-9-54
- Ganguli, R. (2002). Rationale and Strategies for Switching Antipsychotics. *Am. J. Health Syst. Pharm.* 59, S22–S26. doi:10.1093/ajhp/59.suppl_8.s22
- Hong, J., Novick, D., Brugnoli, R., Karagianis, J., Dossenbach, M., and Haro, J. M. (2012). Clinical Consequences of Switching from Olanzapine to Risperidone and Vice Versa in Outpatients with Schizophrenia: 36-month Results from the Worldwide Schizophrenia Outpatients Health Outcomes (W-SOHO) Study. *BMC Psychiatry* 12, 218. doi:10.1186/1471-244x-12-218
- Howes, O. D., Vergunst, F., Gee, S., McGuire, P., Kapur, S., and Taylor, D. (2012). Adherence to Treatment Guidelines in Clinical Practice: Study of Antipsychotic Treatment Prior to Clozapine Initiation. *Br. J. Psychiatry* 201, 481–485. doi:10.1192/bjp.bp.111.105833
- Keks, N., Schwartz, D., and Hope, J. (2019). Stopping and Switching Antipsychotic Drugs. *Aust. Prescr.* 42, 152–157. doi:10.18773/austprescr.2019.052
- Komossa, K., Rummel-Kluge, C., Schwarz, S., Schmid, F., Hunger, H., Kissling, W., et al. (2011). Risperidone versus Other Atypical Antipsychotics for Schizophrenia. *Cochrane Database Syst. Rev.* 1, Cd006626. doi:10.1002/14651858.cd006626.pub2
- Kreyenbuhl, J., Marcus, S. C., West, J. C., Wilk, J., and Olfson, M. (2007). Adding or Switching Antipsychotic Medications in Treatment-Refractory Schizophrenia. *Psychiatr. Serv.* 58, 983–990. doi:10.1176/ps.2007.58.7.983
- Kuipers, E. E. A. (2014). *Psychosis and Schizophrenia in Adults. Treatment and Management. The Nice Guideline on Treatment and Management.* London, UK: National Institute for Health and Care Excellence.
- Leotsakou, C., Sardis, A., and Paterakis, P. (2008). Sex Differences in Side Effects of Second-Generation Antipsychotics. *Ann. Gen. Psychiatry* 7, S106. doi:10.1186/1744-859x-7-s1-s106
- Leposavic, L., Leposavic, I., Saula-Marojevic, B., and Gavrilovic, P. (2015). Paranoid Schizophrenia versus Schizoaffective Disorder: Neuropsychological Aspects. *Srp Arh. Celok. Lek* 143, 391–396. doi:10.2298/sarh1508391l
- Lindamer, L. A., Bailey, A., Hawthorne, W., Folsom, D. P., Gilmer, T. P., Garcia, P., et al. (2003). Gender Differences in Characteristics and Service Use of Public Mental Health Patients with Schizophrenia. *Psychiatr. Serv.* 54, 1407–1409. doi:10.1176/appi.ps.54.10.1407

- Lindner, L. M., Marasciulo, A. C., Farias, M. R., and Grohs, G. E. M. (2009). Avaliação econômica Do tratamento da esquizofrenia com antipsicóticos no Sistema Único de Saúde. *Rev. Saúde Pública* 43, 62–69. doi:10.1590/s0034-89102009000800010
- Lora, A., Kohn, R., Levav, I., Mcbain, R., Morris, J., and Saxena, S. (2012). Service Availability and Utilization and Treatment Gap for Schizophrenic Disorders: a Survey in 50 Low- and Middle-Income Countries. *Bull. World Health Organ.* 90, 47–54B. doi:10.2471/blt.11.089284
- Mattila, T., Koeter, M., Wohlfarth, T., Storosum, J., Van Den Brink, W., De Haan, L., et al. (2015). Impact of DSM-5 Changes on the Diagnosis and Acute Treatment of Schizophrenia. *Schizophr Bull.* 41, 637–643. doi:10.1093/schbul/sbu172
- Murru, A., Hidalgo, D., Bernardo, M., Bobes, J., Saiz-Ruiz, J., Álamo, C., et al. (2016). Antipsychotic Switching in Schizoaffective Disorder: A Systematic Review. *World J. Biol. Psychiatry* 17, 495–513. doi:10.3109/15622975.2015.1012225
- Nyhuis, A. W., Faries, D. E., Ascher-Svanum, H., Stauffer, V. L., and Kinon, B. J. (2010). Predictors of Switching Antipsychotic Medications in the Treatment of Schizophrenia. *BMC Psychiatry* 10, 75. doi:10.1186/1471-244x-10-75
- Oliveira, A. P. C. D., Gabriel, M., Poz, M. R. D., and Dussault, G. (2017). Desafios para assegurar a disponibilidade e acessibilidade à assistência médica no Sistema Único de Saúde. *J. Ciência Saúde Coletiva* 22, 1165–1180. doi:10.1590/1413-81232017224.31382016
- Preda, A., and Bora, R. G. (2019). Esquizofrenia. BMJ Best Practice. Available at: <https://bestpractice-bmj-com.libaccess.lib.mcmaster.ca/topics/en-gb/406/pdf/406.pdf> (Accessed Nov 12, 2019).
- Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., and Teehan, M. (2017). Guidelines for the Pharmacotherapy of Schizophrenia in Adults. *Can. J. Psychiatry* 62, 604–616. doi:10.1177/0706743717720448
- Ringbäck Weitof, G., Berglund, M., Lindström, E. A., Nilsson, M., Salmi, P., and Rosén, M. (2014). Mortality, Attempted Suicide, Re-hospitalisation and Prescription Refill for Clozapine and Other Antipsychotics in Sweden-a Register-Based Study. *Pharmacoepidemiol. Drug Saf.* 23, 290–298. doi:10.1002/pds.3567
- Santos, A., Piassi, I., Godói, I., Vidal, C., and Ruas, C. (2017). Economic Evaluation of Antipsychotics for the Treatment of Schizophrenia: a Systematic Review. *Jbes* 9, 207–228. doi:10.21115/jbes.v9.n2.p207-28
- Schwartz, E., Charlotte, M., Slade, E., Medoff, D., Li, L., Dixon, L., et al. (2015). Gender Differences in Antipsychotics Prescribed to Veterans with Serious Mental Illness. *Gen. Hosp. Psychiatry* 37, 347–351. doi:10.1016/j.genhosppsych.2015.03.018
- Seeman, M. V. (2004). Gender Differences in the Prescribing of Antipsychotic Drugs. *Ajp* 161, 1324–1333. doi:10.1176/appi.ajp.161.8.1324
- Sernyak, M. J., Leslie, D., and Rosenheck, R. (2005). Predictors of Antipsychotic Medication Change. *J. Behav. Health Serv. Res.* 32, 85–94. doi:10.1007/bf02287330
- Siskind, D., McCartney, L., Goldschlager, R., and Kisely, S. (2016). Clozapine V. First- and Second-Generation Antipsychotics in Treatment-Refractory Schizophrenia: Systematic Review and Meta-Analysis. *Br. J. Psychiatry* 209, 385–392. doi:10.1192/bjp.bp.115.177261
- Stroup, T. S., and Gray, N. (2018). Management of Common Adverse Effects of Antipsychotic Medications. *World Psychiatry* 17, 341–356. doi:10.1002/wps.20567
- Van Zuuren, E. J. (2019). Schizophrenia. Available at: <https://www.dynamed.com/condition/schizophrenia> (Accessed Nov 12, 2019).
- Wheeler, A. J. (2008). Treatment Pathway and Patterns of Clozapine Prescribing for Schizophrenia in New Zealand. *Ann. Pharmacother.* 42, 852–860. doi:10.1345/aph.1k662
- Xu, L., and Krishnaswamy, S. (2018). Switch-associated Adverse Events: Focus on Olanzapine. *Australas. Psychiatry* 26, 635–639. doi:10.1177/1039856218810166

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patient Explanation of Adherence and Non-Adherence to Venous Leg Ulcer Treatment: A Qualitative Study

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The aim of this study was to understand which factors influence patients' adherence to venous leg ulcer treatment recommendations in primary care. We adopted a qualitative study design, conducting phone interviews with 31 people with venous leg ulcers in Melbourne, Australia. We conducted 31 semi-structured phone interviews between October and December 2019 with patients with clinically diagnosed venous leg ulcers. Participants recruited to the Aspirin in Venous Leg Ulcer Randomized Control Trial and Cohort study were invited to participate in a qualitative study, which was nested under this trial. We applied the Theoretical Domains Framework to guide the data analysis. The following factors influenced patients' adherence to venous leg ulcer treatment: understanding the management plan and rationale behind treatment (Knowledge Domain); compression-related body image issues (Social Influences); understanding consequences of not wearing compression (Beliefs about Consequences); feeling overwhelmed because it's not getting better (Emotions); hot weather and discomfort when wearing compression (Environmental Context and Resources); cost of compression (Environmental Context and Resources); ability to wear compression (Beliefs about Capabilities); patience and persistence (Behavioral Regulation); and remembering self-care instructions (Memory, Attention and Decision Making). The Theoretical Domains Framework was useful for identifying factors that influence patients' adherence to treatment recommendations for venous leg ulcers management. These factors may inform development of novel interventions to optimize shared decision making and self-care to improve healing outcomes. The findings from this article will be relevant to clinicians involved in management of patients with venous leg ulcers, as their support is crucial to patients' treatment adherence. Consultation with patients about VLU treatment adherence is an opportunity for clinical practice to be targeted and collaborative. This process may inform guideline development.

Keywords: venous leg ulcer, patient experience, evidence-based guidelines, Theoretical Domains Framework, adherence—compliance—persistence

INTRODUCTION

Venous leg ulcers (VLU) are chronic skin ulcers and are the most common chronic wound of the lower limbs in Australian primary care settings (Pacella et al., 2018). VLU are classified as C6 stage of a chronic venous disorder, as per the updated Clinical (C) version of Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification (Lurie et al., 2020). They are caused by chronic venous

insufficiency due to persistent high blood pressure in varicose veins (Meulendijks et al., 2019; Weller et al., 2019). Best practice management recommendations for people with VLU are compression, leg elevation, physical exercise and adequate nutrition (Australian Wound Management Association New Zealand Wound Care Society, 2011).

The estimated VLU prevalence globally is between 1 and 3% of people (Graves and Zheng, 2014b; Domingues et al., 2018; Xie et al., 2018). Chronic wounds represent a considerable social and economic burden (KPMG, 2013; Graves and Zheng, 2014a), with an estimated annual cost of AUD \$3 billion in Australia (Graves and Zheng, 2014), \$32 billion in the United States (Nussbaum et al., 2018) and £50 million in the United Kingdom (Guest et al., 2017). Despite this burden, there is no international consensus on the best strategies for prevention and management of VLU (Franks et al., 2016; Weller et al., 2019). To address this health issue in Australia, the Australian and New Zealand Clinical Practice Guidelines (CPG) for the prevention and Management of Venous Leg Ulcers (Australian Wound Management Association New Zealand Wound Care Society, 2011), (herein referred to as VLU CPG) was published in 2011. Despite the development and dissemination of VLU CPG (Australian Wound Management Association New Zealand Wound Care Society, 2011), a significant number of VLU remain unhealed (Franks et al., 2016), warranting further consideration of contributing factors to develop solutions to this silent epidemic (Pacella et al., 2018). The challenges faced when managing people with VLU are not unique to Australia (Franks et al., 2016). Compression use, as an example, has been reported as being problematic across Switzerland (Probst et al., 2020) and the United Kingdom (Guest et al., 2018).

Current best practice recommendations include assessment and diagnostic evaluation of the lower limb to exclude arterial causes prior to compression application (Weller et al., 2018), including venous ultrasound and/or assessment of Ankle Brachial Pressure Index (ABPI). Once arterial insufficiency is excluded, below knee multi-layer compression therapy is recommended (Andriessen et al., 2017; O'Meara et al., 2013). In instances where there is unclear aetiology or if the ulcer is not healed after three months of treatment, VLU CPG recommends the patient be referred to a specialized wound clinic (Australian Wound Management Association New Zealand Wound Care Society, 2011). In addition to recommendations surrounding assessment and compression, VLU CPG (Australian Wound Management Association New Zealand Wound Care Society, 2011) distinguishes the importance of preparing the VLU patients sufficiently and enabling them to co-participate and share in decision making in wound management (Ritchie and Taylor, 2018). Patients with VLUs would usually consult their GP in the first place. The support-seeking pathway that VLU patients are supposed to follow includes initial consultation by a GP, who should perform clinical assessment, including vascular assessment to exclude arterial involvement. In absence of arterial involvement, compression therapy should be prescribed and other recommendations provided, including leg elevation, adequate nutrition, pain management and physical exercise, as indicated in the guidelines (Australian Wound

Management Association New Zealand Wound Care Society, 2011). In absence of healing improvement over three months, patients should be referred to tertiary clinic for assessment. Clinicians' limited awareness about these guidelines, reliance on their clinical experience and suggestions from colleagues rather than clinical guidelines, and their limited skills in ABPI measurement and health system organisational issues, including absence of duplex ultrasound in some practices, lead to suboptimal management of patients with VLUs (Weller et al., 2019; Weller et al., 2020).

Optimal VLU treatment is collaborative, with patients tasked with specific self-care actions at home after VLU care tasks are demonstrated by clinicians in the clinical setting. These tasks may include, although will not be limited to compression application. Although patients usually attend regular scheduled review appointments, wound care is often done at home independently (Walburn et al., 2017). Current management of VLU continues to challenge patients and clinicians with reports of suboptimal VLU treatment (Franks et al., 2016). A recent study of data from the Bettering the Evaluation and Care of Health (BEACH) program reported only 2.1% of VLU patients are treated with compression (Gethin et al., 2020). Furthermore, another study reported greater proportion of health professionals were unaware of the VLU CPG (Weller et al., 2020). Australia has limited available means for monitoring patterns and quality of care for people diagnosed with VLU as there is no clinical VLU registry (Weller and Evans, 2014) and, as a result, there is variation in the way VLU is managed in primary care settings. Clinician barriers to using and implementing evidence-based interventions for VLU treatment include limited awareness of the VLU CPG, organisational barriers, and suboptimal knowledge and skills of VLU management (Weller et al., 2019; Weller et al., 2020).

Clinicians reported patient adherence to VLU management plans was a key area of concern (Weller et al., 2020), specifically the application and long term use of compression therapy (Probst et al., 2019; Probst et al., 2020). Compression discomfort or pain (Boxall et al., 2019) can impact on compression adherence. Insufficient understanding of the benefits of compression treatment may contribute to non-adherence (Jull et al., 2004; Probst et al., 2020). The consequences of non-adherence to treatment recommendations include chronicity of VLUs, increased recurrence rate (Finlayson et al., 2018), infection (Bui et al., 2019) and secondary squamous cell carcinoma (Reich-Schupke et al., 2015). Disease progression (Meulendijks et al., 2020) and associated complications exacerbate wound pain (Leren et al., 2020), increase wound exudate, and reduce patients' mobility, which in turn contributes to disease progression (Meulendijks et al., 2019), leads to premature disability (Mallick et al., 2020), and inadvertently influences patients' quality of life (Barnsbee et al., 2019). Management of these complications require complex interventions and highlights the need for optimal care for this underestimated condition.

Adherence to evidence-based VLU management is not limited to compression use; education based interventions may improve adherence to leg elevation (Brooks et al., 2004) and therapeutic physical exercises (Kelechi et al., 2014). Despite this, clinician advice and education on VLU management is offered to less

than 3.6% of VLU patients who attended primary health settings (Gethin et al., 2020). Few studies have examined the patient experience of adhering to VLU treatment (Weller et al., 2016) and patient education needs have yet to be fully understood (Shanley et al., 2020). Understanding patients' behavior related to treatment adherence is important in planning and developing effective evidence-based interventions on VLU management (Presseau et al., 2019); and high-quality qualitative studies are required in order to understand patient behavior and to develop successful interventions. The aim of this study was to understand which barriers and enablers influence patients' adherence to venous leg ulcer treatment recommendations in primary care settings.

MATERIALS AND METHODS

Aim/s

The aim of this study was to understand barriers and enablers influencing patients' adherence to venous leg ulcer treatment recommendations in primary care settings.

