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Perspectives in digital health and big data in medicine: Current trends, professional challenges, and ethical, legal, and social implications

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ORIGINAL RESEARCH
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Effects of Virtual Reality Education on Procedural Pain and Anxiety During Venipuncture in Children: A Randomized Clinical Trial

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Background: Venipuncture is one of the most frequent and frightening medical procedures for children. This randomized clinical trial aimed to evaluate whether pre-procedural immersive virtual reality (VR) education could decrease pain and anxiety during venipuncture procedure of children.

Methods: Sixty children scheduled for venipuncture at the phlebotomy unit were randomized into either the control or VR group. Before the procedure, children of the control group received conventional simple verbal instructions, whereas those of the VR group experienced a 4-min VR education regarding venipuncture. The primary outcome was the pain and anxiety of pediatric patients assessed with the children's hospital of eastern ontario pain scale. Secondary outcomes were parental satisfaction, venipuncture time, repeated procedure and procedural difficulty rated by phlebotomists.

Results: The pain and anxiety score during the procedure was significantly lower in the VR group than in the control group (median [IQR], 6.0 [5.0–7.0] vs. 8.0 [6.0–9.8], $P = 0.001$). Parental satisfaction about the procedural process were higher in the VR group than in the control group ($P = 0.029$), and the degree of procedural difficulty was lower in the VR group, compared to the control group ($P = 0.026$).

Conclusion: The preprocedural VR education significantly reduced pain and anxiety of children and decreased the procedural difficulty of phlebotomists during venipuncture procedure.

Clinical Trial Registration: University hospital Medical Information Network Clinical Trials Registry (registration number: UMIN000042968, date of registration: January 9, 2021, URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000049043).

Keywords: anxiety, children, education, pain, venipuncture, virtual reality

INTRODUCTION

Venipuncture is one of the most frequently performed procedures in children. Approximately 50–80% of children aged <12 years experience high levels of pain and distress during venipuncture (1–3). Behavioral interventions to reduce the pain experienced during this procedure are based on the gate-control theory, which suggests that attention, thoughts, and beliefs influence pain sensation (4, 5). Distraction and education are the two most widely adopted behavioral approaches (6, 7). Diverting the attention of children via video games or animated cartoons during venipuncture significantly decreases needle-related pain (7, 8). Additionally, delivering information about painful procedures and teaching coping skills have been reported to alleviate procedural pain and anxiety in children (6, 9).

Virtual reality (VR) refers to a computer-generated realistic environment providing immersive and vivid experiences (10). Recently, VR systems have been utilized to alleviate pain or anxiety during medical procedures (1, 6, 7, 11–16). Distraction using a VR game was reported to effectively reduce "Worst pain" and "Pain unpleasantness" during venipuncture in children (1). Furthermore, VR systems providing procedural information through a simulated experience have been proven as an effective education platform to minimize peri-procedural anxiety in children (13–16). However, these previous studies used VR solely as a distraction tool to manage needle-related pain and anxiety.

To the best of our knowledge, no data exist regarding the effects of VR education on pain and anxiety during venipuncture in children. We hypothesized that VR education could decrease pain and anxiety during venipuncture in children. This randomized clinical trial was aimed to evaluate the effects of immersive VR education about venipuncture on procedural pain and anxiety in children. Additionally, parental satisfaction and procedural outcomes such as venipuncture time, repeated procedure, and difficulty score were also evaluated.

MATERIALS AND METHODS

Study

This prospective randomized clinical trial was approved by the institutional review board of Seoul National University Bundang Hospital (IRB number: B-1911-574-301; date of approval: October 25, 2019) and registered at University hospital Medical Information Network Clinical Trials Registry (registration number: UMIN000042968; date of registration: January 9, 2021). Written informed consent was collected from the parents or guardians of children. Additionally, children aged ≥7 years received detailed instructions on this protocol and signed additional agreements. This study was conducted from February 2, 2021, to June 30, 2021, at Seoul National University Bundang Hospital (SNUBH).

Patients

Children aged 4–8 years who were scheduled to undergo venipuncture at the phlebotomy unit in SNUBH were enrolled in this study. Children with congenital disorders, hearing or visual impairments, intellectual developmental disabilities, cognitive deficits, epilepsy or seizure history, psychoactive medication prescriptions, and prior experience of venipuncture during the past year were excluded.

Randomization and Intervention

Enrolled children were randomly allocated to either the control or VR group via a computer-generated randomization code (Random Allocation Software, version 1.0; Isfahan University of Medical Sciences) in a 1:1 ratio. Randomization was performed by an independent researcher who was only in charge of patient assignment, 10 min before venipuncture. An opaque envelope with a randomization number was transferred to another researcher who performed the intervention in a separated area 5 min before entering the phlebotomy unit. Children in the control group received conventional, simple verbal instructions about the procedure, and those in the VR group underwent a 4-min VR education regarding venipuncture. Before the conventional instructions or VR education, the children were asked to indicate the expected venipuncture-related pain on a visual analog scale [range, 0 (no pain) to 10 (the worst pain)]. During the protocol, the children and their parents or guardians were not blinded to the intervention, whereas the evaluator and phlebotomy technicians were blinded to the group allocation.

Virtual Reality Education

The VR content was produced in collaboration with a VR producing company (JSC Games, Seoul, South Korea). All equipment and facilities in the phlebotomy unit in SNUBH were measured and rendered three-dimensionally to create a 360° three-dimensional virtual environment where users can experience immersive virtual education from a first-person perspective. The storyline of the VR education was written by phlebotomy technicians and anesthesiologists (J-WP, S-HH) and revised by pediatric psychiatrists in SNUBH. The VR education began with characters of "Hello Carbot" (Choi-Rock Contents Factory, Seoul, South Korea), a famous animated film in the Republic of Korea, greeting the children in front of the phlebotomy unit. The children then selected a main character conducting the education (Chatan or Mona; **Figure 1A**) according to their preferences. In a friendly tone, Chatan or Mona explained the purpose and process of venipuncture in detail, reminding the children to be brave and to not move during the procedure. The children underwent venipuncture in the VR phlebotomy unit after learning how to position themselves at phlebotomy desk and were encouraged to cooperate appropriately while trying not to feel anxious (**Figure 1B**). Through a licensing agreement with ChoiRock Contents Factory, we obtained the permission to use the characters. The VR experience was provided with a head-mounted VR display, OculusGo (OculusVR, Menlo Park, CA, United States; **Figure 1C**).

Study Outcomes

After the intervention, the children entered the phlebotomy unit and underwent venipuncture as is usually practiced in SNUBH. The primary outcome was children's anxiety and pain assessed

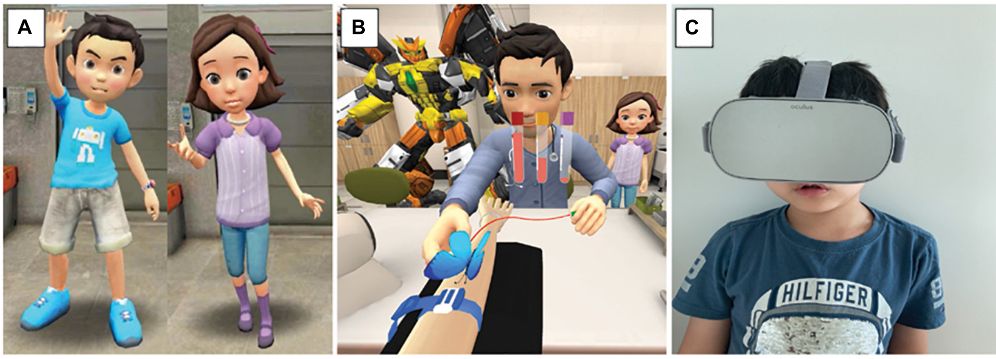

FIGURE 1 | Virtual reality education system. **(A)** Children select Chatan (left) or Mona (right) as a main character; **(B)** and experience venipuncture procedure in a 360° and 3-dimensional virtual phlebotomy unit; **(C)** with a head-mounted virtual reality display.

using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), which was measured by a single blinded assessor during the procedure. The CHEOPS assesses six behaviors—cry, facial expression, verbal response, torso, hands, and legs (**Supplementary Table 1**); each behavior is coded with scores based on its intensity, and the total sum of the scores is considered to assess procedural pain and anxiety (the primary outcome of this study; score range: 4–13) (17).