Design

We adopted a qualitative study design, and conducted 31 semi-structured phone interviews with VLU patients, who had participated in the Aspirin in Venous Leg Ulcer (ASPiVLU) clinical trial (Weller et al., 2016). The ASPiVLU study was a randomized, double-blinded, multicentre, placebo-controlled trial, which investigated if daily oral dose of aspirin (300 mg), as an adjunct to compression, improved time to healing for clinically diagnosed VLU patients (Weller et al., 2016). The study participants were aged 18 years and older with one or more VLUs in the presence of venous insufficiency confirmed by clinical assessment and/or duplex ultrasound. Other eligibility criteria included: 1) the target ulcer, was separated from other VLUs by at least 1 cm; 2) was present for at least six weeks 3) target ulcer area measured by digital planimetry techniques was between $\geq 1 \text{ cm}^2$ to $\leq 20 \text{ cm}^2$; 4) Ankle brachial pressure index (ABPI) was ≥ 0.7 mmHg or systolic toe pressure ≥ 50 mmHg to exclude arterial insufficiency; 5) the patient was able to provide informed consent (as per the medical practitioner's clinical judgement). The participants were randomized to receive either aspirin or placebo for 24 weeks, adjuvant to compression. Time to healing within 12 weeks was the primary outcome of this study. Secondary outcomes were ulcer recurrence, wound pain, quality of life and wellbeing, adherence to compression therapy, adherence to study medication, serum inflammatory markers, number of hospitalisations, and adverse events at 24 weeks.

Sample/Participants

Seventy-two participants from the ASPiVLU study, who expressed their interest to participate in other studies, were given a phone call by the trial coordinator and invited to participate in this nested qualitative study. Nine people said that they were no longer interested in research participation without explaining the reason. Seven people declined because they were too busy working and traveling. Nine people said that they would be unable to participate in the phone interview due to

hearing problems. Eight people were too sick. Their partners/carers said that their health deteriorated and provided the following main health issues: mental health issues, dementia, and a recent fall. Thirty-nine participants confirmed their interest to participate and agreed to be interviewed. Interviews with all participants that agreed to be interviewed were scheduled at a convenient for them time.

Data saturation was reached on 25th interview, while some voice files were still with transcription services. We considered we reached saturation when subsequent analysis did not generate any new TDF construct. In total, we interviewed 31 participants. Participants were reimbursed with a \$25 Coles Myer gift-card for participation. The trial coordinator contacted remaining people who agreed to be interviewed to thank them for their interest in study participation and inform that we were no longer recruiting participants.

Theoretical Framework

To understand patients' behavior related to VLU management adherence we were guided by the Theoretical Domains Framework (TDF) (Michie et al., 2005). This framework provides a theory-informed method for analyzing determinants of behavior. The TDF comprises a collection of domains, the product of a consensus strategy to be used in implementation research (Michie et al., 2005). The first version of this framework was developed in 2005 (Atkins et al., 2017), and later appraised and redeveloped in 2017 (Haardörfer, 2019). The 2017 version (Atkins et al., 2017) of the TDF framework includes 14 domains which guided our research. The TDF domains cover Knowledge, Skills, Beliefs about Capabilities, Beliefs about Consequences, Environmental Context and Resources, Social Influences, Behavioral Regulation, Optimism, Emotions, Goals, Social/Professional Role and Identity, Reinforcement, Intentions and Memory, Attention, and Decision Making.

Data Collection

Data were collected, using the interview guide developed by CW and VT, and refined by LT and CW. The interview guide consisted of open-ended questions loosely matching the TDF domains (2017 version), and did not cover all 14 TDF domains (Table 1). These questions were followed by a series of prompts that probed barriers and enablers influencing patient adherence or non-adherence to VLU treatment recommendations (Michie et al., 2005). Interview questions were able to be modified by the interviewer depending on the flow of the interview. The interview guide was not piloted.

Data collection took place between October 2019 and December 2019. Phone interviews were conducted by two experienced researchers (LT and CR) from the University office. All interviews were audio recorded, using a handheld recording device. Participant verbal consent was obtained prior to recording. The average interviewing time was 35 min, ranging between 12 and 87 min, depending on the participants availability and their willingness to discuss the details of VLU management. The audio files were transcribed verbatim using a professional transcription service. Transcripts were checked alongside voice files by LT and CR to ensure the accuracy of

TABLE 1 | The interview guide: Selected questions and matched theoretical domains.

Question	Prompt	Theoretical domain
If a participant used compression		
What factors or situations helped you in making a decision to adhere to compression therapy?	How did you find out about this as a treatment option?	Knowledge
What was the rationale/pros and cons for having compression therapy explained to you?	What were the benefits and negative aspects of using compression?	Beliefs about consequences
	How did you come to this decision?	Memory, attention, and decision processes
What feelings or emotions did you feel when deciding to use and to adhere to compression?		Emotion
How confident do you feel to self-manage compression application at home?		Skills
Describe your support network during this experience		Social influences
Previous experience: Had you adhered to compression therapy in the past if you have history of VLU's?	What type of compression is the most comfortable?	Memory, attention, and decision processes
	Why do you prefer this one?	
If a participant did not use compression		
How compression impacts on healing outcomes? Did anyone explain to you the importance of wearing compression?	Who? Health professionals, family, friends, ASPIVLU researchers?	Knowledge, social influence
	What was discussed?	
What factors helped you in making a decision to not use compression?	Explain how you came to the decision.	Memory, attention and decision processes
	What were the main influences on your decision?	

the transcribed text. The interview transcripts were not sent back for the participants' verification.

Participant and VLU characteristics data were collected as part of the ASPIVLU RCT study. A comprehensive overview of participant details and wound characteristics enabled a comparison of the VLU participant group of this study and VLU patients in the wider community.

Ethical Considerations

This study was conducted in line with the ethical guidelines of the 1975 Declaration of Helsinki. The University Human Research Ethics Committee approval was obtained for both the main study and a nested qualitative study. Site-specific approvals from the participating tertiary specialist clinics were received from the participating health services ethics committees.

Data Analysis

The data were analyzed using NVivo Version 12. We adopted a theory-driven conceptual analysis (Haardörfer, 2019) and utilized the TDF domains and constructs to guide our analysis (Atkins et al., 2017). Our coding framework was based on the TDF. CR conducted initial coding of the first three transcripts and developed the coding framework. The coding framework was then reviewed by VT and CW. Technically, utterances were mapped across a coding framework based on the TDF domains and associated constructs. We focused on barriers and enablers that influenced VLU patients' decision to adhere to treatment recommendations in their care plan, which were then allocated to the relevant domains.

RESULTS

Participant Characteristics

Thirty-one participants were included in this study: Sixteen participants (52%) were male and 15 (48%) were female. The mean age of participants was 64 years, ranging from 39 to 89.

Medical history/comorbidities included hypertension ($N = 19$; 61%), osteoarthritis ($N = 14$; 45%), knee/hip surgery ($N = 11$, 35%), venous surgery/ligation ($N = 10$; 32%), type 2 diabetes ($N = 10$; 32%), rheumatoid arthritis ($N = 5$; 16%), deep vein thrombosis ($N = 4$; 13%), depression ($N = 4$; 13%), anaemia ($N = 3$, 10%). Additional socio-demographic details of the participants can be accessed in **Table 2**.

Summary of the Theoretical Domains Framework Domains

Patients described the key aspects of VLU treatment process, including compression, appointment attendance, health information, leg elevation and nutrition. Of these, compression was the most frequently discussed recommendation: 64 times by 30 participants (**Figure 1**). The discussed barriers and enablers (**Figures 2, 3**) to treatment adherence discussed by participants related to the following domains: Knowledge (referred 98 times by 96% of participants), Social Influences (referred 88 times by 81% of participants), Beliefs about Consequences (referred 56 times by 67%), Emotions (referred 29 times by 54%), Environmental Context and Resources (referred 52 times by 54%) and Beliefs about Capabilities (referred 50 times by 64%), Behavioral Regulation (referred 24 times by 64%) and Memory, Attention and Decision Making (referred 20 times by 36%). Reinforcement, Intentions and Optimism, Skills, Goals, and Social/professional Role and Identity domains were not discussed by participants since they were not prompted to do so (**Tables 3, 4**).

Knowledge

Twenty-six participants (83%) discussed enablers that pertained to knowledge. Key themes included understanding the rationale for treatment, sources of information and ways these enablers were beneficial to treatment adherence. These included three main categories: 1) knowledge from personal experience: "Since my wounds have healed I've basically done everything myself. Now

TABLE 2 | Participant characteristics (*n* = 31).

Gender (number, percentage)		
Male	16	52%
Female	15	48%
Age		
<45	2	6%
45–54	2	6%
55–64	6	19%
65–74	12	39%
75–84	5	16%
85+	4	13%
Education		
Up to high school graduation	19	61%
Community college or Bachelor's degree	8	26%
Postgraduate or professional degree	4	13%
Prefer not to answer	0	
Employment status		
Retired	24	77%
Working full-time (>30 h per week)	3	10%
Working part-time (<30 h per week)	1	3%
Self-employed	0	
Long term disability	1	3%
No response	1	3%
Not working	1	3%
Self-rated health		
Excellent/very good	4	13%
Good	19	61%
Poor	7	23%
Worse than poor	0	
No response	1	3%
Medical history		
Hypertension	19	61%
Osteoarthritis	14	45%
Knee/Hip surgery	11	36%
Venous surgery/Ligation	10	32%
Type 2 diabetes	10	32%
Rheumatoid arthritis	5	16%
Deep vein thrombosis	4	13%
Depression	4	13%
Anaemia	3	10%

I know what goes on . . . I've learnt little bit and pieces" [P11]; 2) information provided by a healthcare professional: "Staff were very informative as to what I should be using to cut down on the infection, the bacterial load." [P29]; and 3) information from personal search: "I went to a University Library and got some medical books out and had a bit of a read as to what bilateral ulcers are, treatment, and so forth" [P25]. Eighteen participants said that they used Internet to get information on VLUs, while thirteen acknowledged that they relied only on information provided by clinicians as the most trustable source of information. A few participants had limited information technology skills, and perceived this as a barrier to getting information *via* the Internet.

Twenty-one participants (67%) reported they understood the reason for compression: "I do understand that it does help to keep the fluid out, and I do have a lot of problem with fluid getting down into that leg. And I know that the compression helps to relieve all that" [P07]. For example, one of the participants said that this understanding allowed them to accept compression as a necessary treatment: "I'll be burdened with it for the rest of my life, and I've come to grips with that" [P02].

Knowledge and acceptance optimized participants' adherence with compression. P13 outlined his acceptance to wear compression for a past health condition and understood the benefit.

I've had to use compression stockings in the past for different reasons, including just general swelling in my feet and ankles. So, when they mentioned compression I obviously knew what they were talking about . . . It's just when you understand how the venous ulcers work then it like obvious . . . To me it was like this is probably the best way to heal it. So, they didn't really have to sell it to me [P13].

Understanding how compression aided healing was a key enabler for participants when deciding whether to adhere to clinician's treatment suggestions:

Q: And what made you decide to use the compression?

A: Well it was the desire of the medicos to increase the vascular flow. The valves are leaking in the veins, that unfortunately prevents all your blood returning to your heart. So, they put the compression on to force the blood back up, as much as possible [P24].

Conversely, participants reported that complex, inconsistent or incorrect information provided by clinicians all served as barriers to VLU treatment. Compression, for example, was a particular area where participants reported confusion. Participants highlighted that sometimes this confusion originated from the clinician who was treating their wound: "I don't really think the GP (General Practitioner) knew that much about ulcers" [P14]. Participants said they did not conduct research of their own and instead relied on qualified health professionals: "If they said jump, I jumped" [P16]. As such, when P17 was asked why they stopped wearing compression, they reported that it was because they had been told by a vascular surgeon that it was no longer necessary.

When asked about whether there was information or follow up provided about long term prophylactic compression to prevent future ulceration, P17 reported that she'd assumed she didn't need compression because she was now able to exercise: "Well, the next thing was to go on my walking program, so I just thought that's the price to pay for not having compression stockings? Because she (clinician) said, to develop the muscles, to strengthen the muscles in my legs, to help your circulation. I just assumed that's why I didn't need compression stockings."

When participants felt that they understood treatment, they were able to troubleshoot barriers. For example, P20 said that the initial stockings suggested by her GP caused her a lot of discomfort. When she went to the wound clinic, however, they provided her with education and explored methods that would prevent the discomfort, leading to compression adherence:

When I first got the compression stocking and the first ulcer healed, I stopped wearing it because it used to rub a bit on my leg. But since the second one, I haven't

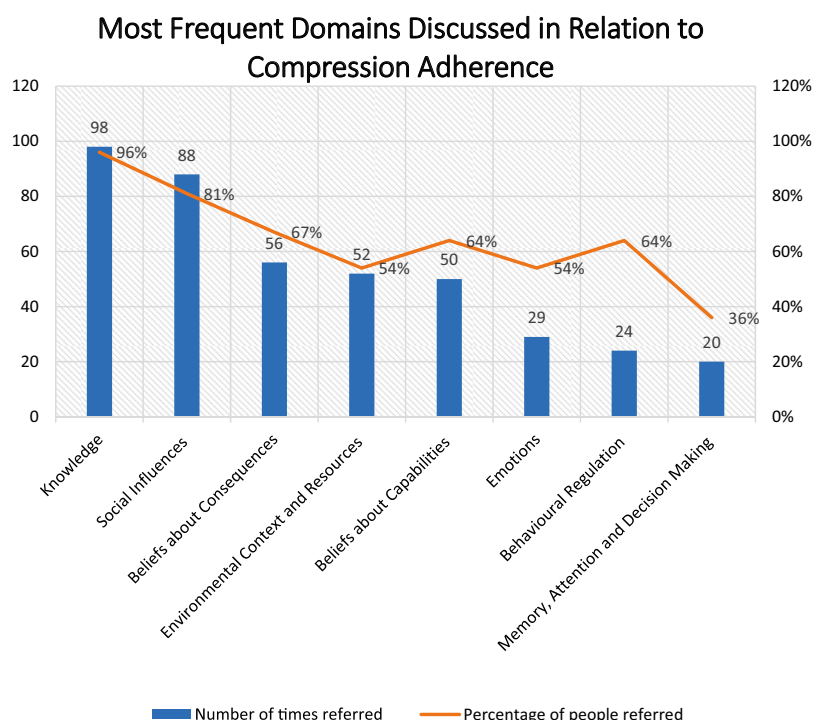


FIGURE 1 | Most frequent domains discussed in relation to compression adherence.

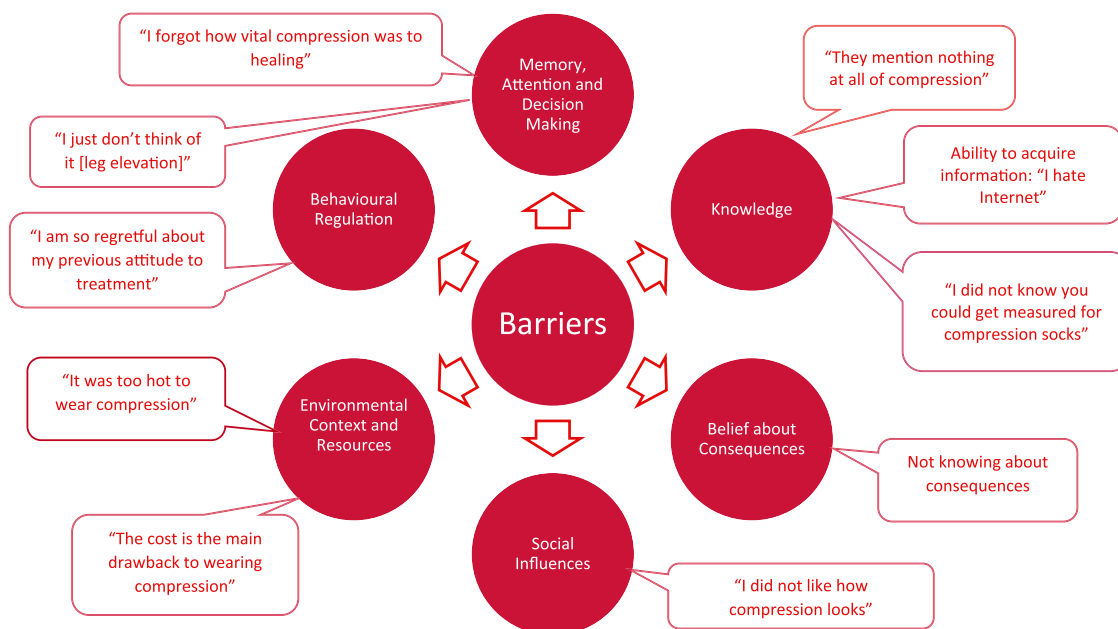
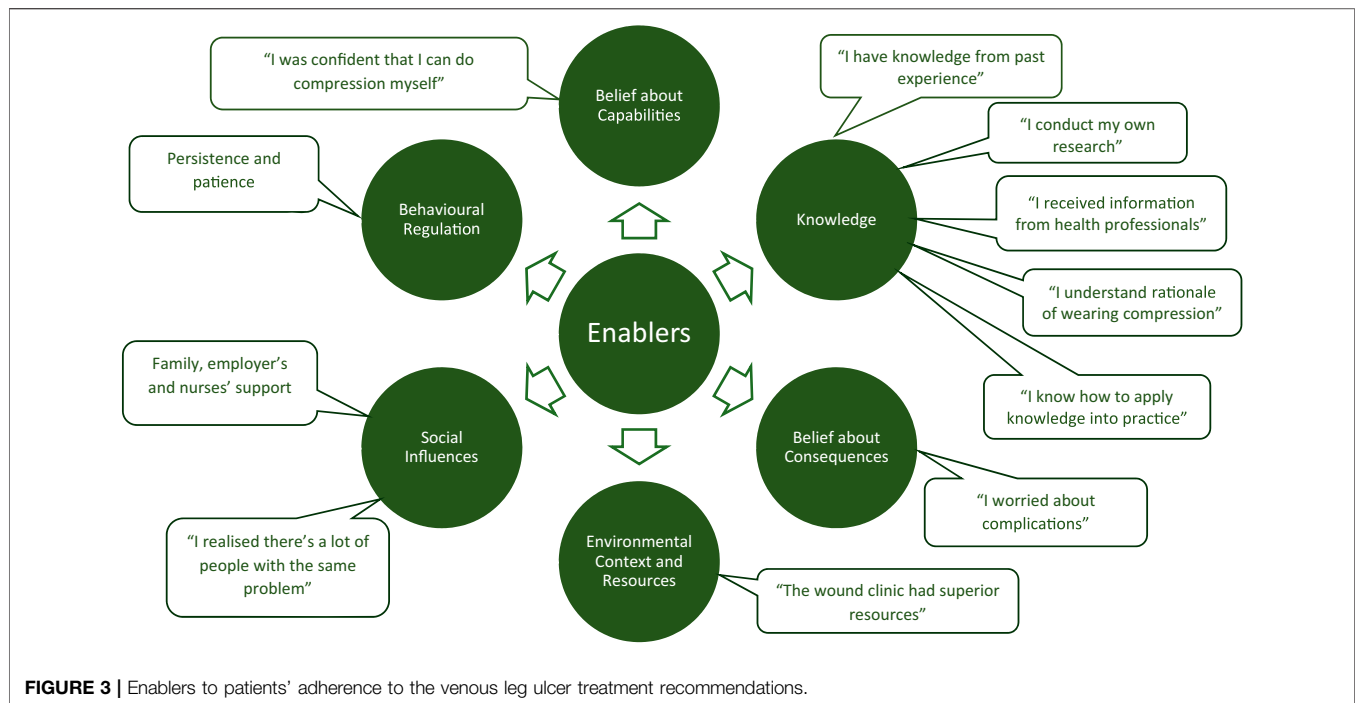