Secondary outcomes were parental satisfaction and procedural outcomes. After the procedure, the parents or guardians of the children were asked to grade their satisfaction regarding the overall process of venipuncture using a numerical rating scale [range, 0 (very dissatisfied) to 10 (very satisfied)]. The time required for the venipuncture procedure (time from sitting at the phlebotomy desk to successful needle insertion for blood sampling) and the requirement of needle re-insertion due to bad patient cooperation were recorded by the blinded evaluator. Phlebotomy technicians rated the level of difficulty in performing venipuncture using the numerical rating scale [range, 0 (very easy) to 10 (very difficult)] immediately after the patients left the phlebotomy unit.

Statistical Analysis

Baseline characteristics included age, gender, height, weight, and preprocedural pain expectation. Continuous data are presented as median [interquartile range (IQR)], and categorical variables are presented as a number (percentage). The Mann–Whitney U test was used to compare continuous outcomes between the two groups. Categorical outcomes were analyzed using Fisher's exact test. We used SPSS, version 21.0 (SPSS Inc., IBM, Chicago, IL, United States) for all statistical analyses. A two-sided P-value < 0.05 was considered to be statistically significant.

Sample Size

We conducted a power analysis using G*Power software, version 3.1.2 (Heinrich Heine University). A previous study reported that the mean and standard deviation of the CHEOPS score during venipuncture in the children were 9.3 and 2.4, respectively (18). A relative reduction in the pain and anxiety scores by 25% during venipuncture was considered clinically significant with respect to the VR education. A sample size of 30 children per group was calculated with a power of 0.9, significance level of 0.05, and an assumed dropout rate of 20%.

RESULTS

Eighty-seven children undergoing venipuncture were screened, and 27 of them were excluded (seven children met the exclusion criteria and 20 declined to participate). A total of 60 children (control group, 30; VR group, 30) participated in the study and none of them dropped out (**Figure 2**). The median (IQR) age was 6.0 (5.0–7.0) years in both groups (**Table 1**). Males accounted for 60.0 and 66.7% of the participants in the control group and the VR group, respectively. Children's height, weight, and expectation of procedural pain were also comparable between the groups (**Table 1**).

Procedural anxiety and pain were assessed via the CHEOPS including six behaviors; the Mann–Whitney U test showed that those were less severe in the VR group. The CHEOPS score during the procedure was significantly lower in the VR group (median [IQR], 6.0 [5.0–7.0]) than in the control group (median [IQR], 8.0 [6.0–9.8]) (P = 0.001; **Table 2**). Parental satisfaction regarding the overall venipuncture process was higher in the VR group (median [IQR], 10.0 [9.0–10.0]) than in the control group (median [IQR], 8.0 [7.3–10.0]) (P = 0.029; **Table 2**).

Venipuncture duration was not significantly different between the groups (**Table 3**). Also, there was no difference in the incidence of repeated procedure. During the protocol, only one child required needle re-insertion due to inappropriate cooperation (in the control group). The degree of procedural difficulty graded by the phlebotomy technicians was lower in the VR group (median [IQR], 1.0 [0.0–2.0]) than in the control group (median [IQR], 2.0 [0.3–5.0]) (P = 0.026).

DISCUSSION

This was the first randomized controlled trial investigating the effects of VR education on pain and anxiety during venipuncture

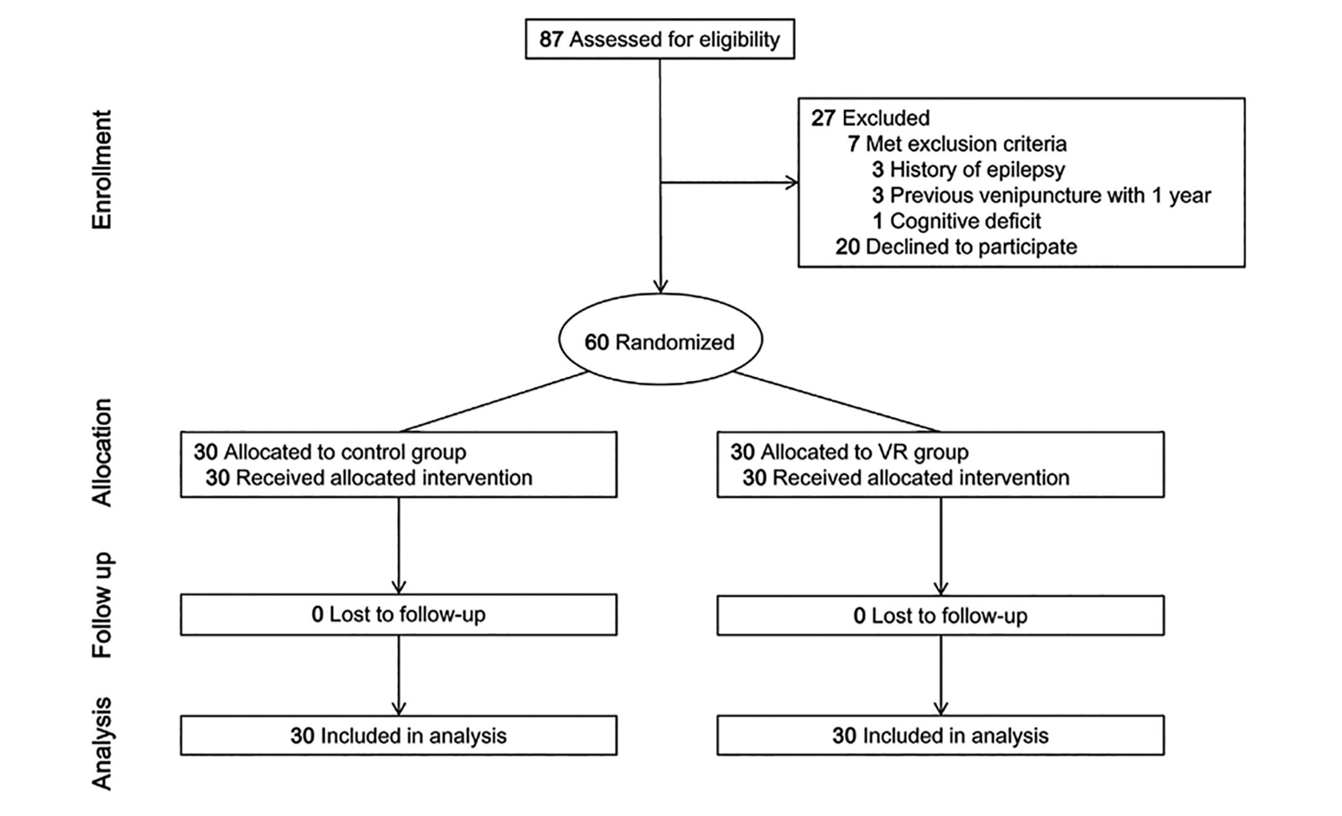

FIGURE 2 | CONSORT flow diagram. VR, virtual reality.

TABLE 1 | Patients' characteristics.

	Control group (*n* = 30)	VR group (*n* = 30)
Age, years	6.0 (5.0-7.0)	6.0 (5.0-7.0)
Male, No. (%)	18 (60.0)	20 (66.7)
Weight, median (IQR), kg	22.0 (18.3-24.8)	21.5 (18.2-24.0)
Height, median (IQR), cm	116.0 (112.0-120.0)	116.5 (110.0-121.5)
Preprocedural pain expectation, median (IQR), VAS	4.0 (0.5-6.0)	4.0 (0.0-4.0)

IQR, interquartile range; VR, virtual reality; VAS, visual analogue scale.

TABLE 2 | CHEOPS and parental satisfaction during venipuncture procedure.

	Control group (*n* = 30)	VR group (*n* = 30)	*P* value
CHEOPS, median (IQR)	8.0 (6.0–9.8)	6.0 (5.0–7.0)	0.001
Parental satisfaction score, median (IQR), NRS	8.0 (7.3–10.0)	10.0 (9.0–10.0)	0.029

CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; IQR, interquartile range; NRS, numeric rating scale; VR, virtual reality.

TABLE 3 | Venipuncture time, the requirement of needle re-insertion, and difficulty score during the procedure.

	Control group (*n* = 30)	VR group (*n* = 30)	*P* value
Venipuncture time, median (IQR), s	50.5 (42.8–72.0)	51.5 (36.0–66.8)	0.956
Repeated procedures, No. (%)	1 (3.3)	0 (0.0)	1.000
Difficulty score for the procedure, median (IQR), NRS	2.0 (0.3–5.0)	1.0 (0.0–2.0)	0.026

IQR, interquartile range; NRS, numeric rating scale; VR, virtual reality.

in children, one of the most common and fear-inducing medical procedures in children. VR education 5 min before entering the phlebotomy unit reduced procedural pain and anxiety in children and increased parental satisfaction, compared with conventional simple verbal instructions regarding the venipuncture procedure. Additionally, phlebotomy technicians reported greater ease in performing the procedure with children who had received VR education than with those who were given conventional instructions.

Previous studies have reported that VR education reduced periprocedural or perioperative anxiety in children, which is consistent with our results (13–16). Compared to 2-dimensional video education, 360°C 3-dimensional VR experience of the same content significantly reduced periprocedural anxiety in children undergoing chest radiography, which demonstrated the superior educational effect of VR (14). In the field of psychiatry, VR is utilized as an emerging method of exposure (19, 20). VR exposure in cognitive behavior therapy could be more effective than conventional *in vivo* approach in patients with social anxiety disorders (21). In a recent study, a VR adaptation of the Trier Social Stress Test showed the potential to induce endocrine responses comparable to those observed in the *in vivo* test (22). Clearly, VR technology is evolving into creating immersive and vivid experiences as realistic as *in vivo* experiences (20–23).

Prior to the present study, no data were available regarding the effects of pre-procedural VR education on pain and anxiety in children undergoing painful medical procedures. Immersive education regarding the procedure and a vivid virtual experience using a VR system might modulate the children's knowledge, attitude, and expectations regarding venipuncture positively; this can influence pain sensation according to the gate-control theory (4, 5). Before the intervention, no significant difference was noted between the two groups in the expectations for needle-related pain.

Unmanaged pain and anxiety associated with medical procedures might not only cause short-term suffering but also lead to negative long-term complications such as post-traumatic stress syndrome, avoidance of medical treatment, and needle phobia (6, 11, 13). Therefore, the fact that VR education significantly decreases pain and anxiety during painful medical procedures is of great clinical value. To measure pain and anxiety objectively in the present study, we utilized the CHEOPS score, which has been applied to evaluate procedural pain and anxiety in children during acute pain-inducing situations such as venipuncture, fracture reduction, burn dressing, and laceration repair (17, 24, 25).

Patient or parental satisfaction is an important indicator of the quality of health care (26–28). Adequate satisfaction improves compliance with treatment; parents who are satisfied with the medical treatment for their child might pay more attention to their child's health care and carefully follow doctors' recommendations (29). Appropriate pain management is considered the most critical factor for parental satisfaction (30). Furthermore, venipuncture in children is a fairly challenging and stressful task for phlebotomists (31, 32). When performing needle-related procedures with anxious children (or parents), they report experiencing a high level of stress (31). Because children are easily influenced by the mood or stress of parents and healthcare providers, parental dissatisfaction or difficulty regarding the venipuncture procedure might worsen pain and anxiety in children (4, 31). In this study, encouragingly, the VR group children showed higher parental satisfaction and lower procedural difficulty than the control group children.

At the phlebotomy unit in SNUBH, children showing moderate or severe anxiety are allowed to sit on the parent's lap in order to allow the parents to easily immobilize the children's extremities during venipuncture (33). No significant difference was noted in the venipuncture duration and incidence of repeated procedure between the two groups probably because of active parental participation. The position was also reported to reduce children's fear regarding the procedure (33). However, obvious difference was noted in the behaviors objectively assessed using the CHEOPS between the two groups in this study.

CONCLUSION

Immersive and vivid VR education prior to venipuncture significantly decreased procedural pain and anxiety in children, indicating that pre-procedural VR education could be an effective behavioral intervention. Further studies involving pre-procedural VR education in children undergoing painful medical procedures are required to support our findings.

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 Institutional Review Board of Seoul National University Bundang Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images included in this article.

AUTHOR CONTRIBUTIONS

J-HR and S-HH conceptualized and designed the study, collected data, conducted the initial analysis, and drafted the initial manuscript. SH and JL designed the study, coordinated and supervised data collection, and reviewed the manuscript. S-HD and J-HK designed the study, conducted the initial analysis, and reviewed the manuscript. J-WP conceptualized and designed the study, supervised data collection, conducted the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.849541/full#supplementary-material

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Conflict of Interest: S-HH and J-WP are the co-inventors of the patent, "Medical experience in hospitals provided with VR or AR system", application of which is pending.

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ORIGINAL RESEARCH
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Application of Smartphone Otoscope in Telemedicine in Rural Medical Consortium in Eastern China in the COVID-19 Era

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Purpose: This study aimed to evaluate the effectiveness of smartphone otoscope telemedicine in the rural medical consortium in East China in the COVID-19 era.

Methods: This prospective study was conducted within a rural medical consortium that provides health care services by integrating medical resources in the same area. When a patient visited primary health care (PHC) for ear diseases, the PHC provider used a smartphone otoscope to examine the patient's external ear canal and eardrum, and then sent photos or videos of the patient's ear to the otolaryngologist at the lead hospital *via* WeChat group. The otolaryngologist provided remote diagnosis and management recommendations to the PHC provider. The following data were recorded: age and gender, outpatient diagnosis, disease duration, sides, duration of treatment, telemedicine visits, treatment outcomes, patient satisfaction, and PHC providers' self-evaluation score.

Results: A total of 83 patients were included in the study, including 43 males and 40 females, with a mean age of 44.6 ± 19.7 years (range 3–83 years). The duration of treatment for these patients was 14.0 (7,14) days. PHC visits were 2.2 ± 1.1 times (range: 1–7 times). Telemedicine visits ranged from 1 to 5, with a mean of 1.8 ± 0.9. Among of patients, 62 (74.7%) were cured, 21 (25.3%) improved, and 0 (0%) were ineffective. Sixty-five patients (78.3%) were very satisfied, 16 (19.3%) patients were somewhat satisfied, and two patients (2.4%) were dissatisfied. Based on the self-reported helpfulness, the primary health care providers assessed telemedicine as very helpful ($n = 63$, 75.9%), helpful ($n = 20$, 24.1%), and unhelpful ($n = 0$, 0%).

Conclusions: Smartphone otoscope telemedicine in the medical consortium can effectively improve the ability of rural PHC providers to diagnose and treat ear diseases, save time and costs for patients, and improve patient satisfaction.

Keywords: telemedicine, smartphone, otoscope, primary health care, medical consortium, WeChat, COVID-19

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INTRODUCTION

Primary health care (PHC) serves as the first point of contact for individuals and families in their community with a national health system by providing universally accessible, necessary health care services (1). China's PHC system guarantees that the general population access to comprehensive clinical care and essential public health services (1). However, physicians delivering PHC in community health centers frequently lack adequate training skills in some areas of medicine or some specialties. As a result, the efficacy of PHC has been compromised.

A medical consortium (MC) is a medical alliance created by integrating medical resources from the same region to deliver health care services (2, 3). The MC policy in China aims to improve the efficacy of health care delivery by encouraging collaboration among local health care professionals (4). Residents have accepted and recognized the approach (4). The rural MC is critical for improving the capability of primary medical services in rural areas (5). However, after the coronavirus disease 2019 (COVID-19) outbreak, rural PHC providers focused their efforts on tracing, screening, and educating critical public health responsibilities, which significantly influenced rural PHC operations (6).