FIGURE 2 | Barriers to patients' adherence to the venous leg ulcer treatment recommendations.

stopped wearing it. Because when I went back and they said: "Well, you should be wearing it" I said "Well it rubs!" Apparently, I wasn't told, I was supposed to have

something done to it so it wouldn't rub... just putting it on the leg. So, the second lot of nurses were more informative than the first [P20].



One participant explained that though they understood that clinics were busy, they really appreciated when they were given VLU education: "I know they're really busy as they are; and I understand that. I think it probably would have helped, if they had explained it a little bit more as to what was actually happening ..." [P14].

Social Influences

Participants discussed social influences as an enabler to adhering to treatment plans under the TDF constructs social support and social norms. Participants reported improved adherence when they saw other people in the wound clinic undergoing similar treatment: "when I went to the wound clinic, I saw people with things on their legs and bandages, and I thought, 'Well, they must know what they're doing here because there's a lot of people with the same problem'" [P28]. This quote could also be interpreted as an expression of trust in health professionals.

Social support was a very important enabler to accessing VLU care. Family members were highlighted as the key members providing social support. The following caregiving activities increased patients' adherence with the VLU treatment recommendations: assistance with dressing or/and compression application; assistance with computer technology to access health information; explanation of medical information and terminology; taking to medical appointments; helping to make treatment decisions; and encouraging treatment. Social support was also provided by formal carers and (community) nurses who visited patients at home. Participants also relied on supportive work-related environment with employees providing flexible arrangements for the patients to attend frequent medical appointments.

Some participants raised body image concerns related to wearing compression: "Out of vanity, I don't like wearing (compression)—I don't like having one thing on my legs. I look like a— yeah, it's self—a self-conscious thing, I suppose you call it" [P25]. One participant acknowledged health professionals' support, including related to the body image issues: "I said to him, 'How am I going to work at a shopping centre with a big, fat thing like this on my leg?'" He said, "I was dealing with a lady that sells fur coats in the top end of (Street name), and she could manage it, so you can too" [P28].

Beliefs About Consequences

Understanding the benefits of treatment and consequences for non-adherence were the key factors driving participants' adherence. In particular, understanding the consequences of not using compression was an important factor influencing participants' adherence. Participants reported a belief that failure to act quickly would cause their condition to worsen. Those who experienced VLU for the first time explained that they sought out medical advice because they could see that their wound was getting worse, and they feared that an inaction or a delay would lead to serious health consequences: "I have to look for a solution because it's not getting any better, it's getting worse", and you become quite desperate" [P28].

Participants who had experience with VLUs before, knew that VLUs were difficult to heal, necessitating prompt action:

A: I had it (a VLU) when I was 30, so I knew what it was, and—yeah, I wanted to get on top of it as quickly as I could, so. Q: The one that you had when you were 30,

TABLE 3 | Barriers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Knowledge	23	32	Knowledge	Inadequate information given	Q: Yeah. And they didn't suggest to you about wearing compression then when you were going for dressing? A: Well, not at all. Nothing. They didn't mention nothing at all of compression. [P11] They did suggest compression, but they didn't enforce it as absolutely necessary then. And they used different ways of cleaning the wound and dressing the wound. That was just interesting to see. They weren't really that experienced in dealing with those thing [P19] Q: So, they gave you a lot of information on the benefits that you said before. Had you ever heard about, besides the Tubigrip, had anyone else ever talked to you about compression, or the use of it in your management of your ulcers, or the care? A: They talk to you about compression, but I didn't really know you could go and get measured for the socks for compression, which I've got. But the Comprilan is even better than the hand-made compression stockings [P01] Q: So, did you always feel like you had enough information about compression? Or... A: Yeah. Since I've started going to (the specialist wound clinic), yes. Q: Yeah. A: From original years ago, when I went to the hyperbaric clinic? No. Q: Okay. And what makes you say not so much with the earlier venous leg ulcer? A: No, they didn't—they just sort of fixed it and sent me on my way. They didn't give me a maintenance plan or anything really. They just said, "Just keep wearing this Tubigrip every day. Take it off at night, and,"—but they never said, "Make sure it's a new one every day," or—yeah, they never gave me a lot of information at all really, no [P31] Q: So, do you use the Internet at all to look for information? A: No, I hate it [P04]
Social influences	19	44	Modelling	Ability to acquire information	Q: Did they say that you might have to keep wearing them (compression stockings) in the future or anything like that? Have they got a plan? A: That was funny though because (the GP) was sort of like, yeah, you can stop wearing them you don't have to worry about them anyway. But the doctors and the GPs in the wound clinic were all saying that I was going to have to wear it for the rest of my life. So is a bit of a mixed message there [P19] Q: Okay. And when was that, that you were wearing the stockings? A: Ah, I didn't wear it for very long. And I can't remember how long. Q: Okay. Was that—when you say you didn't wear it for very long, was that because it was uncomfortable? Because the doctor asked you to stop wearing them? Or A: No, I decided not to, just for vanity. I couldn't stand the look of them [P04] A: I still wear them (compression stockings) now and then but I should wear them all the time... but I feel like an old man. There's something about them, I don't know. They're daggy [P11] A: Oh, summertime, I like to wear shorts and like the beach and stuff like that, and then I don't want to be wearing bandages on my legs, so I guess that's part of the reason why I stopped doing it as well. Getting looks fine when I wear jeans and stuff more. I don't mind so much, but it's just seems like a pain. No, just gets in the way, which is frustrating [P19] I'm maybe a bit self-conscious wearing it then. But I wear it all, all the other times, when I'm wearing long trousers [P23] Q: Did you have any emotions or were you concerned about doing compression when they said you had to do it? A: Ah it's—what'd you call it? Out of vanity, I don't like wearing—I don't like having one thing on my legs. I look like a - yeah, it's self - a self-conscious thing, I suppose you call it? [P31]
			Social norms	I didn't like how the compression looks	(Continued on following page)

TABLE 3 | (Continued) Barriers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Beliefs about consequences	20	35	Consequence	Worried about health complications	Q: I'm still looking what factors might have pushed you to say, "I have to wear this (Compression)" A: ... Well; I just saw the consequences of not wearing it. Q: ... what are the consequences if you don't wear all it? A: Well, to be less healing than ... I could see my veins were in a terrible state and that they were swollen, and I could see that it would help keep them ... The compression would help with the swelling right down from my side to the ankle, and especially around the knee area, above and below the knee, there were very pronounced and worsening veins, so I just thought that would help. Also, I didn't like looking at everything in that state. The stocking could have helped keep it all tight. I'm not talking about how it looked, because I felt it might help the veins from popping out [P17] My sister is recently retired, a carer for (facility name removed for privacy), and it was at Christmas time I just said to her, "Look at my leg. It's getting worse. Look at it. It's awful", and she said to me, "Look, you really should be trying to put a compression stocking or something on it", and she was trying to get me to put something on it to keep the fluid out of my leg, and that's the best information I possibly had from her because she'd seen them on elderly people, and I was saying to her, "But I'm not old. I shouldn't have this happening to my leg", and then I started to get really concerned, and I thought, "I have to look for a solution because it's not getting any better, it's getting worse", and you become quite desperate because your legs have to hold you, and I was terrified someone was going to hit me or bump me [P28] Q: Okay. And when was that, that you were wearing the stockings? A: Ah, I didn't wear it for very long. And I can't remember how long. Q: Okay. Was that—when you say you didn't wear it for very long, was that because it was uncomfortable? Because the doctor asked you to stop wearing them? Or -A: No, I decided not to, just for vanity. I couldn't stand the look of them. [P04] Q: No, tell me about it. I know. And so you said before that about compression, so who sort of instructed or gave you information about compression to start? A: One of the doctors at (Location). I still wear them now and then but I should wear them all the time... but I feel like an old man. There's something about them, I don't know. they're daggy [P11] Q: And how did you feel about compression to begin with? I know you mentioned that you sort of do, you stopped doing it for a little bit. What was it that made you decide? A: Oh, summertime, I like to wear shorts and like the beach and stuff like that, and then I don't want to be wearing bandages on my legs, so I guess that's part of the reason why I stopped doing it as well. Getting looks fine when I wear jeans and stuff more. I don't mind so much, but it's just seems like a pain. No, just gets in the way, which is frustrating [P11] Q: How did you feel when deciding to use or like—adhere to the compression treatment? A: Well, it doesn't worry me because I've used it ... [inaudible], being a bit self-conscious but I've usually got jeans on anyway, but when I'm wearing shorts around that or thongs I'll make sure I don't wear the compression bandage, stockings—yeah. Q: You won't wear it? A: I don't wear it. Not when I've got thongs on. Q: Okay. Why is that? Is it because they've got close toes or? A: No, they haven't ... I'd say open toes but no I just don't I'm maybe a bit self-conscious wearing it then. But I wear it all, all the other times, when I'm wearing long trousers [P23] At the time, when there was this total irregularity and an inconsistency of treatment ... I was very irritated indeed [P21] Q: And you felt secure with that? Did you ever doubt them? A: Not really, I suppose the only thing is I might have got a bit frustrated when it didn't heal as quickly as I wanted it to [P26]
Emotions	16	26	Stress	I felt self-conscious	
				Frustration	

(Continued on following page)

TABLE 3 | (Continued) Barriers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Environmental context and resources	19	43	Environmental stressors	Too hot to wear compression	Q: And how did you feel about doing compression therapy? The bandage? A: The bandages are awful especially when it's 40 degrees outside, it's the last thing you feel like wearing but you have to do it. Sorry, you just have to do it [P14] If my feet are fat or swollen I should say, and I'm on my feet a lot. It was a bit hard in summer because I got too hot, I've got wool pants on and these stockings, it was just too hot. But yeah just so I wouldn't have swollen feet, it's a seven-hour shift and I'm on my feet for six hours, so I wear them then [P25] Q: Okay. And do you wear the compression stockings now? A: No, I don't. Q: Okay. A: I should, but I don't. Q: When you say you should, was that something that the A: Well, oh you know they said, "You should wear the compression stockings," and I do - in the winter time, I do wear them. Q: Yes. A: But in the summertime, I just want - at first, it was too hard to put on. And they're too hot [P30] Q: Yes, probably you would be able to use the other one with the Velcro as opposed to the pull-up ones (compression hosiery)? A: Yeah. But there's issues with ... no, they're very expensive, although I was told about it. [P13] Q: Is there any other drawbacks to wearing compression vs. the Tubi vs. ... A: The cost [P28]
			Resources/material resources	Cost	Q: Yeah. Or why do you think it wasn't quite healing? Did the doctors say anything about that? A: Uh, I have other health issues that probably contributed. I think they did take that into account, and my immune system is deficient. Q: And so did that sort of, do you think prevented healing or it prevented you from doing these exercise? A: yeah, had a lot to do with it. Yeah, definitely [P14]
Beliefs about capabilities	20	35	Perceived competence	Other health issues	Q: Did you have anything else that you wanted to add in? Anything that we might have missed about venous leg ulcer treatment? A: Not specifically about the treatment. It was my attitude to the treatment that I'm so much regretful about. I should have shown more appreciation of it, as it has finally healed, but I'm sure that's because I did what I was told [P12]
Behavioral regulation	14	24	Breaking habit	Commitment to treatment	After I came back, I forgot how vital the compression was to the healing process. So, there was a period of time there where I wasn't treating the compression as seriously as I should have been. They need to have the compression on 24/7 [P19]
Memory, attention and decision making	11	16	Attention	Attention not directed toward VLU management	

what was that one like? A: Yeah, that lasted—ah, for three years. It was terrible. Because I went to GPs over and over and over, and getting dressings and all that sort of stuff [P31].

Another participant commented that they were very meticulous with following self-care instructions provided by their healthcare practitioner; driven by fear that they will develop multiple ulcers: “I’m better now, because I don’t want to get them [VLUs] again, I worry more about what I do. I don’t touch my legs, if they’re feeling puffy, I put them up” [P25].

Emotions

Participants described a range of emotions that influenced VLU treatment adherence. These ranged from feeling daunted or overwhelmed by their diagnosis; to feeling desperate and distressed as their VLU worsened: “I got desperate” [24]. One participant explained that she was very concerned by her wound: “I started to get really concerned, and I thought, ‘I have to look for a solution because it’s not getting any better, it’s getting worse’, and you become quite desperate because your legs have to hold you, and I was terrified someone was going to hit me or bump me.” [P28]. Pain also made participants feel distressed: “I talked about my pain . . . I couldn’t function before. I was probably yelling at (Name) a lot and was just grumpy, full stop. But once I got that on, I could actually do stuff, I could go places and enjoy life a bit more. It is pretty depressing being in so much pain [P25].

Environmental Context and Resources

Patients reported a number of environmental and financial issues that interfered with VLU management. Transport related issues, such as living a distance from their local practice and/or limited parking spaces were discussed by eight participants: “It is quite a problem getting from here to (the clinic) by public transport” [P12]. Proximity and ability to meet appointment times greatly impacted on the patient’s ability to attend their scheduled appointments. For example, P31 found that he was unable to continue working due to the barriers imposed by managing his wound as his appointments were so frequent, time consuming and disruptive. Other barriers under this domain included hot weather and related discomfort when wearing compression on hot days: “Well, the bad points are that it’s constrictive, and it’s hot in the summer when you’re trying to get to sleep is hard.” [P02].

Lastly financial issues related to VLU management were discussed by all patients. They were related to absence from work due to medical appointments, the cost of transport and parking, and the out of pocket cost of compression hosiery and adjunct therapies: “There’s no comparison of the Comprilan in terms of getting compression. They sell it for like 70 bucks a pair as well. They’re so expensive” [P19].

Beliefs About Capabilities

Participants reported that agency to perform wound care, especially compression, was an enabler to self-care. Some participants were unable to adhere to evidence-based interventions due to limited mobility and physical constraints:

Q: Would you say that your immobility prevents you from doing any sort of exercise or anything that the GP might . . . (have recommended)?

A: It inhibits that, yes. I’ve got to use crutches, and sometimes I get a bit worn under the arms and so forth. Over the last six months, they’ve recommended that I elevate my leg during the day. So, it’s complicated, because I can only get on and off the bed when there’s a carer present with me. I can’t get either on or off myself, and so I have some limited funds to have carers, and I have them seven days a week, but for two or three hours at a time [P09].

Nine participants reported they could apply compression and wound dressings on their own at home. P19 (Table 4) explained that he was shown how to perform compression and change wound dressings at home. Being capable to perform these procedures on his own, he was not required to attend the clinic as frequently. Other participants also reported beliefs about one’s own capabilities was an enabler for adherence to management plans.

Behavioral Regulation

Participants discussed behaviors that related to their behavioral regulation, under the constructs Generating Alternatives and Self-monitoring. For example, one participant who was in full-time employment had made a request at their primary care to have nurses available afterhours, who would change dressings and apply compression. This example of generating alternatives, meant that participants found it easier to adhere to VLU management and meet their care plan.

Five participants discussed the importance of patience and persistence. For example, when P16 was asked why she persevered with her frequent dressings and compression, she described that though her wound was “a nuisance” and “a frustration,” she was “determined to stick it out.” Furthermore, participants could see the link between persisting with treatment, and subsequent wound healing:

Q: What do you think made your ulcer heal? Or what do you think helped it the most?

A: Well, I think that silver stuff you put on it, I think that’s a great thing. I think persistence, and actually doing as I was told with it, to be perfectly honest [P30].

Though care tasks were identified as being arduous, participants believed their wound would heal faster when they demonstrated resilience.

Memory, Attention, and Decision-Making

Older participants reported barriers that pertained to memory, attention and decision making. They found it difficult to recall aspects of their care and VLU management. They forgot who has made their VLU diagnosis, if diagnostic imaging was performed in the initial consultation and what information was provided: “I can’t remember getting any paperwork, but that doesn’t mean anything. I could have reams of it in a place somewhere at home.”—[P30]. The latter presents a barrier for patients to perform self-management of their VLU. When they are unable

TABLE 4 | Enablers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Knowledge	26	66	Knowledge	My past experience gave me knowledge	A: No, I think, what's happens is it's almost like a little blister. That's how it sort of starts, can, you can feel the flesh underneath it feel very sensitive and sort of bulging thingy. Q: And so when you felt that coming on, you went to the clinic or you went to your doctor? A: I usually go to the doctor [P15] Q: Was it easy to understand what they (clinicians) were telling you, or difficult to understand some of the things or concepts they talked about? A: Some of the things, I had to ask a second time as to what you mean, but mostly, it was understandable after reading up about ulcers and so forth and looking through the journals in the medical section of the library. Yeah, I went to the (University) Library and got some medical books out and had a bit of a read as to what bilateral ulcers are, treatment, and so forth... I just wanted to check a couple of things I'd been told, but also look at some pictures of what happens, if I leave them for a lot longer than they were [P25] Q: Did you get any information given to you about what an ulcer is and what you need to do to help it improve to heal or any of that sort of information in the early days? A: We did discuss going to a vein specialist at the time, but nothing definite, but what I actually did, I came home and Googled information on it [P28]
				I conduct my own research	Q: When you started doing the compression or when you first were told to do compression, what information were you given by your doctors and nurses? A: Well I bought the Comprilan in and they showed me how to do it myself [P19] Q: Did you ask any questions the wound clinic staff, or did they give you anything printed, or were you able to recall what they told you? A: They told me moisturizing was really good, something that I probably had neglected too, rubbing moisturiser all over my feet, heels. Q: Why is that good for you? A: To stop any little cracks getting into your heels and getting an infection in there, making sure the shower is totally clean of bacteria, watching that you don't walk around in bare feet, and keeping yourself really extra clean, fungal infections and all that sort of thing, we discussed [P28] Staff were very informative as to what I should be using to cut down on the infection, the bacterial load. They were more helpful in recommending where to buy things, obviously knowing that, as a public patient, it's very hard to afford to buy top-line wound management kits. So, they had to refer me off to places where they aren't very expensive. [P29]
			Education received from healthcare professionals	Application of knowledge	I was shown how to look after it (wound) and I think I'd find that, trying to think of the problem. Oh, I'm now qualified how to look after it. Like I know what I'm doing and I know what I'm looking at [P05] Q: And what do you believe helped your ulcer heal? A: I think the advice that I got from the clinic. I think also probably with my nursing background, understanding perhaps whereas maybe other nonmedical people perhaps don't fully understand how the body works [P16] I think if people haven't had any background in science, for example, and can't quite grasp what the medical profession are telling them, it would be useful for them to have someone explain it to them in general terms. That would probably apply to most people, they haven't done science or chemistry and they can't grasp what's being done [P24]
				I understood the rationale for using compression	Yeah, I'd much rather have them (compression) not on when it's 40 degrees. They get a bit warm in summer, but that's a small price to pay for not spending another ten days in hospital [P01] Q: Would you consider keep using compression? A: Yeah, yeah, yeah. I mean, they've told me that I'll be burdened with it for the rest of my life, and I've come to grips with that. Q: Do you know why? Even if it heals?

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TABLE 4 | (Continued) Enablers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Social influences	19	44	Social support	Family support	A: I guess it's blood flow, and that's probably why I'm on the list for something to go back and see the vascular people again [P02] A: I went to see the compression sock I saw in (a specialist clinic). And he (the vascular specialist) told me that I must wear a compression sock on that leg. Q: Okay. And what did he why you had to wear it? A: Yes, because of poor circulation. And at that time I had the ulcer as well [P05] Q: Did you get information about why compression works? A: I guess so. I must have, but I do understand that it does help to keep the fluid out, and I do have a lot of problem with fluid getting down into that leg. And I know that the compression helps to relieve all that [P07] A: The bandages are awful especially when it's 40 degrees outside, it's the last thing you feel like wearing but you have to do it. Sorry, you just have to do it. Q: When you say you have to do it, why do you have to do it? A: Well, I had to do it because that was what I told would cure the ulcer... or get rid of the ulcer [P14] A: And that's what they pushed at the wound clinic was compression, compression, compression. Q: And what did they tell you about it, why? A: To increase the blood flow to go back up, and to reduce the swelling. It's not just what you put on the wound, it's not just debridging. It's because my feet were fat, swollen, so it was reducing the fluid in them, that's why I wasn't allowed to stand up for long periods of time, I had to keep my legs up to reduce the fluid and increase the venous flow [P25] My family helps out. Like I said, in terms of it just makes my life a little bit simpler to just get a lift to (the hospital) [P13]
				Nurses' support	A: My son actually dresses it for me and he's almost turned into a nurse. Q: Yeah, you would with all of those experience. A: Alright. He does the dressings and then I've had two broken wrists, so I can't, I haven't got the strength in my hand to pull the elastic cotton stockings on and off. So, he puts them on and pulled them off for me. I'm very thankful that he is near me [P15] One of the reasons why we go with each other to appointments is to take on board all this information in case one misses something the other picks up on it. That's always been an important thing with us when we go to appointments. We'd both be there and sometimes some of the stuff can be a little overwhelming depending on what you're doing. If someone else asks the questions you might forget to ask you say, "Oh, I forgot to ask that question. It slipped my mind." So, there is a benefit in both going to these things. . . .My wife basically did most of that because I couldn't put bandages on and all that sort of stuff. She was often worried she'd put them on a bit too firm. Basically, she did the best she could and she was confident on what she had done at home and the idea of doing it at home was to save a lot of trips [P27] A: One of my daughters who is a nurse practitioner in drug and alcohol. She had attended a lecture by Doctor (Name) because in her field they get a lot of patients. And she had told me how he was saying you don't use antibiotics, you don't use cream, you just use this, whatever the pad was and you know, Liofoam, and the three layers of compression stockings [P16] Q: I remember you saying before that you felt like they were a bit ugly the stockings. Was this a different type of stocking that looked better? Or you just decided to start wearing them? Or ... A: No, I wouldn't go against the nurses, they know what they were doing. They're experienced, and no, it gave me confidence, and what they said was right [P04] Q: Did you trust the nurses? A: Absolutely.

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TABLE 4 | (Continued) Enablers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
				Employers' support	Q: At both clinics? A: Yes. Ah, absolutely [P30] It's toward eight to ten years or so that I've been treated for the leg ulcers. And actually, and I just recall now, when I was working, I was officially working five days a week, but my department would let me actually work from home two days a week. So, I don't - where I didn't have to go into the city, and that was because of the ulcer conditions being or beginning to develop at that time [P09] Q: You said that your boss was quite supportive. Were you able to talk to them about it? Did you feel what was going ... A: Yes, I told them I couldn't work, I was in hospital, "What's your problem? Are you not well?" I said, "I've just got an intravenous drip because I've got an infection in my leg", "You take as much time off as you need", that sort of thing [P28] Q: Was this from casualty, after the antibiotics, or from the wound clinic? A: No, from casualty. Q: Before you got into the wound clinic appointment. A: But then when I went to the wound clinic, I saw people with things on their legs and bandages, and I thought, "Well, they must know what they're doing here because there's a lot of people with the same problem." Q: Was that the first time you'd seen people with bandages on legs or thought it was ... A: Well, yes, I've never noticed it before, but now I'm preoccupied and I see people in these tubigrips or whatever, swollen legs. Q: You know now. A: They've got one, he's got one, I've got one too [P28]
				Social Norms	A: There's a plastics specialist at the (Hospital) and a wound consulting team recommended a graft on both legs, and then elevation, rest, and hospital stay for seven to 10 days, then back dressings, and then home. Q: Okay. They've got a plan, and then everyone's on to that. That sounds good. A: Correct. Q: How do you feel about that plan? A: It's going to be daunting taking two months of bed rest, but at the end of the day, two months or no legs, take your pick [P29] Q: So, you've got the stocking now. A: And I wear them every day. They are an absolute pain in the butt to put on, they're a pain in the butt to take off. I can sort of get them on myself, but my husband does it for me on and off. So we bought an adapter and I've got, you know, an adapter that you put the stocking over. But I put them on every day and my legs don't swell anymore and you know, it's worth it. I didn't know how I'd go in the summer time, but I survive, which has been a pretty hot summer. And I hate the heat. Q: What made you keep persevering? A: Because my legs feel so comfortable and I figure, it's easier than going and having a varicose vein strip. Because I've had some surgery and I just don't want it anymore if I can avoid it. So my legs are very ... and I'm not a small person. I'm very, very comfortable [P16] A: I also take a lot more care of my legs and my feet now than what I used to. Q: why is that? A: Because I don't want to get any more ulcers [P01]
Beliefs about consequences	11	21	Consequence	Worried about health complications	

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TABLE 4 | (Continued) Enablers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Emotions	2	3	Positive effect	It felt good when I was reassured	I'm much more aware of preventive. If I get the cellulitis, like I had a bout of cellulitis two weeks ago, I s'pose, and in the past I might have been tending to been a bit slow in treating it. Now if I feel any warmth get into my legs, or my legs get at all sore, or start to swell a bit, I just go straight onto the antibiotics. Whereas, if in the past, I used to let it go a bit, the cellulitis would take hold, or my legs would tend to peel, all the skin would peel off them. And I'd finish up with a week or ten days in hospital on an antibiotic drip [P01] A: I would like to know if it's going to get worse because, if I had known it's going to get worse. I could've been more prepared for just emotionally and mentally at least prepare for it getting worse rather than thinking that it's going to clear off and be okay. Whereas I think when it got to the point where it wasn't clearing up, and going to be okay. They should sort of say, well it's going to come down to a skin graft [P14] Q: Coming to see the podiatrist, how did that feel for you? A: It felt good. They were not judgmental. They unwrapped everything, and they said, "We can heal those, we can move forward. You don't have to wear bandages the rest of your life." Q: How did you feel when they told you that? A: Felt fantastic [P29]
Environmental context and resources	5	10	Material resources	The wound clinic had superior resources	Q: When the treatment you were having for your ulcer, while you were at the clinic, was it similar to the treatment you were having prior, like dressings and things like that? A: Well yeah, it was, but it was the type of dressing that they were using. It was the actual wound care product that they were putting on the skin graft. It was the product they were using before they put the Comprilan, the Comprilan pressure dressings are a bonus. The actual dressings they were putting on the wound rather than most of the time, in hospital, they put on some dressings, some gauze, and a bit of tape. Whereas the ladies at clinic, they're using some designated dressing for that particular problem. Q: Yeah, that's true, they have a big range too, don't they? A: And they take one look at it, and in consultation with the Wound Care doctors there, and with your blood tests you've had done, they take a look and they say, "Well we need to use this." And it's this, out of about six or seven different products they could use. But it's the right one for the job [P01] Q: How confident would you say you feel about managing your stockings at home?
Beliefs about capabilities	10	15	Perceived competence	I can do compression	A: Oh, very confident. Q: Is that from years of just having, you know, ulcers or of looking at different compression stockings or? A: Just I've been wearing them for a long time now, so that just doesn't bother me. You put them on [P05] Q: How competent do you feel managing your compression applications at home? Putting them on. A: Just got no problems. I've been doing it for so long now. It's just so dramatic, you know, because I now if I'd done them, I've tried not wearing them. Right. I'm a like feel dreadful [P06] Q: Well, I'll just jump back to compression. So did you do your own stockings and things at home and you felt confident to do all of your compression by yourself? A: Yes, I was fine. I would make sure when I went there then I showed them how I was doing it and also they'd see when they were taking marks, you know, they seemed pretty happy with what I was doing. I knew how to do it. It was, just the hassle of keeping it on, getting it off sometimes. Just all [P14] Q: So you felt comfortable enough sort of hinting at your doctor or asking or? A: well, it was probably the nurse because I was having visits to the nurse. I would call the doctor in if you know, because I was going twice a week. And doing it myself at home and the benefits of a nursing background. So I feel that I've put a lot of effort into looking after the two, once I was even that way to do it. So I was quite happy to change the dressings. If I changed them four times a day, I changed them. I just bought bulk supply [P16]

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TABLE 4 | (Continued) Enablers to patients' adherence to the evidence-based guideline recommendations for venous leg ulcer management.

Domains	No of participants mentioned	No of times referred	Main constructs	Main themes	Sample quotes
Behavioral regulation	11	12	Action planning	Providing input that influences the care that is delivered at an organization (i.e., GP clinic)	A: It's easier for them to do them because they come into the wound clinic and seen what's going on, and then they've now managed it and they know what to look for when it starts to get smelly. They know what to look for when they start looking infected, and they know all the tell-tale signs. There might be an underlying infection. Q: How did that come about, that they got to get to the clinic and get educated? A: I invited them there one day because they needed to learn, as they're going to be treating me more often than what (the hospital) was." [P29] A: I mean, when they don't have the nurses on, like after work time or on the weekends or whatever, I'll sort of - you know, I have asked them: "can they?" and "how come?" and then like within a week, the owner of the clinic in (Location) said, "No, we need nurses here on - at night time all the time," so. Because the nurses are rostering themselves. Yeah, with picking up kids and all that sort of stuff, and then he said, "Yeah well, it's getting on." Like I didn't complain. I mean, to the reception people I said: "Ah, this is getting a bit hard. I work here, so it's too hard to get to during lunch break, or whatever," and they said, "Ah, it's just how it is." And then within a week, it had changed [P31] Q: Did you feel you had any other options when they were discussing the stockings with you or things you could. . . A: I don't think they gave me any options. They just said, well this is what you have to, probably they said this is what we'll do. It's like my feet the podiatrist surgeon said to me, you need to get specially made boots so that your foot doesn't, trying to hold your foot from collapsing anymore. So, I went, got them. The cost me \$1,900 each oh, but I did it. The next fortnight when I went back to him, he nearly fell off his chair because someone had actually done what he'd suggested would be best for their feet. Q: So you did decide . . . the costs didn't put you off? A: Well, no, we've always put health first and so if you know for both my husband and I and for our children. That we had private health, you know, if you need to go to the doctor . . . we've done it, you know what I mean? We've spent the money and okay, it's a lot of money sometimes, but it's not quite unnecessarily miserable because you don't want to spend any money on getting something done, for your own benefit [P16] A: But once they put those compression things on, I think the pain went to about 12 out of 10. But that was after I went home. Do you know what I mean? But I could feel and I could see the benefits because my legs during the day would swell, my ankles would swell. And then night time they would go down. But those stockings were pushing the fluid, they were sort of almost washing the leg from inside every time. I was changing those dressings three and four times a day. Sometimes it was so much, you know, each day or whatever. And then after a week or 10 days, the pain in them started to ease off. I persevered [P16] Q: What made you keep coming back if in those initial stages you were finding the pain? A: I just made myself come back! [P25] Q: Do you feel quite confident and capable at the appointments of asking questions or going prepared with questions or taking in all the information at the time? A: Yes, that's not a problem. Q: Do you take notes at all? A: No, I've got a very good memory. [P28]
			Self-monitoring	Persistence and patience	
Memory, attention and decision making	3	4	Memory	I have a good memory	

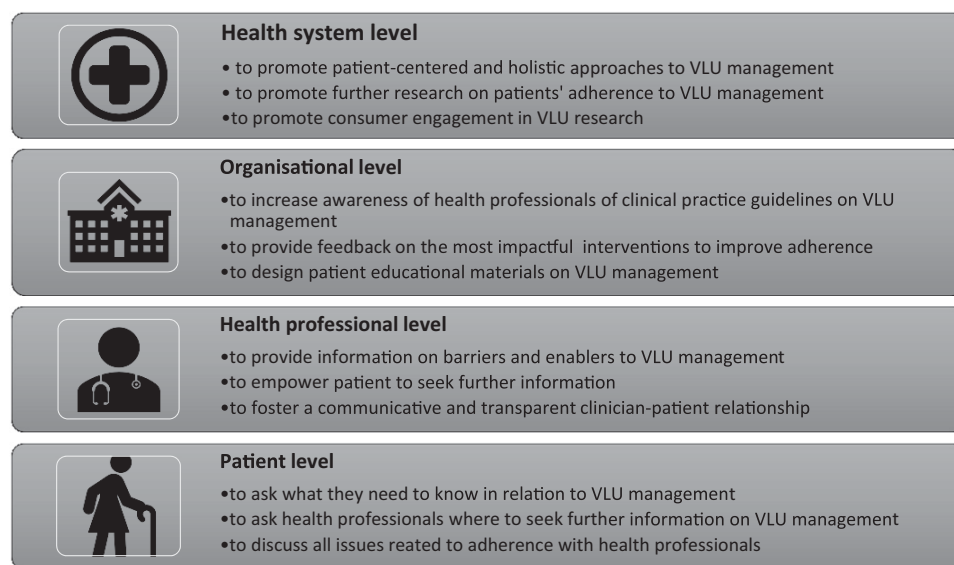


FIGURE 4 | Strategies to improve adherence to the venous leg ulcer treatment recommendations.

to recall the specifics of their treatment plan (or the rationale for doing so) then they may be less likely to comply with their care directives.