Telemedicine, a component of digital health, is a rapidly growing area that employs communication technology to provide precise medical services to patients (7). Telemedicine and telehealth services have increased significantly in recent years, especially during the COVID-19 pandemic (8, 9). Smartphone apps have been applied to all aspects of health care, including telemedicine, cardiovascular disease prevention, older adults care, hearing screening, etc. (10–13). The smartphone otoscope (SO) is a relatively new electronic accessory device capable of capturing pictures and videos of patients' external auditory canal and tympanic membrane (TM) using a dedicated smartphone app (14). Image data can be stored on smartphones, computers, or shared over the Internet, allowing doctors, patients, and researchers to work closely. SO has been successfully applied in clinical diagnostics, telemedicine, procedural skills development, medical student education, and animal experiments (15–19). Our previous studies have shown that telemedicine with SO reduces outpatient visits, reduces the risk of cross-infection, and improves telemedicine accuracy during COVID-19 outbreak and the prevention and control phase of COVID-19 normality (14, 20). The telemedicine service was based on patients' self-examination with SO; unfortunately, some elderly patients were less able to use their smartphones, posing a challenge for telemedicine implementation (14).

Therefore, we endeavored to provide telemedicine services under the rural MC model by utilizing SO based on the WeChat platform. The purpose of the present study was to evaluate the effectiveness of smartphone otoscope telemedicine in the medical consortium (SOTITMC) in East China in the COVID-19 era.

Abbreviations: PHC, primary health care; MC, medical consortium; COVID-19, coronavirus disease 2019; SO, smartphone otoscope; TM, tympanic membrane; SOTITMC, smartphone otoscope telemedicine in the medical consortium; QSCHC,Qianqiao Street Community Health Center; SHC, Shitangwan Health Center; MCTWG, Medical Consortium Telemedicine WeChat Group; Fungal otitis externa (FOE); SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

PATIENTS AND METHODS

Patients

This prospective observational study was conducted in a rural MC. The leading hospital of this medical association is Wuxi Huishan District People's Hospital, located in the western suburbs of Wuxi. It is a tertiary referral center and teaching hospital. Qianqiao Street Community Health Center (QSCHC) and Shitangwan Health Center (SHC), two PHC institutions in the same area, are members of this MC, which provides PHC services. Patients with ear disease who visited the outpatient departments of QSCHC and SHC from May 2021 to December 2021 were chosen. Patients who actively engaged in this telemedicine program were chosen, rather than all consecutive patients treated at PHC institutions. The inclusion criteria for patients were: (1) external ear or middle ear disease; (2) residents of the same community; (3) adults; and (4) children accompanied by their parents. Exclusion criteria were: (1) Patients who were residents from other communities or who came from outside the area for consultation; (2) Patients who were not interested in telemedicine; and (3) Patients who could not cooperate in completing the assessment of treatment effects.

According to the Declaration of Helsinki, the study was performed and granted by the Medical Ethics Committee of Wuxi Huishan District People's Hospital (Grant number: HYLL20210604001). All included individuals provided written informed consent. The informed consent form for children under 18 years of age was signed by the participant and by either a parent or a legal guardian.

Telemedicine in Medical Consortium

The initial face-to-face diagnosis of the patients was performed in the outpatient settings of QSCHC or SHC. When PHC providers come across a patient who fits the eligibility requirements, they recommend enrollment in the MC telemedicine program. The Mebird T5 SO [Black Bee Intelligent Manufacturing (Shenzhen) Technology Co., Ltd., China] is an external ear canal or TM examination device. The device connects wirelessly to cellphones *via* a dedicated app. It features a built-in 3-megapixel camera that can take photos with a resolution of 2,048 × 1,536 pixels and videos with a quality of 480 × 480 P. Furthermore, the device comes with a directional gyroscope that maintains a steady angle of vision while the body rotates, making it simple to take correct ear photographs.

During an initial visit, PHC providers collected information from patients, such as the primary complaint and complete medical history, inspected their ears with a SO, and recorded pictures and videos of their ears. Then, the PHC providers transmitted the photos and videos of their patients stored on their smartphones to the Medical Consortium Telemedicine WeChat Group (MCTWG). Meanwhile, information regarding the patient's condition was given to the MCTWG by text or voice. We have established the MCTWG exclusively for

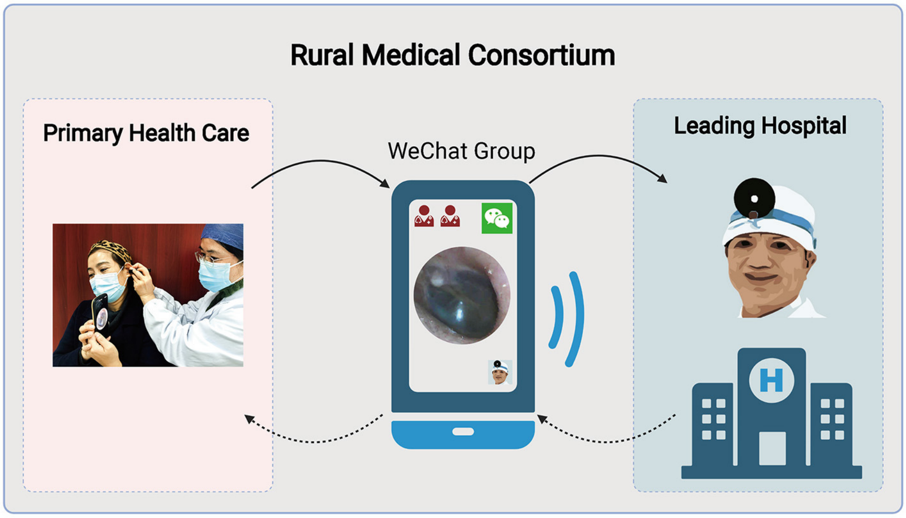

FIGURE 1 | Flowchart of WeChat-based smartphone otoscope telemedicine within a rural medical consortium. The flowchart was created with BioRender.com.

medical services in medical consortia. Otolaryngologists from leading hospitals and PHC providers are members of this group. Following the information alert in the MCTWG, the otolaryngologist analyzed the patient's pertinent information as soon as possible, offered a quick remote diagnosis, and provided treatment recommendations to the patient's PHC provider. Finally, PHC providers prescribed medications based on the advice of the otolaryngologists and scheduled patients for outpatient follow-up visits (**Figure 1**). This approach can complete the telemedicine visits in approximately 10 min. When the patient returned, they were still receiving telemedicine services in this manner. Following completing a patient's telemedicine, PHC providers and the otolaryngologist would remove the WeChat data held on their smartphones concerning the patient.

After completing one or more diagnoses and treatments for the disease, the PHC providers asked the patient to rate the face-to-face visit in combination with the telemedicine service based on their overall experience. Satisfaction was assessed using a simple visual analog scale ranging from 0 to 10, with 0 being the lowest level of satisfaction and 10 representing the highest level of satisfaction. Satisfaction scores ≤5 were rated "dissatisfied," those with scores of 6–8 were rated "somewhat satisfied," and those with scores ≥9 as "very satisfied."

Primary health care providers rated themselves according to how they benefited from telemedicine for the disease in question. The helpfulness scores were divided into three categories: unhelpful (score ≤ 5), helpful (score 6–8), and very helpful (score ≥9).

Data recorded for all patients included patient age and gender, outpatient diagnosis, disease duration, sides, duration of treatment, telemedicine visits, treatment outcomes, patient satisfaction, and PHC providers' self-evaluation score. According to the clinical criteria, treatment outcomes were categorized as cured, improved, or ineffective.

TABLE 1 | The characteristics of the patients and the outcomes of the treatment (*n* = 83).

Characteristic and outcomes	Value
PHC institutions [*n* (%)]	
QSCHC	62 (74.7%)
SHC	21 (25.3%)
Age (mean ± SD; years)	44.61 ± 9.7
Gender [*n* (%)]	
Male	43 (51.8%)
Female	40 (48.2%)
Sides [*n* (%)]	
Left	38 (45.8%)
Right	33 (39.8%)
Both	12 (14.5)
Disease duration (IRQ; days)	6.5 (2, 15)
Duration of treatment (IRQ; days)	14.0 (7, 14)
Telemedicine visits (mean ± SD; times)	1.80 ± 0.9
PHC visits (mean ± SD; times)	2.21 ± 0.1
Treatment outcomes [*n* (%)]	
Cured	62 (74.7%)
Improved	21 (25.3%)
Ineffective	0 (0%)

IRQ, interquartile range; PHC, Primary health care; QSCHC, Qianqiao Street Community Health Center; SHC, Shitangwan Health Center.