Some people found it difficult to remember to keep their legs elevated. For example, after explaining key details of needing to elevate her leg, P30 explained that they frequently forgot to do this:

A: (General practitioner) explains “You’re supposed to have your legs up all the time,” but I can’t—I wouldn’t say no . . . The answer would be yes, but I don’t do it.
 Q: Why is that?
 A: I don’t know. I just don’t think of it, I suppose [P30].

One participant described that they often had many self-care tasks prescribed to them that were often monotonous, and thus they found their attention was not directed to their self-care:

I guess, sometimes, when you’re getting ready for bed, if you’re tired and you’ve got about four or five things to do, they seem monotonous. Then I’ll get to bed and, if you are really tired, that seems like a load on your mind. But other times, you might say get them over and done with; and it’s all over in about five minutes [P27].

This participant indicated that a sense of persistence was important for overcoming the feeling of burdensome monotony associated with self-care.

DISCUSSION

We analyzed patients’ experiences, with the aim of identifying the barriers and enablers influencing patients’ adherence to venous leg ulcer treatment recommendations in primary care settings. There is a paucity in the literature examining strategies to enhance health-

promoting behaviors in patients with venous disease (Miller et al., 2014). Through utilizing the TDF, however, researchers can explain factors that influence patient adherence or non-adherence to VLU treatment. In this article, we specifically examined patient adherence to the main components of their venous leg ulcer management plan, including compression use, leg elevation, nutrition and exercise. In addition, patients also discussed their experience in scheduling and attending appointments—a key aspect of achieving optimal outcomes for their VLU. Compression adherence was of particular importance, given that current literature reflects that adherence to compression use on daily basis is as low as 28% (Atkin, 2019). We found that the most frequently discussed domains related to VLU patients’ adherence to VLU management plans included Knowledge, Social Influences, Beliefs about Consequences, Emotions, Environmental Context and Resources, Beliefs about Capabilities, Behavioral Regulation and Memory Attention and Decision Making (Tables 3, 4).

Participants often did not understand the significance of continued use of compression; and discontinued compression once healed. This is unsurprising, as the particular age demographic in our study (older adults) often prefer to acquire health information from a GP or other clinicians (Turner et al., 2018) rather than engage in self-directed inquiry through the use of the Internet (Chaudhuri et al., 2013). A few participants received either incorrect or inconsistent information from their clinicians (a nurse, a doctor and a vascular surgeon) in this regard. In some instances, participants did not get any health information on VLU management at all. This most certainly appears to be a missed opportunity for clinicians to build patients’ agency and provide an opportunity for shared decision making (Weller et al., 2021). Previous studies have examined the relationship between the delivery of health information, the development of greater patient health literacy and improved adherence to health-promoting behaviors (Miller et al., 2014). This is consistent with

our findings, as participants explained that once they understood the reason for their treatment, they were more motivated to adhere to treatment (Please refer to **Figure 4** for this and other suggestions on how to improve VLU treatment adherence). The proposed topics for health education may include the discussion of the main barriers to wearing compression therapy, body image issues, family support, and consequences of not wearing compression. It is pivotal that a GP, who first diagnoses a patient with a VLU, and the nurse, who changes dressings and applies compression provide a thorough assessment during consultation to empower patients to seek further information.

Other barriers to adherence to the VLU management plans include uncontrolled pain or discomfort; body image issues pertaining to societal norms, inadequate social support and competing commitments. These multiple factors need to be considered in order to change patients' behavior and improve their adherence to VLU treatment. Fostering a communicative and transparent clinician-patient relationship has been found to be mutually beneficial (Janamian et al., 2016). Clinicians may benefit from feedback on adherence interventions that are most impactful for the patients. Patients benefit from the opportunity having their opinions and experiences considered, and to be able to troubleshoot issues that impede VLU treatment adherence, particularly their adherence to compression (Castro et al., 2016). A patient centred approach may serve to improve the evidence-practice gap in VLU management that exists across primary care (Weller et al., 2020; Weller et al., 2020). A recent study determined that patient centred care in the management of chronic wounds led to greater patient satisfaction, increased patient knowledge, enhanced patients' adherence to VLU management, and improved quality of life (Gethin et al., 2020). Further research into the role of clinicians in VLU patient centred care may be warranted; as would identifying suitable strategies to foster engagement of patients in research and policy development (Weller et al., 2020).

CONCLUSION

Our article demonstrates the value in exploring the patient experience of adhering to evidence-based treatment of VLU. Though patient non-adherence has been described as challenging for clinicians, the issue is multifaceted and complex. There is a need to further explore factors that influence VLU patients' behaviors and provide an opportunity to plan interventions that best support both patients and clinicians in a shared decision-making capacity. The findings from this article will be relevant to clinicians involved in management of patients with venous leg ulcers, as their support is crucial to patients' treatment adherence. Consultation with patients about VLU treatment adherence is an opportunity for clinical practice to be targeted and collaborative. This process may inform guideline development.

Adequacy of the Selected Theory

The applied TDF (Atkins et al., 2017) was a useful approach to providing a theory-driven analysis to identify barriers and enablers to patients' adherence to VLU treatment. The

identified target behaviors of VLU patients may help to inform future implementation strategies in primary care settings (Phillips et al., 2015). However, these findings should be interpreted with caution. Qualitative approach, including theory-driven analysis aiming to identify barriers and enablers is frequently used in behavior change and implementation research. It is important note that researchers applying this approach may easily overlook the attribution of behavior (Sabini et al., 2001) or failure to behave as expected or prescribed, which may influence trustworthiness (Elo et al., 2014). Consideration should always be given to the attitude-behavior or intention-behavior gap (Godin et al., 2005).

In this study, some of the participants have mentioned that they have complete trust to their clinicians and health information they provide, nevertheless they did not follow their recommendations once compression was prescribed. Further, the participants discussed various factors that they believed had influenced their adherence to treatment. For example, they discussed that they did not use compression because of the body image-related issues, discomfort during hot weather, limited understanding the benefits of wearing compression and consequences of not wearing compression, the lack of family support with wearing compression stockings, and other barriers that fit well with the TDF constructs and domains. However, most of the participants did not wear compression because it was not prescribed to them by their GP, which was a real barrier. After prolonged suboptimal treatment in primary care, which has had no effect on VLU healing, they were referred to the specialist tertiary clinic, where compression was prescribed.

It is important to note that the TDF was developed for understanding the behavior of healthcare professionals related to implementation of evidence-based guidelines in clinical practice (Michie et al., 2005). We utilized this theory to explain patients' adherence to VLU treatment, aiming to bring patients' perspective on VLU management and to complement our study on the use of the VLU CPG recommendations in primary health care settings located in Melbourne metropolitan and rural Victoria, Australia (Weller et al., 2020).

As we already mentioned, our interview guide consisted of open-ended questions loosely matching the TDF domains (2017 version), and did not cover all 14 TDF domains. Therefore, the collected data are largely influenced by what questions the participants were asked, limiting the "richness" of data that could have been obtained using the qualitative approach alone (Phillips et al., 2015).

The theory-driven deductive analysis itself may limit the interpretative process, leaving no space for ideas that are not related to the theoretical domains of the TDF to be elicited (McGowan et al., 2020). By using the TDF domains as first-level codes and the TDF constructs as secondary level codes there is a danger that data are forced into the codes, limiting the interpretation.

Although we quantified how often or by how many participants references are made to specific constructs and domains, it is important to note that these numbers are highly influenced by the way the interviews were conducted, e.g., we much more explicitly asked for experiences and thoughts regarding compression adherence rather than the other VLU treatment

recommendations; and, this was not identical in all interviews. This, of course, is in accordance with qualitative methodology, but one of the reasons why counting how often or by how many participants references are made to has limited value.

Study Limitations and Recommendations for Research

As patients with VLU require complex treatment, comprising a number of different evidence-based approaches, it can be expected that barriers and enablers playing an important role in the several measures differ, as what they appeal to or need, indeed, differs. In this study, we focused predominantly on patients' adherence to compression therapy as it is the mainstay treatment identified by the VLU CPG. Future research about VLU patients' adherence to exercise, leg elevation and nutrition recommendations would be beneficial. Further studies may also explore individual factors that influence VLU patients' behaviors related to adherence to compression therapy. For example, VLU patients' body image issues related to VLUs and wearing compression garments may be an area to be explored in greater depth. Studies that explore patients' understanding the consequences of not wearing compression and not following other recommendations may also be of value to patients and clinicians to optimize healing outcomes in primary care.

We explored barriers and enablers that influence patients' adherence to VLU treatment using a qualitative inquiry. Future studies on patient adherence to VLU treatment may identify predictors and extent of patient adherence to the VLU treatment recommendations, using validated questionnaires about patients' adherence to health recommendations. Findings of these studies may provide information on the effectiveness of patient care management and outcomes, and identify patients with higher risk for poor adherence to inform and evaluate targeted interventions.

REFERENCES

- Andriessen, A., Apelqvist, J., Mosti, G., Partsch, H., Gonska, C., and Abel, M. (2017). Compression Therapy for Venous Leg Ulcers: Risk Factors for Adverse Events and Complications, Contraindications - a Review of Present Guidelines. *J. Eur. Acad. Dermatol. Venereol.* 31 (9), 1562–1568. doi:10.1111/jdv.14390
- Atkin, L. (2019). Venous Leg Ulcer Prevention 3: Supporting Patients to Self-Manage. *Nurs. Times* 115 (8), 22–26. <https://www.nursingtimes.net/clinical-archive/long-term-conditions/venous-leg-ulcer-prevention-3-supporting-patients-to-self-manage-29-07-2019/>
- Atkins, L., Francis, J., Islam, R., O'Connor, D., Patey, A., Ivers, N., et al. (2017). A Guide to Using the Theoretical Domains Framework of Behaviour Change to Investigate Implementation Problems. *Implement Sci.* 12 (1), 77. doi:10.1186/s13012-017-0605-9
- Australian Wound Management Association, New Zealand Wound Care Society (2011). *Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers*. Barton, ACT: Cambridge Publishing.
- Barnsbee, L., Cheng, Q., Tulleners, R., Lee, X., Brain, D., and Pacella, R. (2019). Measuring Costs and Quality of Life for Venous Leg Ulcers. *Int. Wound J.* 16 (1), 112–121. doi:10.1111/iwj.13000

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Monash University Human Research Ethics Committee and participating health services ethics committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CW developed the study proposal and secured the grant. VT and CW designed the interview guide. CR and LT conducted the interviews. VT, CR, and CW developed coding framework. CR coded the interview transcripts. LT was responsible for project administration. All authors contributed to data analysis and article writing. CR and VT prepared the first draft. The final version was approved by all authors. VT designed the infographic.

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- Boxall, S., Carville, K., Leslie, G., and Jansen, S. (2019). Compression Bandaging: Identification of Factors Contributing to Non-concordance. *Wpr* 27 (1), 6–20. doi:10.33235/wpr.27.1.6-20
- Brooks, J., Ersser, S. J., Lloyd, A., and Ryan, T. J. (2004). Nurse-led Education Sets Out to Improve Patient Concordance and Prevent Recurrence of Leg Ulcers. *J. Wound Care* 13 (3), 111–116. doi:10.12968/jowc.2004.13.3.26585
- Bui, U. T., Finlayson, K., and Edwards, H. (2019). The Diagnosis of Infection in Chronic Leg Ulcers: A Narrative Review on Clinical Practice. *Int. Wound J.* 16 (3), 601–620. doi:10.1111/iwj.13069
- Castro, E. M., Van Regenmortel, T., Vanhaecht, K., Sermeus, W., and Van Hecke, A. (2016). Patient Empowerment, Patient Participation and Patient-Centeredness in Hospital Care: A Concept Analysis Based on a Literature Review. *Patient Educ. Couns.* 99 (12), 1923–1939. doi:10.1016/j.pec.2016.07.026
- Chaudhuri, S., Le, T., White, C., Thompson, H., and Demiris, G. (2013). Examining Health Information-Seeking Behaviors of Older Adults. *Comput. Inform. Nurs.* 31 (11), 547–553. doi:10.1097/01.ncn.0000432131.92020.42
- Domingues, E. A. R., Kaizer, U. A. O., and Lima, M. H. M. (2018). Effectiveness of the Strategies of an Orientation Programme for the Lifestyle and Wound-Healing Process in Patients with Venous Ulcer: A Randomised Controlled Trial. *Int. Wound J.* 15 (5), 798–806. doi:10.1111/iwj.12930