Statistical Analyses

All statistical analyses were performed with the R statistical software (Version 4.1.2, http://www.R-project.org). Continuous data were summarized using descriptive statistics; categorical data were summarized using counts and percentages. Age, telemedicine visits, and PHC visits were presented as mean ± standard deviation. Disease duration and duration of treatment were expressed as medians (25th percentile; 75th percentile).

RESULTS

Patients

A total of 83 patients were enrolled in the study, 62 ($n = 74.7\%$) of whom were from QSCHC and 21 ($n = 25.3\%$) from SHC. Of these patients, 43 ($n = 51.8\%$) were males, and 40 ($n = 48.2\%$) were females, aged 3–83 years, with a mean of (44.6 ± 19.7) years. There were 38 cases (45.8%) on the left side, 33 cases (39.8%) on the right side, and 12 cases (14.5%) on both sides. The duration of ear disease was 6.5 (2,15) days. Characteristics of the patients are presented in **Table 1**.

The types of ear disease in the 83 participants who completed the study are shown in **Figure 2**. As we can see in **Figure 2**, the most involved disease types in this study were fungal otitis externa (FOE), chronic otitis media, acute otitis externa, and acute otitis media, in that order.

The mean duration of treatment for these patients in PHC was 14.0 (7,14) days. PHC visits was 2.2 ± 1.1 times (range: 1–7 times). Telemedicine visits by otolaryngologists ranged from 1 to 5, with a mean of 1.8 ± 0.9. The results showed that of 83 patients, 62 (74.7%) were cured, 21 (25.3%) improved, and 0 (0%) were ineffective. The treatment and outcomes of all patients are summarized in **Table 1**.

All but two patients were satisfied with the telemedicine service. Sixty-five patients (78.3%) were very satisfied, 16 (19.3%) patients were somewhat satisfied, and two patients (2.4%) were dissatisfied.

Primary Health Care Providers

Primary health care providers stated they benefited from and improved their abilities due to telemedicine. Based on the self-reported helpfulness, the PHC providers assessed telemedicine as very helpful ($n = 63$, 75.9%), helpful ($n = 20$, 24.1%), and unhelpful ($n = 0$, 0%).

DISCUSSION

In the present study, we investigated the effectiveness of SOTITMC. To the best of our knowledge, it is the first study involving SO in a rural MC for telemedicine applications. Most patients have expressed satisfaction with this telemedicine service, which is likely due to improved treatment outcomes and convenience of access to health care. SOTITMC improved diagnosis and treatment in PHC while also facilitating skills training for PHC providers, according to our findings. The PHC providers were satisfied with what they learned from all the telemedicine encounters when dealing with their patients.

Although the number of patients with otitis media decreased during the epidemic compared to the previous period, otitis externa and otitis media were still common in PHC. FOE was ranked first in this study, which might be related to the MC's geographical location and climatic environment. Wuxi city is the subtropical monsoon climate zone, with sufficient heat and abundant precipitation (21). This climatic characteristic causes an increased incidence of FOE. FOE is more common in hot, humid climates (22).

Previous studies have shown that SO plays a beneficial role in clinical diagnosis and telemedicine. Mousseau et al. (15) found that the accuracy of SO in diagnosing acute otitis media in young children was comparable to that of using conventional otoscopy in the pediatric emergency department of a tertiary care hospital. Don et al. (16) revealed that SO for tympanostomy tube monitoring is workable, allowing otolaryngologists to remotely track children's tympanostomy tubes and providing greater parental satisfaction. With high severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load in the nose and throat and anosmia as one feature of COVID-19, otolaryngology is a high-risk department for COVID-19 (9, 23, 24). As a result, several studies used SO for telemedicine services during COVID-19. Bayoumy et al. reported a case of self-monitoring in a patient with surgically corrected TM retraction, suggesting that SO can be a worthy addition to regular follow-up (9). A digital USB otoscope (model D13L22) was used to obtain good images of the TM in this case report (9). A previous study we conducted also investigated patient satisfaction with SO telemedicine, with 71.9% of patients being very satisfied and 28.1% being somewhat satisfied (14). The SO model used in our previous study was the Mebird M9pro, manufactured by the same company as the SO used in the present study, which has similar imaging quality (14).

This study has brought many benefits to the clinical practice of PHC. First, SOTITMC has expanded and strengthened its technical assistance to medical institutions members of the MC. Before the COVID-19 outbreak, an otolaryngologist from the lead hospital scheduled weekly visits to QSCHC and SHC, both PHC institutions, to provide routine outpatient services and technical support. However, due to the COVID-19 pandemic, this technical collaboration became erratic and even discontinued for an extended period, negatively impacting PHC. This strategy compensated for the absence of face-to-face expert visits. Second, SO made up for the lack of equipment for otolaryngology examinations in rural PHC institutions. The ear has complex anatomy that necessitates specialized equipment to inspect.

With SO, the PHC providers can accurately examine a patient's external ear canal and TM and send the information to an otolaryngology specialist. The otolaryngology specialist could visualize the patient's ear performance with still photos and accurately judge dynamic performance, such as the mobility of the TM, with video data. Third, WeChat is the most popular communication application in China, with over 1 billion users (25). WeChat employs the Client-Server encryption security model to ensure security, encrypting the entire database SQLite file with a 256-bit long key and the AES encryption technique (26). The 4G mobile phone network in China has become popular, and some users are already using 5G phones. The robust mobile phone network ensured that image data was delivered quickly. The otolaryngology specialist and PHC providers could communicate and exchange ideas in a timely and effective manner through the MCTWG. In other words, SOTITMC allows otolaryngologists to provide access to PHC providers with around-the-clock technical guidance *via* the Internet. Fourth, SOTITMC saved the time and cost for the patients and provided them with convenient access to medical services. Since the COVID-19 outbreak, the health authorities in China have been implementing strict preventive and control measures (27). Even under the control of COVID-19, the

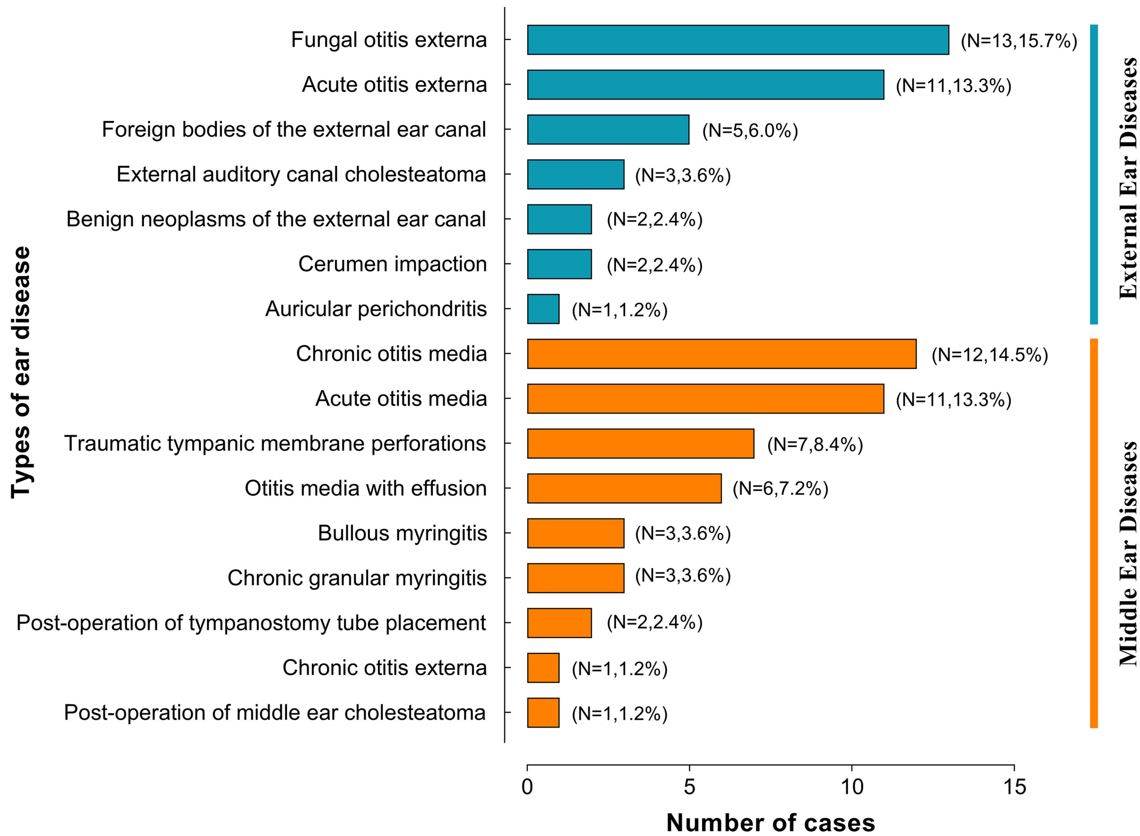

FIGURE 2 | Types of ear disease in patients enrolled in a smartphone otoscope telemedicine study within a rural medical consortium.

hospitals also implemented standard measures, such as reviewing health QR codes and healthy travel routes, monitoring body temperature, etc. (14). It took more time for patients to visit the hospitals. Patients attended a community PHC institution closer to their home rather than being referred to a tertiary hospital farther away from their home. It saved time and transportation costs and reduced the aggregation and mobility of the population, which facilitates the prevention and control of pandemics. Furthermore, the ethical and legal implications of storing patient data on smartphones should be considered (8). Since the WeChat connection is not end-to-end encrypted, the use of WeChat may not comply with the relevant laws and regulations in some countries, so it is essential to consider this when practicing telemedicine.

Despite its many strengths, the present study has some limitations. There was a relatively large gap between the image quality of a SO and that of an otoscope equipped with a high-definition camera. It might affect the ability of the otolaryngologist to identify minor lesions in the ear of the patient. In addition, the number of patients included in this study was not large enough. Because of the frequent assignment of PHC providers who participated in this work to COVID-19 pre-screening triage, COVID-19 vaccination, and COVID-19 isolation sites, the SOTITMC program was frequently interrupted, resulting in a limited sample size. The included patients were not successive, and there might have been selection bias. We need to gain more experience with SO telemedicine by having more patients in the future. Additionally, the otolaryngologists at the leading hospital documented fewer patient data in this study, which has to be improved.

CONCLUSION

In summary, SOTITMC can effectively improve the ability of PHC providers in the rural MC to diagnose and treat middle and external ear diseases, save time and costs for patients, and improve patient satisfaction. It has also facilitated skills training for PHC providers, with positive feedback. In addition, this telemedicine modality reduces population aggregation and mobility, decreases the risk of cross-infection, and provides new ideas for preventing and controlling the ongoing COVID-19 pandemic.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Wuxi Huishan District People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XM: conceptualization, methodology, data curation, project administration, funding acquisition, and writing—reviewing and editing. ZD: methodology and project administration. YiW, XH, XG, JG, and YJ: investigation and data curation. YaW: investigation and software. CH: supervision and formal analysis. All authors contributed to the article and approved the submitted version.

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Systematic Bibliometric Analysis of Research Hotspots and Trends on the Application of Virtual Reality in Nursing

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Background: With the emergence of the metaverse, virtual reality, as a digital technology, must be getting hotter. High quality virtual reality related nursing knowledge scene learning is gradually replacing traditional education and intervention skills.

Objective: This systematic study aimed to gain insights into the overall application of virtual reality technology in the study of nursing.

Methods: Citations downloaded from the Web of Science Core Collection database for use in VR in nursing publications published from January 1, 2012, to December 31, 2021, were considered in the research. Information retrieval was analyzed using https://bibliometric.com/app, CiteSpace.5.8. R3, and VOS viewer.

Results: A total of 408 institutions from 95 areas contributed to relevant publications, of which the United States is the most influential country in this research field. The clustering labels of cited documents were obtained from the citing documents. Virtual simulation, virtual learning, clinical skills, and dementia are the clustering labels of co-cited documents. The burst keywords represented the research frontiers in 2020–2021, which were knowledge and simulation.

Conclusion: Virtual nursing has had an impact on both nurses and clients. With the emergence of the concept of the metaverse, the research and application of virtual reality technology in nursing will gradually increase.

Keywords: nursing, virtual reality, bibliometric, CiteSpace, VOS viewer

INTRODUCTION

Virtual reality (VR), also known as virtual simulation, is a completely synthetic world in which participants and observers can immerse themselves in and interact with (1). Mixed reality (MR) and Augmented Reality (AR) are subclasses of VR that are developed by VR technology (2, 3). Virtual reality can be utilized to generate a safe environment for activities (4); for example, it has many applications in the field of medicine. In many countries, virtual nursing is widely employed in nursing programs such as basic nursing, internal medicine and surgery, obstetrics, and pediatric nursing (5–8). According to the technology usage forecast of the United States in 2018, VR will experience the largest development in nursing in the next 5 years, and the adoption rate will increase to 45% from the current 10% (9). Previous studies have proven that VR can carry out effective nursing training or intervention in both disaster and community situations (10, 11). Besides, both home care and staff stress care based on VR technology have also been prove to be desirable in normal times (12–14).

This study aims to gain insight into the overall application of VR technology in nursing research through the following aspects: We analyzed Science Citation Index (SCI) papers for VR in nursing research using bibliometric methods. The citations of countries, regions, institutions, periodicals, study categories, keywords, and references were included in the data. Furthermore, as the core of this study, we established a visual and unbiased approach to exploring hotspot knowledge frontiers in the research area. The distribution and research influence of countries, regions, institutions, and journals are discussed using the research methods proposed in this study. The hotspots, future development space, and potential challenges of using virtual reality in nursing were all discussed. This provides references for computer researchers, nurses, educators, and experts in the field of medical engineering.

METHODS

Selection of Citation Data

On March 15, 2022, all citation data published between January 1, 2012, and December 31, 2021, were retrieved from the Web of Science Core Collection (WoSCC). They were independently verified by two authors (YL and WY). The search formula was TS= (VR or "virtual reality" or "virtual simulation" or AR or "augmented reality" or MR or "mixed reality") and (nursing or nurse*). We selected English Literature articles, excluding book chapters, data papers, early access papers, and proceedings. In order to obtain more accurate results from the analysis, we manually removed publications unrelated to the application of VR in nursing. The following are the exclusion criteria: (1) The research topic is not virtual reality; (2) The research direction is unrelated to nursing; (3) The research is not a piece about the use of virtual reality in nursing. Finally, 408 documents remained. From each publication, we gathered the following basic data: title, publication year, country or region, institution, journal, references, and keywords. The detailed search and analysis processes are depicted in **Figure 1**.

Statistical Analysis

Using https://bibliometric.com/app describes the situation in which documents are sent in different countries or areas. Vosviewer is being used to generate the heat of keywords. Cluster analysis of nations or regions, institutions, journals, research categories, keywords, and references using CiteSpace 5.8. CiteSpace program generates centrality. The WoSCC is used to calculate the H-index.

RESULTS

Distribution of Articles by Publication Year

As shown in **Figure 2**, the trend line formed by the number of annual publications has a small slope of 4.115 from 2012 to 2019. The increase in the number of papers published in was relatively gentle, with an average annual increase of <5. The number of literatures increased by 58.5 between 2020 and 2021. The number of published papers has increased dramatically in comparison to previous years.

Countries or Regions

A total of 95 nations or territories were mentioned in the citations. The color block area in **Figure 3** represents the number of documents issued, and the connecting lines of different colors represent the cooperative relationship between regions. Compared with the area of other color blocks, the countries represented by red, purple, and light orange blocks have published more articles. These three-color patches represent the United States, Canada, and China. The red block has more connecting lines, indicating that the United States collaborates with other countries more frequently. CiteSpace software forms a cooperative network between countries or regions in **Figure 4**, in which each node represents a country or region. The purple ring area size indicates the influence of the regional articles, which is equal to centrality. We can see that the United States (101), Canada (54) and China (26) have published the greatest number of articles, and England (0.32), China (0.28), the USA (0.24), Canada (0.22), and Australia (0.16) have strong centrality. The data in **Table 1** reflects the aforementioned conclusions. The H-index can accurately reflect academic achievements, the higher the h index, the greater the influence of the paper.

Institutions

Table 2 lists the top 10 institutions with the highest number of documents, which are Centennial College (15), Ryerson University (14), University of Ottawa (12), Queen's University Canada (10), Wright State University (8), University of Michigan America (8), George Brown College (8), Duke University (7), University of Toronto Canada (7), University of Central Florida (6). All organizations are located in the United States and Canada. The connecting line between each of the two labels in **Figure 5** shows that the institutions in the same country cooperate closely.