- Elo, S., Kääriäinen, M., Kanste, O., Pölkki, T., Utriainen, K., and Kyngäs, H. (2014). Qualitative Content Analysis: A Focus on Trustworthiness. *SAGE Open* 4 (1), 2158244014522633. doi:10.1177/2158244014522633
- Finlayson, K. J., Parker, C. N., Miller, C., Gibb, M., Kapp, S., Ogrin, R., et al. (2018). Predicting the Likelihood of Venous Leg Ulcer Recurrence: The Diagnostic Accuracy of a Newly Developed Risk Assessment Tool. *Int. Wound J.* 15 (5), 686–694. doi:10.1111/iwj.12911
- Franks, P. J., Barker, J., Collier, M., Gethin, G., Haesler, E., Jawien, A., et al. (2016). Management of Patients with Venous Leg Ulcers: Challenges and Current Best Practice. *J. Wound Care* 25 (Suppl. 6), S1–S67. doi:10.12968/jowc.2016.25.sup6.s1
- Gethin, G., Probst, S., Stryja, J., Christiansen, N., and Price, P. (2020). Evidence for Person-Centred Care in Chronic Wound Care: A Systematic Review and Recommendations for Practice. *J. Wound Care* 29 (Suppl. 9b), S1–S22. doi:10.12968/jowc.2020.29.sup9b.s1
- Godin, G., Conner, M., and Sheeran, P. (2005). Bridging the Intention-Behaviour 'gap': the Role of Moral Norm. *Br. J. Soc. Psychol.* 44 (Pt 4), 497–512. doi:10.1348/014466604x17452
- Graves, N., and Zheng, H. (2014a). Modelling the Direct Health Care Costs of Chronic Wounds in Australia. *Wound Pract. Res.* 22 (120-4), 6–33. doi:10.3316/informit.272218893716909
- Graves, N., and Zheng, H. (2014n). The Prevalence and Incidence of Chronic Wounds: A Literature Review. *Wound Pract. Res.* 22 (1), 4–19. doi:10.3316/informit.272162994803134
- Guest, J. F., Ayoub, N., McIlwraith, T., Uchegbu, I., Gerrish, A., Weidlich, D., et al. (2017). Health Economic burden that Different Wound Types Impose on the UK's National Health Service. *Int. Wound J.* 14 (2), 322–330. doi:10.1111/iwj.12603
- Guest, J. F., Fuller, G. W., and Vowden, P. (2018). Venous Leg Ulcer Management in Clinical Practice in the UK: Costs and Outcomes. *Int. Wound J.* 15 (1), 29–37. doi:10.1111/iwj.12814
- Haardörfer, R. (2019). Taking Quantitative Data Analysis Out of the Positivist Era: Calling for Theory-Driven Data-Informed Analysis. *Health Educ. Behav.* 46 (4), 537–540. doi:10.1177/1090198119853536
- Janamian, T., Crossland, L., and Wells, L. (2016). On the Road to Value Co-creation in Health Care: the Role of Consumers in Defining the Destination, Planning the Journey and Sharing the Drive. *Med. J. Aust.* 204 (S7), S12–S4. doi:10.5694/mja.16.00123
- Jull, A. B., Mitchell, N., Aroll, J., Jones, M., Waters, J., Latta, A., et al. (2004). Factors Influencing Concordance with Compression Stockings after Venous Leg Ulcer Healing. *J. Wound Care* 13 (3), 90–92. doi:10.12968/jowc.2004.13.3.26590
- Kelechi, T. J., Mueller, M., Spencer, C., Rinard, B., and Loftis, G. (2014). The Effect of a Nurse-Directed Intervention to Reduce Pain and Improve Behavioral and Physical Outcomes in Patients with Critically Colonized/infected Chronic Leg Ulcers. *J. Wound Ostomy Continence Nurs.* 41 (2), 111–121. doi:10.1097/won.0000000000000009
- KPMG (2013). An Economic Evaluation of Compression Therapy for Venous Leg Ulcers. *Australian Wound Management Association*. Canberra: KPMG at the request of the Australian Wound Management Association.
- Leren, L., Johansen, E., Eide, H., Falk, R. S., Juvet, L. K., and Ljoså, T. M. (2020). Pain in Persons with Chronic Venous Leg Ulcers: A Systematic Review and Meta-analysis. *Int. Wound J.* 17 (2), 466–484. doi:10.1111/iwj.13296
- Lurie, F., Passman, M., Meisner, M., Dalsing, M., Masuda, E., Welch, H., et al. (2020). The 2020 Update of the CEAP Classification System and Reporting Standards. *J. Vasc. Surg. Venous Lymphatic Disord.* 8 (3), 342–352. doi:10.1016/j.jvsv.2019.12.075
- Mallick, S., Sarkar, T., Gayen, T., Naskar, B., Datta, A., and Sarkar, S. (2020). Correlation of Venous Clinical Severity Score and Venous Disability Score with Dermatology Life Quality index in Chronic Venous Insufficiency. *Indian J. Dermatol.* 65 (6), 489–494. doi:10.4103/ijdd.485_20
- McGowan, L. J., Powell, R., and French, D. P. (2020). How Can Use of the Theoretical Domains Framework Be Optimized in Qualitative Research? A Rapid Systematic Review. *Br. J. Health Psychol.* 25 (3), 677–694. doi:10.1111/bjhp.12437
- Meulendijks, A. M., Franssen, W. M. A., Schoonhoven, L., and Neumann, H. A. M. (2019). A Scoping Review on Chronic Venous Disease and the Development of a Venous Leg Ulcer: The Role of Obesity and Mobility. *J. Tissue Viability* 29 (3), 190–196. doi:10.1016/j.jtv.2019.10.002
- Meulendijks, A. M., Welbie, M., Tjin, E. P. M., Schoonhoven, L., and Neumann, H. A. M. (2020). A Qualitative Study on the Patient's Narrative in the Progression of Chronic Venous Disease into a First Venous Leg Ulcer: a Series of Events. *Br. J. Dermatol.* 183 (2), 332–339. doi:10.1111/bjd.18640
- Michie, S., Johnston, M., Abraham, C., Lawton, R., Parker, D., and Walker, A. (2005). Making Psychological Theory Useful for Implementing Evidence Based Practice: A Consensus Approach. *Qual. Saf. Health Care* 14 (1), 26–33. doi:10.1136/qshc.2004.011155
- Miller, C., Kapp, S., and Donohue, L. (2014). Examining Factors that Influence the Adoption of Health-Promoting Behaviours Among People with Venous Disease. *Int. Wound J.* 11 (2), 138–146. doi:10.1111/j.1742-481x.2012.01050.x
- Nussbaum, S. R., Carter, M. J., Fife, C. E., DaVanzo, J., Haught, R., Nussgart, M., et al. (2018). An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. *Value in Health* 21 (1), 27–32. doi:10.1016/j.jval.2017.07.007
- O'Meara, S., Cullum, N., Nelson, E. A., and Dumville, J. C. (2013). Compression for Venous Leg Ulcers. *Cochrane Database Syst. Rev.* 11, CD000265. doi:10.1002/14651858.CD000265.pub3
- Pacella, R., Tulleners, R., Cheng, Q., Burkett, E., Edwards, H. S. Y., et al. (2018). Solutions to the Chronic Wounds Problem in Australia: A Call to Action. *Wound Pract. Res.* 26 (2), 84–98. doi:10.3316/informit.733666000861426
- Phillips, C. J., Marshall, A. P., Chaves, N. J., Jankelowitz, S. K., Lin, I. B., Loy, C. T., et al. (2015). Experiences of Using the Theoretical Domains Framework across Diverse Clinical Environments: A Qualitative Study. *J. Multidiscip Healthc.* 8, 139–146. doi:10.2147/JMDH.S78458
- Presseau, J., McCleary, N., Lorencatto, F., Patey, A. M., Grimshaw, J. M., and Francis, J. J. (2019). Action, Actor, Context, Target, Time (AACTT): A Framework for Specifying Behaviour. *Implement Sci.* 14 (1), 102. doi:10.1186/s13012-019-0951-x
- Probst, S., Allet, L., Depeyre, J., Colin, S., and Skinner, M. B. (2019). A Targeted Interprofessional Educational Intervention to Address Therapeutic Adherence of Venous Leg Ulcer Persons (TIEIVLU): Study Protocol for a Randomized Controlled Trial. *Trials* 20 (1), 243. doi:10.1186/s13063-019-3333-4
- Probst, S., Séchaud, L., Bobbink, P., Skinner, M. B., and Weller, C. D. (2020). The Lived Experience of Recurrence Prevention in Patients with Venous Leg Ulcers: An Interpretative Phenomenological Study. *J. Tissue Viability* 29 (3), 176–179. doi:10.1016/j.jtv.2020.01.001
- Reich-Schupke, S., Doerler, M., Wollina, U., Dissemmond, J., Horn, T., Strölin, A., et al. (2015). Squamous Cell Carcinomas in Chronic Venous Leg Ulcers. Data of the German Marjolin Registry and Review. *JDDG: J. der Deutschen Dermatologischen Gesellschaft* 13 (10), 1006–1013. doi:10.1111/ddg.12649
- Ritchie, G., and Taylor, H. (2018). Understanding Compression: Part 2 - Holistic Assessment and Clinical Decision-Making in Leg Ulcer Management. *J. Community Nurs.* 32 (3), 22–29. https://www.semanticscholar.org/paper/Understanding-compression-%3A-part-2-%E2%80%94-holistic-and-Ritchie-Taylor/1b601612434de81974753ebd27111056c3fb0330
- Sabini, J., Siepmann, M., and Stein, J. (2001). Target Article: "The Really Fundamental Attribution Error in Social Psychological Research". *Psychol. Inq.* 12 (1), 1–15. doi:10.1207/s15327965pli1201_01
- Shanley, E., Moore, Z., Patton, D., O'Connor, T., Nugent, L., Budri, A. M., et al. (2020). Patient Education for Preventing Recurrence of Venous Leg Ulcers: A Systematic Review. *J. Wound Care* 29 (2), 79–91. doi:10.12968/jowc.2020.29.2.79
- Turner, A. M., Osterhage, K. P., Taylor, J. O., Hartzler, A. L., and Demiris, G. (2018). A Closer Look at Health Information Seeking by Older Adults and Involved Family and Friends: Design Considerations for Health Information Technologies. *AMIA Annu. Symp. Proc.* 2018, 1036–1045. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6371280/
- Walburn, J., Weinman, J., Norton, S., Hankins, M., Dawe, K., Banjoko, B., et al. (2017). Stress, Illness Perceptions, Behaviors, and Healing in Venous Leg Ulcers: Findings from a Prospective Observational Study. *Psychosom Med.* 79 (5), 585–592. doi:10.1097/psy.0000000000000436
- Weller, C., and Evans, S. (2014). Monitoring Patterns and Quality of Care for People Diagnosed with Venous Leg Ulcers: The Argument for a National Venous Leg Ulcer Registry. *Wound Pract. Res.* 22 (2), 68–73. doi:10.3316/informit.376731229504153
- Weller, C., Richards, C., Turnour, L., Green, S., and Team, V. (2019). Vascular Assessment in Venous Leg Ulcer Diagnostics and Management in Australian

- Primary Care: Clinician Experiences. *J. Tissue Viability* 29 (3), 184–189. doi:10.1016/j.jtv.2019.12.005
- Weller, C., Team, V., Ivory, J., Crawford, K., and Gethin, G. (2018). ABPI Reporting and Compression Recommendations in Global Clinical Practice Guidelines on Venous Leg Ulcer Management: A Scoping Review. *Int. Wound J.* 15 (1), 53–61. doi:10.1111/iwj.13048
- Weller, C. D., Barker, A., Darby, I., Haines, T., Underwood, M., Ward, S., et al. (2016). Aspirin in Venous Leg Ulcer Study (ASPiVLU): Study Protocol for a Randomised Controlled Trial. *Trials* 17, 192. doi:10.1186/s13063-016-1314-4
- Weller, C. D., Buchbinder, R., and Johnston, R. V. (2016). Interventions for Helping People Adhere to Compression Treatments for Venous Leg Ulceration. *Cochrane Database Syst. Rev.* 3, CD008378. doi:10.1002/14651858.CD008378.pub3
- Weller, C. D., Bouguettaya, A., Britt, H., and Harrison, C. (2020). Management of People with Venous Leg Ulcers by Australian General Practitioners: An Analysis of the National Patient-encounter Data. *Wound Rep. Reg.* 28 (4), 553–560. doi:10.1111/wrr.12820
- Weller, C. D., Richards, C., Turnour, L., Patey, A. M., Russell, G., and Team, V. (2020). Barriers and Enablers to the Use of Venous Leg Ulcer Clinical Practice Guidelines in Australian Primary Care: A Qualitative Study Using the Theoretical Domains Framework. *Int. J. Nurs. Stud.* 103, 103503. doi:10.1016/j.ijnurstu.2019.103503
- Weller, C. D., Richards, C., Turnour, L., and Team, V. (2020). Rationale for Participation in Venous Leg Ulcer Clinical Research: Patient Interview Study. *Int. Wound J.* 17 (6), 1624–1633. doi:10.1111/iwj.13438
- Weller, C. D., Richards, C., Turnour, L., and Team, V. (2020). Understanding Factors Influencing Venous Leg Ulcer Guideline Implementation in Australian Primary Care. *Int. Wound J.* 17 (3), 804–818. doi:10.1111/iwj.13334
- Weller, C. D., Team, V., Ivory, J. D., Crawford, K., and Gethin, G. (2019). ABPI Reporting and Compression Recommendations in Global Clinical Practice Guidelines on Venous Leg Ulcer Management: A Scoping Review. *Int. Wound J.* 16 (2), 406–419. doi:10.1111/iwj.13048
- Weller, C., Richards, C., Turnour, L., and Team, V. (2021). Venous Leg Ulcer Management in Australian Primary Care: Patient and Clinician Perspectives. *Int. J. Nurs. Stud.* 113, 103774. doi:10.1016/j.ijnurstu.2020.103774
- Xie, T., Ye, J., Rerkasem, K., and Mani, R. (2018). The Venous Ulcer Continues to Be a Clinical challenge: An Update. *Burns Trauma* 6 (1), 18. doi:10.1186/s41038-018-0119-y

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Meager Perception of Preconception Care Among Women Desiring Pregnancy in Rural Areas: A Qualitative Study Using Focus Group Discussions

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Background: India has the second-highest number of under-five deaths in any country in the world. WHO and the Government of India recommended the rollout of preconception care (PCC) to reduce maternal and child mortality. However, very few countries, including India, have started a comprehensive package of PCC services. It implies that women, mainly from rural and tribal areas, are not aware of PCC. PCC has been rolled out through the government health system in two blocks of Nashik district in Maharashtra state, India, among all women who desire to be pregnant within 1 year. This project is the first of its kind in India. To assess basic perceptions, knowledge, and behavior of women on PCC before the implementation of the project, focus group discussions (FGDs) were carried out. The authors think that the finding may help to develop strategies for behavioral change communication.

Methods: From each of the four blocks, two villages having subcenter were selected for conducting FGD. A house-to-house survey was conducted by Accredited Social Health Activist (ASHA) to enlist women who desire a baby in 1 year and invite them to subcenter for FGDs, which were conducted in June 2018.

Results: A total of 76 women having a mean age of 23.97 years participated in the FGDs. Most of them (46.05%) had completed 10 years of education. About 50% of pregnancies were planned. The decision about the timing of the first pregnancy is influenced by the mother-in-law. Women knew that they should not conceive before 20 years of age, and their suboptimal weight may have an adverse impact on the health of the newborn. There are many myths about food like "hot and cold foods" and "forbidden food" etc. Women had some knowledge about the adverse effects of tobacco and alcohol; very few

consumed these. Most of them did not practice behaviors or accessed services related to PCC.

Conclusions: Women neither have the knowledge nor adopt behaviors or accessed services related to PCC. Roll out of PCC among them may help in further reduction of maternal and neonatal morbidity and mortality in India.

Keywords: knowledge, behavior, preconception care, food habits, height and weight, tobacco consumption, alcohol consumption, Maharashtra

INTRODUCTION

In India, the total number of deaths below 5 years of age reduced from 3.2 million in 1990 to 0.82 million in 2019. In 2019, India had the second-highest number of under-five deaths (1). There are wide inter and intrastate variations in under-five mortality and neonatal mortality (2). The common causes of neonatal mortality are preterm birth, birth asphyxia, and infection (3). The indirect causes are unplanned pregnancies, maternal undernutrition, pregnancies in adolescents, poor quality services, or inability to access care during the antenatal period, most notably intrapartum care and the neonatal period, etc. (4). Hence, WHO recommended the rollout of preconception care (PCC) in all the countries in 2013 (4). *Rashtriya Bal Swasthya Karyakram* Government of India published a report in 2018, which focused on creating awareness about PCC among couples. The commitment of the Government of India to the global community for ending preventable newborn death in India is articulated in the India Newborn Action Plan 2014, (5) based on Pan American Health Organization (PAHO) and WHO guidelines (6, 7). One of the six pillars of the India Newborn Action Plan is promoting PCC. However, PCC has not been rolled out systematically in India and most countries. Presently, PCC activities are limited to family planning and peri-conceptual folic acid administration. The coverage of peri-conceptual folic acid is low in most countries, and it is not captured in the routine health management information system. Behavioral changes constitute a major share of components of recommendations by WHO (4). The Government of Maharashtra, with the support of UNICEF, has started PCC in one tribal block (Peint) and one nontribal block (Sinnar) in Nashik district since 2018. Fourteen recommended interventions by PAHO are relevant for India (6). PCC package must address 13 categories of risk factors (4). The authors identified the following seven interventions for PCC implementation at the primary health-care level in these two blocks: enlisting of women who are planning pregnancies, clinical examination supported by laboratory testing, treatment, referral to higher facilities, prophylactic supplementation, monthly follow-up, and the overarching strategy of behavioral change communication using different media. The main criteria for the identification of these interventions were the magnitude of the problem in the community, cost, and feasibility of implementation at the primary health-care level.

The perception of health-related issues is determined by several factors. They may be grouped under biological (age and sex), socioeconomic (education, income, occupation, cultural

practices, and past experiences), topographical, psychological factors, etc. Knowledge is one of the strong determinants. The assessment as well generation of perception is an intricate process. In the absence of any uniform PCC services in the public sector, the near absence of specialists in rural/tribal areas, low female literacy level, we felt that basic perceptions based on past experiences and culture could be recognized. These will be useful in deciding the contents of Behavior Change Communication (BCC) material and the resources required for the implementation of the PCC project.

To our knowledge, in India, this is the first qualitative study at the community level on preconception knowledge and behavior among women desiring pregnancy in near future.

The objectives of these focus group discussions (FGDs) were to find out whether women have any knowledge about PCC, to identify PCC-related behavior, and access the PCC services.

MATERIALS AND METHODS

Consolidated criteria for reporting qualitative research (COREQ) have been adopted to report the findings.