Journals and Research Category

The documents in the cited journals constitute the knowledge base of the citing journal articles. The research fields in high count citing journals constitute a recent research hotspot. **Tables 3**, **4** show the top 10 citing journals and cited journals, respectively. In terms of research types, the field of medicine/nursing accounts for most of the research in these two journals. At the same time, the research hotspot also includes interdisciplinary application research, including computer science and education. The left and right portions of **Figure 6** shows the research field of citing journals and cited journals, respectively. The color curve depicts the citations of journals from various disciplines. The arrow points to the cited publications from various disciplines that are typically

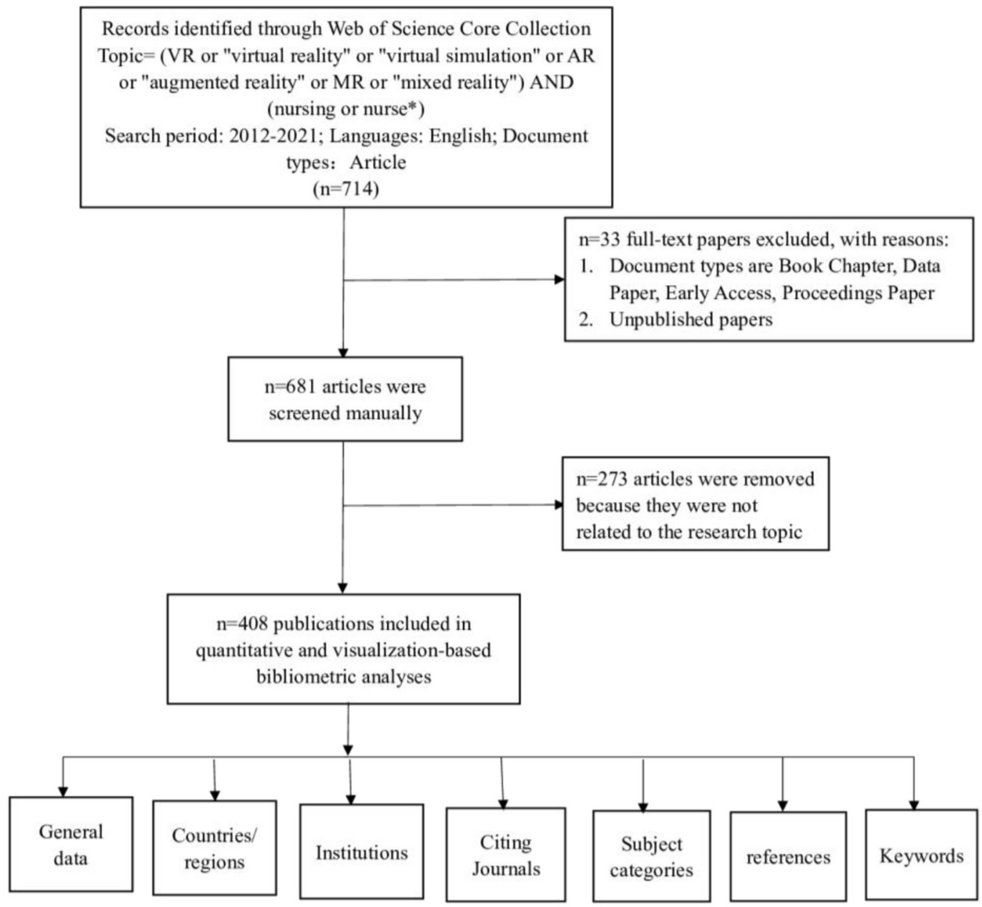

FIGURE 1 | A frame flow diagram showing the detailed selection criteria and bibliometric analysis steps of applying VR to the study of nursing. Basic data of 408 literatures were included in the analysis.

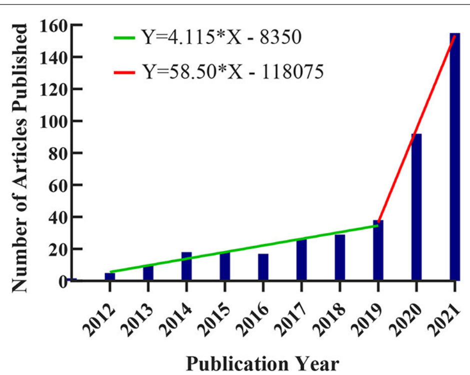

FIGURE 2 | Trends in the number of publications on applying VR to the study of nursing from 2012 to 2021. The number of documents issued each year is represented by the blue bar. The green and red trend lines, respectively, represent the trend in which the number of published documents remains stable and the trend in which the number of published documents increases sharply.

referred to by citing journals. The green path shows articles in the research fields of MEDICINE / MEDICAL / CLINICAL that are more likely to cite articles in the field of HEALTH / NURSING / MEDICINE. The blue path shows the subject fields of PSYCHOLOGY / EDUCATION / SOCIAL, which are probably cited by PSYCHOLOGY / EDUCATION / HEALTH. In addition, the picture also shows some research on neurobiology, economics, sports, and ophthalmology in both citing and cited journals.

Keywords

We can analyze the hot keywords of citations using the default setting of the vosviewer software modular clustering algorithm. In **Figure 7**, the higher the number and frequency of citations, the closer the keyword is to the yellow color block, and the lower they are, the farther it is. Virtual reality, simulation, and nursing education appear to have been the more active keywords used in the research in the past 10 years. At the same time, we use CiteSpace software to analyze the emerging keywords. The default settings parameters were as follows: # Years PerSlice = 2, Top N% = 0.5, pruning algorithm was adopted and minimum duration was 1. **Table 5** lists the emergent keywords from the time dimension, which are "virtual reality" (2013–2019),

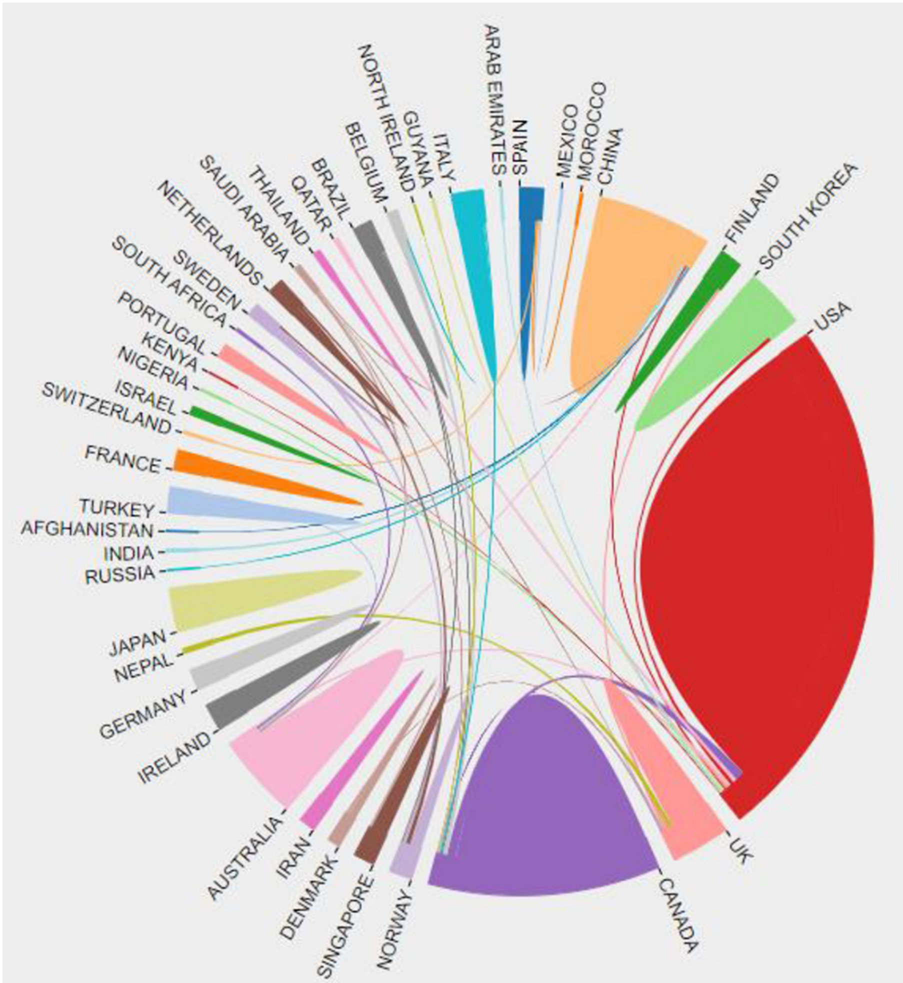

FIGURE 3 | The cooperation of countries or regions that contributed to publications on applying VR to the study of nursing from 2012 to 2021. Different colored areas represent various countries. The size of the color block area describes the number of documents sent. The connection between different color blocks represents the countries' cooperative relationship.