The Research Team and Reflexivity

Personal Characteristics

Four faculties from the Department of Community Medicine and authors of the study conducted FGDs acting as moderators. They are postgraduates in community medicine, and one is Doctorate. Two moderators are male and two are females. The moderators have experience ranging from 15 to 42 years. Two research coordinators acted as facilitators and helped moderators. Both are women with postgraduation in public health.

Relationship With Participants

The moderators and facilitators met the participants for the first time during FGDs. However, health-care workers like Accredited Social Health Activist (ASHA) and Auxiliary Nurse Midwife (ANM) had briefed them about the authors and the study and the planned actions after the FGDs.

Study Design

Theoretical Framework

The study comprised eight FGDs. After conducting FGDs, the authors carried out the content analysis.

Participant Selection

Trained ASHAs conducted a house-to-house survey using structured, validated, and pretested formats. ASHAs specifically

asked each woman in the reproductive age group about her desire to have a child succeeding 1 year. A village-wise list of all such women was prepared. The authors randomly selected eight subcenter villages for conducting FGDs. ASHAs invited all eligible women for FGD and communicated to them the time and place of discussion. About 20% did not attend the discussions.

Setting

The study was conducted in Nashik district situated in north Maharashtra, India. The district has a population of 6,107,187 (census, 2011) scattered in 15 blocks. The proportion of the rural population in the district is 57.47%, inclusive of 31.55% tribal population. Before the intervention, four FGDs were conducted in these selected blocks (Tribal, Peint, and nontribal Sinnar) and an additional four control blocks (Tribal block, Trimbakeshwar, and non-tribal block Niphad). The total population of these four blocks is 976,149, of which the tribal population is 38.56%. The Tribal blocks have hilly terrain, suboptimal transportation facilities, and are away from urban areas. The literacy, particularly among women, is low. Blocks identified for the study are depicted in **Figure 1**.

The information like literacy rate, number of villages in these blocks, number of villages selected for FGDs with the number of households, and population in these villages are given in **Table 1**.

The FGDs were conducted in subcenter buildings. The ANMs of the subcenters were not involved. The age group and education of participants are given in **Tables 2, 3**. The FGDs were conducted in June 2018.

Data Collection

The authors, through the consultative process, prepared a guide for conducting FGDs. The authors first validated and pretested it in an area that was not a part of the study. It had the following themes.

1. Planning of pregnancy
2. Age of the woman
3. Height and weight of the woman
4. Physical work
5. Nutrition
6. Tobacco and alcohol consumption
7. Medical/health assistance before pregnancy
8. Preconception services

The moderators had interactions with the women once only. All the communication was in the local language (Marathi). In each FGD initially, the moderator explained the purpose of the meeting and appealed active participation in the discussion. Their written informed consent was obtained for participation, audio recordings, and subsequent publication. The numbered placards were given to each participant to avoid personal identities. The authors encouraged the non-speaking women to speak. The discussion was initiated by few words about subthemes. Further probing was done if the discussion was digressed. All procedures were recorded. The facilitator also took written notes. The average time taken for one FGD was about 55 min. The transcripts were read and heard many times before translation into English. The transcripts are deposited in the department and UNICEF.

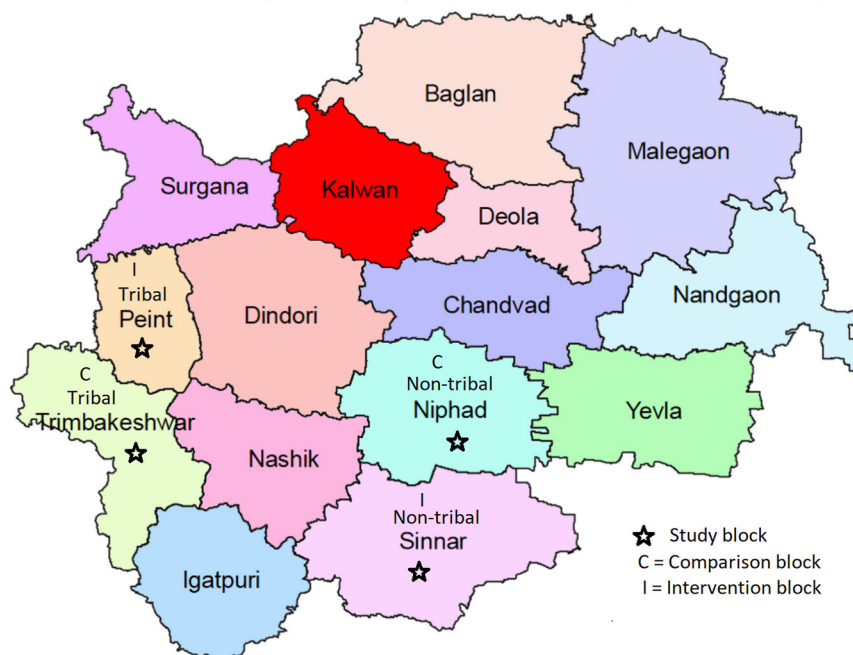


FIGURE 1 | Blocks in Nashik district, India.

TABLE 1 | Blocks and villages in the study area, Nashik District, India, 2018.

S. No.	Block	Female literacy rate %	Villages in the block	FGD number name of villages in which conducted	Households	Village population
1	Peint (T)	53.34	145	1. Bhaygaon 2. Gonde	298 254	1,447 1,276
2	Sinnar (NT)	48.93	131	3. Kundewadi 4. Datli	284 429	1,959 2,356
3	Trimbakeshwar (T)	63.93	126	5. Torangan, 6. Shirasgaon	367 280	1,984 1,795
4	Niphad (NT)	66.34	137	7. Chitegaon 8. Kothure	881 1,022	4,616 5,022
	Total	61.19	539	8	3,815	20,455

FGD, Focus group discussion; T, Tribal; NT, Nontribal.

TABLE 2 | Age of the women participating in FGD, Nashik, India, 2018.

Age group (years)	Number	%
15-19	5	6.58
20-24	42	55.26
25-29	21	27.63
30-34	7	9.21
35-39	1	1.32
Total	76	100.00

Mean age = 23.97 years (SD = 4.12); range 18 to 39 years.

TABLE 3 | Educational status of the woman participating in FGD, Nashik, India, 2018.

Educational status	Number	%
Illiterate	3	3.95
Up to primary (1st–7th std.)	12	15.79
Up to secondary- SSC (10th)	35	46.05
Up to HSC (12th)	17	22.37
Up to graduation	9	11.84
Total	76	100.00

SSC, Secondary School Certificate; HSC, Higher Secondary Certificate.

Ethical Considerations

Approval from the Institutional Ethics Committee was obtained before the initiation of the study. Authors obtained informed consent for participation and publication from all the women. All personal identifiers were removed before the data analysis; only de-identified data were analyzed.

RESULTS AND ANALYSIS

The number of participants in the FGDs ranged from 6 to 12. More than 92% of women were in the age group of 20 to 40 years. About 80% had school-level education. The number of participants and FGD number are given in bracket in the

script while including specific quotes. Moderators observed that in most of the FGDs, and participants needed a little more persuasion to initiate the discussion. For all the FGDs, the discussions were initiated with an inquiry about the details of family members, including the number of children the participants had. This initial discussion helped to break the ice. The moderator initially led the discussion toward pregnancy care for a short time and then the perception of participants about the care before pregnancy. The analysis was done using MAXQDA. Two researchers independently coded themes and codes, and any discrepancy was discussed among researchers and resolved.

Following are the key observations that are documented during the FGDs as per the subthemes.

Pregnancy Planning

It was a concern, and its decision was taken by the family rather than the couple. In-laws or elderly persons in the family expect a child from the couple immediately after the marriage. However, many times a couple wants to postpone the pregnancy, discontinue the unplanned pregnancy, but it is carried forward, and the right of a woman to decide about abortion or to make choices is not given any importance. "...no, the first baby was eight months old, and I had conceived that time, but my family did not support abortion. They said let anything happen, but not to do abortion as it is another life" (7/3).

However, it was observed that some couples are having a dialogue on pregnancy planning. Such a process of joint decision-making positively impacts the health and empowerment of women. Few women narrated their experiences. "I had asked my husband if we want a child or not. We decided that time, after check-up... now we don't want a second baby, let's see..." (2/8). It was also noted that some women are not having clarity on whether they should have a child or when to have it. This was observed among recently married women, including those educated. The reason may be the lack of empowerment for decision-making among married women despite being educated. In many cases, women are unable to express and execute their wish not to have a child. A woman wanted to join the school and was unwilling to have a child; however, she did not communicate

this with her husband, and both of them were not using any contraceptives (2/2).

Another observation was that people do not have any gender preference when the woman has conceived for the first time; however, the second time, gender opposite of the first child is desired. Usually, in such cases, the first girl child is accepted; however, the pressure on the woman to have a son is more when she plans for a second child.

"I have the first daughter. Now, my family desires that there should be a son" (4/8).

"Son is preferred... my husband also wants a son" (1/8).

FGD facilitator: "Are you worried that you may not give birth to a son?"

"Yes, it is expected. It is good if there is a son..." (2/8). The pregnancy planning concept is not yet widespread or widely practiced in the community. Instead, the term "family planning" is understood as the spacing between two children or not having a child. This perception in the community could be a result of government efforts. Various contraceptive methods were introduced for population control under, "family planning program." It was also observed that planning is not done for the first pregnancy; however, after the first child, spacing between the first and the second child is practiced.

Women narrated experiences of domestic violence if they are unable to give birth to a child. Contrarily, women think that violence stands as a barrier in conception.

Concept of a Healthy Mother and a Healthy Baby

Women think that a healthy mother will deliver a healthy child. They feel that a child with a fair skin complexion looks chubby, has a minimum 3 kg weight at birth, does not have deformity, is healthy, etc. A woman said, "a healthy should understand the touch, his/her nutritional needs, and should have got mental development" (3/4).

Women also shared the concept of a full-term baby. "The baby should be born after completing 9 months and 9 days in the mother's womb... the baby needs to be kept in the glass box if the baby is born premature... the weight of the baby should not be less than 2.5 kg. preferably, it should be between 2.5 to 3.5 kg at birth..." (9/3). Participants also described the concept of a healthy mother in various ways. Few women knew that height is also a determinant of weight and some women have weight disproportionate to their height, concept of body mass index (BMI). According to them, if the weight of a mother is low, the child will be malnourished and will have low birth weight. Participants described the following criteria about a healthy mother.

- The age of a mother should be more than 18- to 20 years and less than 30 years; however, some women said an expecting mother should be of 24 years as they are matured to become a mother. "19 years is not the age to become a mother; at this age, the baby does not grow properly in her womb. She becomes weak after delivery" (3/7).
- The mother should have positive thinking during pregnancy.
- The mother should have sufficient blood in the body.

A woman ideally should conceive 2 years after her marriage because by then, she gets some information about caring for the child. Some women think that girls should not get married before 21; otherwise, they cannot complete their education. Women are generally unaware of the consequences of early marriage; they feel that it will cause some problems during delivery. "The gap between two children should be a minimum of 2 years. Because I think that a woman does not suffer more if the gap between the two is longer..." (2/4).

Physical Work

Participants think that before conception rest is not needed, because inactivity may lead to obesity, which would result in the inability to conceive. Instead, the woman should rest well after she conceives. Apart from physical activity and diet, few women talked about the mental health of a pregnant woman. They also shared their experience that a woman having stress may have difficulty in conceiving.

Nutrition/Diet Concepts

Concepts of "hot food" and "cold food" are prevalent as traditional knowledge of food and its close association with health is firmly rooted. Most of the women used the concept of a "balanced diet" for a pregnant woman. Only one woman mentioned Take-Home Ration (THR) food served from Anganwadi, which indicates the low awareness and utilization of government programs.

Traditionally, some women use iron vessels for cooking, which serves as a good source of iron, and its use has been documented for addressing iron deficiency, anemia. However, it was also observed that aluminum and steel vessels are commonly used for cooking. In contrast, an iron pan was popularly used to make roti (bread of wheat flour)/ bhakari (bread of sorghum millets), an Indian bread made of wheat or sorghum flour. The food items to be eaten or not be eaten by a pregnant woman or a woman who wants to conceive, mentioned by them, are given in **Table 4**. Apart from the list, women provided the following thumb rules to be followed by a pregnant woman:

- Must eat a minimum of three times a day.
- Must eat on time.
- Must not keep fast as it causes weakness.

Tobacco and Alcohol Consumption

Most women said older women mainly use Mishri, and alcohol consumption is highly prevalent among men. Women are aware that cigarette causes cancer. They also said that if a pregnant woman consumes alcohol or cigarette, then it harms the fetus. A woman narrated an experience of a woman who used Mishri even during her pregnancy. Her fetus was found abnormal, and later it was aborted (5/8). Some of the women said that few women drink locally produced alcohol. Some women reported that "Older women consume tobacco." Though they are unaware of the consequences of alcohol consumption, tobacco consumption on pregnant mothers and fetuses, they understand it is bad for the health of the child. Women think that it will cause an abnormality in the fetus or lead to abortion or die inside the womb.

TABLE 4 | Perceptions of women about food items during preconception and pregnancy.

Must eat food items	Don't eat food items
Milk	Oily/ fried food items
Fruits	Spicy foods as they are considered to be hot food
Available green leafy vegetables, Shepu (Dill leaves), Chavali (black eyed beans)	Papaya and banana
Cereals	Salty food
Eggs	Eggs in summer as they are considered as hot food
Chicken	
Fruit vegetables	
Curd, buttermilk is cold and beneficial	
Dal Khichadi (a dish made of rice and lentils)	

Health Services Before Pregnancy

Women seek health care before pregnancy only when they are unable to conceive despite trying. Women think that doctors can ascertain the need for conception treatment. For PCC, women enlisted the following problems/tests during a checkup:

- Calcium deficiency.
- Tablets to increase blood amount.
- Blood pressure.
- HIV test.
- Swine flu test.
- Hemoglobin.
- Blood sugar levels.
- Height and weight.
- Thyroid.
- Jaundice.
- Vaccination.
- Ultrasound.

Family decision plays a vital role for accessing health services. A woman cannot get treatment without the concurrence of her family. Most of the women think that care should be taken after conception. However, it was seen that very few women are aware of PCC, right from the planning of pregnancy, so that the child will be healthy. However, the majority were not aware of the PCC.

Women from tribal areas seek help from Bhagat (local spiritual healer) if they are not conceiving. Bhagat asks them to keep fast and worship the goddess. Also, prescribes herbal medicines. Women were not aware of the blood group and its significance. Women are also unaware of sexually transmitted diseases. Women are generally unaware of when to seek health care.

However, they are aware that overweight or obese women may have difficulty while conceiving. Women also explicitly said that if the husband does not communicate well with his wife, then planning a child does not make any sense as it is a mutual decision. "Husband should be sensible... if we say something,

and what if he does not listen?" (2/2). Women are also aware that a low-weight mother gives birth to low-weight baby.

Women listed some of the do's and don'ts for a woman who wants to conceive:

"Not to eat tobacco" (1/5)

"Do not apply Mishri (roasted tobacco applied on teeth/gums)" (3/5)

"Do not fast" (5/5)

"Not to eat spicy food" (6/5)

Figure 2 depicts in a usual format the themes and subthemes that emerged after analysis (8).

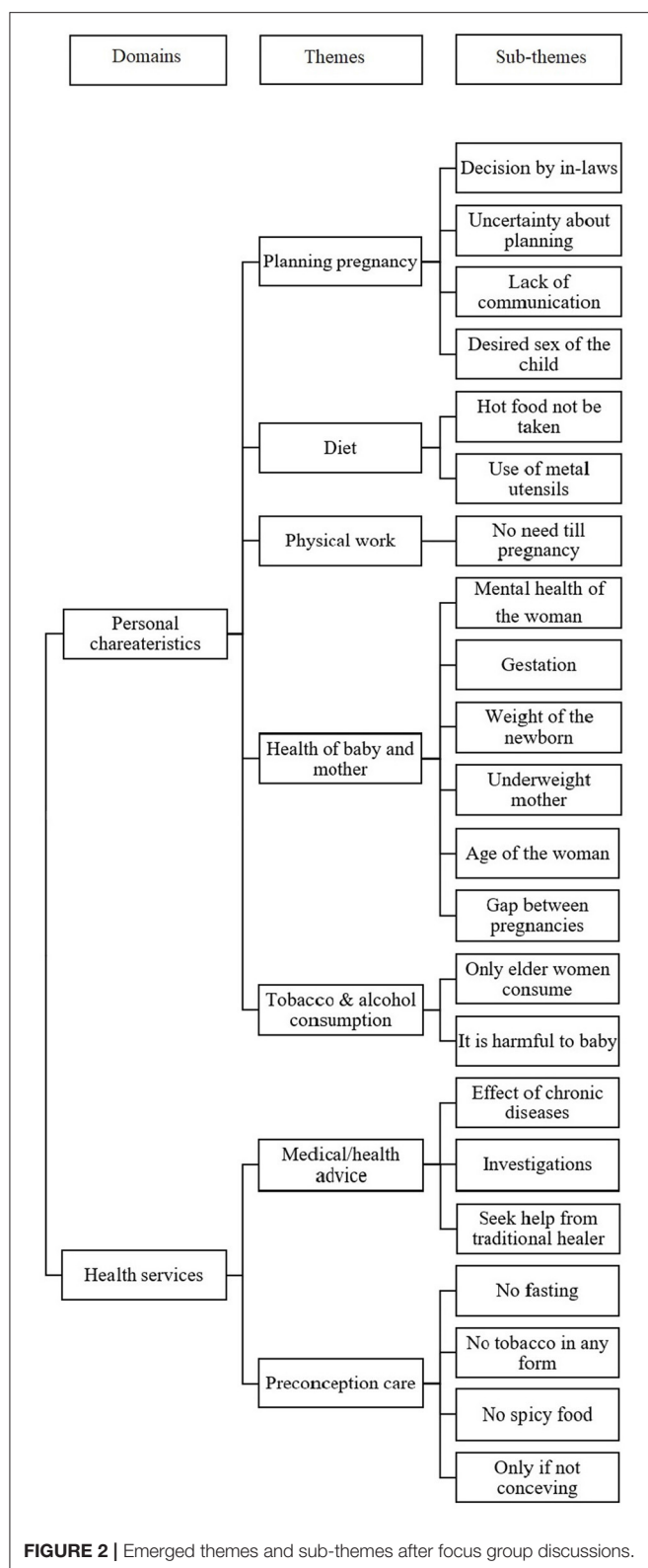
There was no difference between the two groups regardless of the proposed intervention.

DISCUSSIONS

The study participants were only from rural areas, including two tribal blocks. Considering the one million population and 539 villages of these four blocks, we conducted two FGDs per block. The women in these groups were more or less having the same age and educational level, hence, disaggregation by age or education to control for its differing effects was not necessary. It was not intended also. The study showed that overall knowledge about PCC is low among women desiring pregnancy within 1 year. A few of them practiced behavior associated with optimizing the BMI, improving hemoglobin levels and very few accessed services related to PCC. The PCC is not rolled out in the government and the private health sector as yet. Health promotion, self-care may be necessary for promoting PCC (9). Many studies on PCC conducted among women visiting hospitals also reported similarly low levels of knowledge (10–16). In a study in the United States of America (USA), lack of knowledge was identified as the most crucial barrier to the practice of preconception behavior, the second most crucial barrier was the cost (17). China is a world leader in the implementation of PCC, covering its entire rural population. National Preconception Health Care Project was scaled up to all the rural areas of the country since 2013, and all couples planning pregnancy within 6 months were assessed for risk factors using an ABCDX category of preconception risk factors. It was found that 68.29% of couples had one or more preconception risk factors. The spectrum included avoidable risks like smoking and alcohol consumption; manageable through medical interventions like anemia, reproductive tract infections in women, abnormal liver or renal functions in men; controllable risk factors including diseases and conditions that cannot be cured, but risk factors can be modified (18). In India, PCC is largely restricted to contraceptives for family planning purposes and peri-conceptual supplementation of folic acid, rather than for promoting land of woman and man, and health of the newborn.

Planning of Pregnancy

The mother-in-law influences the decision for planning the first pregnancy. However, the couples have greater decision-making power for planning subsequent pregnancies. In India, it is estimated that in 2015, out of 48.1 million pregnancies, 48% were unintended; of which, 33% were aborted, 5% were miscarriages



from unintended pregnancies, and 11% were unintended births (19). Unintended pregnancies every year result in 25 million unsafe abortions and 47,000 maternal deaths globally, as per

estimates of WHO (20). Implementation of comprehensive PCC will go a long way for preventing unintended pregnancies, thereby reducing the burden on women for abortion and thus prevent maternal ill-health and deaths due to unsafe abortion.

Nutrition and Body Weight

Women were knowledgeable about the intake of various types of food groups. However, they did not know about the appropriate weight, when they should conceive. The women were not aware of the use of multiple micronutrients for preventing adverse pregnancy outcomes. In the USA, women had better knowledge about folic acid supplementation before pregnancy (15).

Tobacco and Alcohol Consumption

In Kenya, most women know that they should avoid alcohol both before pregnancy and during pregnancy (10). In the USA, women know about alcohol and drug consumption risk during the preconception period (15). The discussions pointed out that the habit of tobacco consumption is decreasing among young girls, which is in concordance with national-level surveys (19).

Medical Advice Before Pregnancy

Women have limited knowledge about the effect of chronic medical conditions like diabetes and hypertension on pregnancy planning and thereby on the health of the newborn (18). Contrarily in another study, many women opined that they must seek treatment for anemia, obesity, and diabetes before pregnancy, and hypertension before or during pregnancy causes miscarriage (10).

Preconception Services: Knowledge and Utilization

Knowledge or awareness about PCC differs widely in different countries. A systematic review of 34 studies from 2000 to 2017 from 14 countries revealed that the tools assessing preconception health knowledge usually focus on fertility, folic acid supplementation, alcohol consumption, mental health, and some issues about the health of men (13, 21, 22). Another systematic review of studies done during 1998 and 2008 focusing on factors related to preconception health behaviors among childbearing age women in the United States, developed countries, and developing countries identified six major thematic areas: frequency of alcohol intake before and during pregnancy, glycemic control/diabetes management, physical activity before and during pregnancy, pregnancy planning behavior, cystic fibrosis carrier screening, and other risk factors (13, 21, 22). In the United Kingdom, women from different geographical regions have only modest knowledge (23). Women in the USA have low to moderate knowledge of issues related to preconception health (24). The proportion of women knowing PCC varied from 7 to 85% in different countries (11, 12, 14, 15, 25–27). Usually, most of the women have a positive attitude toward seeking PCC (14, 16, 22, 26). About one-third of men and 60% of women in Jordan strongly agreed that parental health might seriously affect the health of the expected baby (28). In a study in South Ethiopia, about 20% of the women who just delivered were found to have good knowledge about PCC. In a study in Colorado, USA,

young women have greater motivation for pregnancy prevention and contraception than promoting preconception health. In another study, participants agreed on improving preconception health, mostly among the predominantly low-income group, the Mexican American population in the United States. Most of the desired information is from obstetricians (15). There was a lack of knowledge about PCC among women having chronic non-communicable diseases and a lack of intent for preconception health promotion and pregnancy planning among women in Hershey (18). About 15% of women were aware of preconception folic acid supplementation in North-western Ethiopia (29). The highest knowledge was about Reproductive and Child Health (RCH) risk factors and the lowest about health promotion (27). Most women have average knowledge of PCC, including verbal, physical, and sexual abuse (15).

Irrespective of knowledge and attitudes, only about 32 to 50% of women seek PCC in Nepal, Nigeria, Malaysia, and Iraq (11, 13, 14, 26).

Barriers include lack of social support and lack of awareness; women opined that the objectives of the program might be promoting healthy babies rather than preventing unhealthy babies (30).

Knowledge on PCC is usually found to be associated with education, age of the woman, number of children, family planning measures, receipt of information, chronic health problems, and monthly income in Zambia, Northwest Ethiopia, and Nepal (12, 25, 29, 31).

PCC is comparatively new in India. The women consulting obstetricians may receive some information and services. Federation of Obstetric and Gynecological Societies of India in 2016 formulated the National PCC guidelines for their members recommending actions are based on the strength of recommendation and extent of evidence for providing PCC to women. However, only a few private practitioners comprehensively provide PCC in India (32). In the study area, there are no specialists.

Readers should view all these findings in the background of rural and tribal women who are poor, have low educational levels, and lack access to the services of specialists. The government of India is already planning the uniform implementation of PCC. In the background of findings of this study, the government must pay attention to three major aspects: the contents, communication with in-laws including husband, and counseling training to all frontline health workers, including ASHAs. These activities should go parallel to the provision of medicines and equipment. The financial implications are not high compared to the potential accrued benefits.

Strengths and Limitations

The moderators and facilitators are experienced and qualified personnel. They conducted the FGDs in the local language (Marathi) and are fluent in that language. There were no distractors. All eligible women from selected villages were invited. The findings are representative of women from an entire district population of more than 6 million.

The mothers-in-law were not included in the study. The group of participants mainly consisted of women having low levels of

education. Emphasis on preconception health of men was almost lacking. The place of FGD was a subcenter building, which may affect their expressions. We conducted the study in rural and tribal settings; the findings may not represent the urban areas.

CONCLUSIONS

The women had some knowledge about antenatal care only. About 50% of the pregnancies were planned. The women had very little knowledge about PCC, and service utilization was unsatisfactory. No participant knew about specific health conditions needing treatment before conception and their adverse impact on the health of the newborn. The participants were aware of some hazards of tobacco and alcohol consumption. A small proportion of participants had an addiction to tobacco and alcohol, but men in the family had. The behavior of smoking and alcohol consumption of the husband was not considered as a risk for pregnancy. There is an urgent need to educate the community about PCC and provide PCC services to promote maternal and newborn health and prevent maternal and newborn mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Institutional Ethics Committee (DCGI Regd. No. ECR/313/Inst/MH/2013/RR-16) approved the study vide reference number; BVDUMC/IEC/11 Dated; 30-04-2018. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PD, JG, PP, SP, AP, MK, AS, and KB designed the concept of assessment of the PCC programme in Nashik District. PD, JG, PP, SP, and AC conducted the FGDs. AD and MK helped to assemble women. PD, JG, and AC performed data analysis. PD wrote the first draft of the manuscript. JG and KB revised the manuscript extensively. All authors approved the final version for publication. All authors have the appropriate permissions and rights to the reported data.

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REFERENCES

1. UNICEF, WHO, WORLD WBG. *UN IGME Child mortality report 2019*. (2019). Available online at: <https://www.unicef.org/media/60561/file/UN-IGME-child-mortality-report-2019.pdf>
2. Office of the Registrar General Government of India. *Estimates of mortality indicators*. (2018).
3. WHO. Newborns: improving survival and well-being. (2020) Available online at: <https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality> (accessed September 21, 2020)
4. World Health Organization. *Preconception care: Maximizing the gains for maternal and child health*. (2013).
5. Ministry of Health & Family Welfare Government of India. INAP India Newborn Action Plan. (2014).
6. Pan American Health Organization. *Neonatal IMCI evidence-based interventions*. (2011).
7. WHO. Sixty-Seventh World Health Assembly. *WHA67/2014/Rec/1*. (2014) 1–5. Available online at: https://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=59
8. Dumont-Mathieu TM, Bernstein BA, Dworkin PH, Pachter LM. Role of pediatric health care professionals in the provision of parenting advice: A qualitative study with mothers from 4 minority ethnicocultural groups. *Pediatrics*. (2006) 118:e839–48. doi: 10.1542/peds.2005-2604
9. Bhuyan KK. Health promotion through self-care and community participation: elements of a proposed programme in the developing countries. *BMC Public Health*. (2004) 12:1–12. <http://www.biomedcentral.com/1471-2458/4/11>
10. Wanyonyi M, Victor D. Maternal knowledge on preconception health care topics at moi teaching and referral hospital in Eldoret, Uasin Gishu County, Kenya. *Int J Adv Res*. (2017) 5:2176–85. doi: 10.21474/IJAR01/4366
11. Nepali G, Sapkota SD. Knowledge and practice regarding preconception care among antenatal mothers. *Int J Percept Public Health*. (2017) 1(4):224–7.
12. Mutale P, Kwangu M, Chishala MKM, Muchemwa C, Silitongo M, Chileshe M. Knowledge and preconception care seeking practices among reproductive-age diabetic women in Zambia. *Int J Transl Med Res Public Heal*. (2017) 1:36–43. doi: 10.21106/ijtmrph.48
13. Olowokere AE, Komolafe A OC. Awareness, knowledge and uptake of preconception care among women in ife central local government area of Osum State, Nigeria. *J Community Med Prim Heal Care*. (2015) 27:83–92.
14. Kasim R, Draman N, Kadir AA, Muhamad R. Knowledge, attitudes and practice of preconception care among women attending appointments at a rural clinic in Kelantan. *Educ Med J*. (2016) 8:57–68. doi: 10.5959/eimj.v8i4.475
15. Coonrod D V., Bruce NC, Malcolm TD, Drachman D, Frey KA. Knowledge and attitudes regarding preconception care in a predominantly low-income Mexican American population. *Am J Obstet Gynecol*. (2009) 200:686.e1–686.e7. doi: 10.1016/j.ajog.2009.02.036
16. Frey KA, Engle R, Noble B. Preconception healthcare: What do men know and believe? *J Mens health*. (2012) 9:25–35. doi: 10.1016/j.jomh.2011.11.001
17. Cairncross ZF, Ravindran S, Yoganathan S, Dennis CL, Enders J, Graves L, Mill C, et al. Measurement of preconception health knowledge: a systematic review. *Am J Heal Promot*. (2019) 33:941–54. doi: 10.1177/0890117119835518
18. Chuang C, Velott D, Weisman C. EXploring knowledge and attitudes related to pregnancy and preconception health in women with chronic medical conditions. *Matern Child Health J*. (2010) 14:713–9. doi: 10.1007/s10995-009-0518-6
19. International Institute for Population Sciences. National Family Health Survey 4. (2016)
20. World Health Organization. High rates of unintended pregnancies linked to gaps in family planning services: New WHO study. Available online at: <https://www.who.int/news-room/detail/25-10-2019-high-rates-of-unintended-pregnancies-linked-to-gaps-in-family-planning-services-new-who-study> (accessed April 30, 2020)
21. Paulsen AM. Preconception Health Knowledge among Undergraduate Women. *ProQuest Diss Theses*. (2017) 52. Available online at: http://libproxy.library.wmich.edu/login?url=https://search.proquest.com/docview/1904507338?accountid=15099%0Ahttp://primo-pmtna01.hosted.exlibrisgroup.com/openurl/01WMU/01WMU_SERVICES?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:dissertation&genre
22. Jafari F, Rashidi S. Iranian women's knowledge and attitude regarding preconception health: 12 years after integration inot the primary health care network. *J Nurs Midwifery Sci*. (2017) 4:89–96. doi: 10.4103/JNMS.JNMS_14_17
23. Tuomainen H, Cross-Bardell L, Bhoday M, Qureshi N, Kai J. Opportunities and challenges for enhancing preconception health in primary care: Qualitative study with women from ethnically diverse communities. *BMJ Open*. (2013) 3:1–9. doi: 10.1136/bmjopen-2013-002977
24. Corbett E. *Preconception Health and Wellness: Knowledge and Attitudes of Undergraduate Women*. Dissertation; Colorado State University. (2003). p. 1–18.
25. Ayalew Y, Mulat A, Dile M, Simegn A. Women's knowledge and associated factors in preconception care in adet, west gojjam, northwest Ethiopia: a community based cross sectional study. *Reprod Health*. (2017) 14:1–10. doi: 10.1186/s12978-017-0279-4
26. Ahmed HA, Piro T. Research paper: knowledge, practice, and attitude of married women about preconception care. *J Client-Centered Nurs Care*. (2017) 3:37–44. doi: 10.32598/jccnc.3.1.37
27. Gautam P, Dhakal R. Knowledge on preconception care among reproductive age women. *Saudi J Med Pharm Sci*. (2016) 2:1–6. <http://scholarsmepub.com/sjms/>
28. Al-Akour NA, Sou'Ub R, Mohammad K, Zayed F. Awareness of preconception care among women and men: a study from Jordan. *J Obstet Gynaecol (Lahore)*. (2015) 35:246–50. doi: 10.3109/01443615.2014.958145
29. Goshu YA, Liyeh TM, Simegn Ayele A. Preconception care utilization and its associated factors among pregnant women in adet, north-western Ethiopia (Implication of Reproductive Health). *J Women's Heal Care*. (2018) 07:2167–0420. doi: 10.4172/2167-0420.1000445
30. Squiers L, Mitchell EW, Levis DM, Lynch M, Dolina S, Margolis M, Scales M, Kish-Doto J. Consumers' perceptions of preconception health. *Am J Health Promot*. (2013) 27(3):S10–9. doi: 10.4278/ajhp.120217-QUAL-95
31. Giri K, Gautam S. Knowledge on Preconception Care Among Reproductive Aged Women in Kaski District, Nepal. *Janapriya J Interdiscip Stud*. (2018) 7:46–56. doi: 10.3126/jjis.v7i1.23049
32. Federation of Obstetrics and Gynecological Societies of India. Good Clinical Practice Recommendations on PRECONCEPTION CARE Good Clinical Practice Recommendations on. (2016)

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