"knowledge" (2020–2021), and "simulation" (2020–2021). These active keywords represent research hotspots.

References

We used CiteSpace software with unchanged default settings to analyze the co cited literature. The cited literature constitutes the research basis. The frequency of references represents their influence. The analysis of co-cited documents can show the research theme and development context of a field. **Table 6** shows the top 10 cited literature in terms of citation frequency. Among them, two articles supplement and revise the practice standards of the International Nursing Association for clinical simulation and learning. Other literatures, including randomized controlled trials and systematic reviews, all indicate the application of VR as a promising technology in nursing education. The clustering labels of cited documents are obtained from the citing documents. **Figure 8** indicates that #0 "Virtual simulation" was the cluster with the widest range. The remaining clusters that have continued into 2020 include #1virtual learning, #2clinical skills, and #4dementia.

DISCUSSION

Principal Results

The above results show that the number of literatures on the integration of VR and nursing has increased sharply. This is because the COVID-19 pandemic that began in the spring of 2020 hindered many traditional clinics and nursing skill laboratories from providing clinical practice experience for nursing students. Therefore, many nursing students relied on interaction with virtual scenes to progress and complete nursing courses (15). Due to the nursing curriculum proposed by the National Council for State Boards of Nursing in 2016 (16), which recommends the use of simulation as a clinical substitute for traditional clinical experience, research in the field of VR in nursing in the United States has become relatively rich than other

FIGURE 4 | The cooperation of countries or regions that contributed to publications on applying VR to the study of nursing from 2012 to 2021. The number of documents sent by the country is represented by the size of the green node. Countries' cooperation is represented by connecting lines. The purple ring area size indicates the influence of the regional articles, which is equal to centrality.

TABLE 1 | The top 10 countries or regions with publications on the application of VR in nursing from 2012 to 2021.

Rank	Countries or regions	Count	Centrality	H-index
1	USA	161	0.24	20
2	Canada	54	0.22	11
3	Australia	26	0.16	7
4	People's Republic of China	23	0.28	7
5	South Korea	21	0.00	7
6	Turkey	15	0.00	4
7	England	15	0.32	7
8	Taiwan	13	0.00	4
9	Spain	11	0.01	4
10	Netherlands	9	0.10	4

TABLE 2 | The top 10 institutions with publications on the application of VR in nursing from 2012 to 2021.

Rank	Institutions	Country	Count	H-index
1	Centennial College	Canada	15	7
2	Ryerson University	Canada	14	6
3	University of Ottawa	Canada	12	4
4	Queen's University Canada	Canada	10	3
5	Wright State University	America	8	6
6	University of Michigan	America	8	4
7	George Brown College	Canada	8	5
8	Duke University	America	7	7
9	University of Toronto	Canada	7	6
10	University of Central Florida	America	6	5

FIGURE 5 | The cooperation of institutions that contributed to publications on applying VR to the study of nursing from 2012 to 2021. Each label in the figure is a research institution. The connecting line between labels indicates the cooperative relationship between institutions.

countries. In terms of cooperation intensity, Britain, China, the United States, Canada, and Australia have stronger centrality than other countries. It demonstrates that developed countries are the driving force in the medical field and virtual reality in nursing research, but some developing countries are also conducting scientific research. This conclusion is comparable to the national document situation in medical research with virtual reality (17–19). The analysis results of the organization show that the United States and Canada have more research in this field, which is consistent with Garrett, Bernard M (5). **Figure 5** shows that there are still a few references among the institutions. However, in **Figure 6**, the subject fields of both citing and cited journals are very rich, suggesting more room for expansion in this field. At the same time, through keyword co-occurrence and reference cluster analysis, the direction of active topics changing with time is obtained.

Research Hotspots

Burst Keywords

By using VOS viewer and CiteSpace to analyze the similar active keywords, it is calculated that the research hotspots over time are "virtual reality" (2013–2019), "knowledge" (2020–2021) and "simulation" (2020–2021). This shows that research on VR in the nursing industry tends to simulate real scenes in conducting nurse training.

Knowledge

Virtual reality nursing related systems transfer health care knowledge, which can be applied in schools, practice bases, and clinical practice. Virtual humans can be built in a virtual world to show anatomical knowledge or develop nurse-patient communication skills (20, 21). Various types of operational training, such as catheterization or tracheal insertion (22, 23), can be realized using the same virtual scene as in an actual laboratory. Generating self-assessment tests as a system that generates self-assessment tests for both teachers and nursing students can also be done through virtual scenes (24, 25). A VR scene can also help new medical and nursing interns by reducing incidences of needle stabbing injury or sharp instrument injury (26). This can benefit new nursing interns who may be afraid of occupational exposure events during practice-based learning. During clinical application, a VR system not only brings convenience to staff, but also actively and effectively interferes with patients' physical and mental health (27, 28).

TABLE 3 | The top 10 citing journals of publications on the application of VR in nursing from 2012 to 2021.

Rank	Citing journals	Research fields	Count	2020 Journal impact factor
1	Clinical Simulation in Nursing	Medicine / Nursing	74	2.391
2	Nurse Education Today	Medicine / Subject education	28	3.442
3	Cin-Computers Informatics Nursing	Computers: Interdisciplinary Applications / Medicine / Nursing	12	1.985
4	Journal of Medical Internet Research	Medicine / Health Care and Services	9	5.428
5	Nurse Educator	Medicine / Nursing	9	2.082
6	Journal of Nursing Education	Medicine / Nursing	8	1.726
7	Nursing Education Perspectives	Medicine / Nursing	7	0.693
8	Journal of Clinical Nursing	Medicine / Nursing	6	3.036
9	Journal of Perianesthesia Nursing	Medicine / Nursing	6	1.084
10	Nurse Education in Practice	Medicine / Nursing	6	2.281

TABLE 4 | The top 10 cited journals of publications on the application of VR in nursing from 2012 to 2021.

Rank	Cited journals	Research fields	Count	2020 Journal impact factor
1	Clinical Simulation in Nursing	Medicine / Nursing	168	2.391
2	Nurse Education Today	Medicine / Subject education	162	3.442
3	Journal of Nursing Education	Medicine / Nursing	98	1.726
4	Nursing Education Perspectives	Medicine / Nursing	94	0.693
5	Journal of the Society for Simulation in Healthcare	Medicine / Health Care and Services	78	1.929
6	Journal of Medical Internet Research	Medicine / Nursing	77	5.428
7	Nurse Educator	Medicine / Nursing	68	2.082
8	Nurse Education in Practice	Medicine / Nursing	66	2.281
9	Journal of Clinical Nursing	Medicine / Nursing	66	3.036
10	Journal of Advanced Nursing	Medicine / Nursing	65	3.187

Simulation

Virtual reality can be used to address the situational or economic limitations of traditional education methods that are used to cultivate the skills of medical personnel in dealing with medical and health emergencies. Modern simulation has been developed from the "blue box" in the 1920's (29). In 2013, Daniel Cohen et al. conducted a cohort study with clinicians to determine the feasibility of a low-cost simulated world environment in major event response preparation and training using a virtual pre-hospital bomb explosion scene (30). During the outbreak of COVID-19, VR was used to realize a simulation course to train nurses in dealing with infectious disease disasters. The course included simulated nursing video consultations, a pre-hospital setting, home visits, arrivals at the emergency room, and follow-up rehabilitation home visits (31, 32). In today's community basic health care, which emphasizes humanistic care, nursing training based on a virtual scene is not limited to schools and hospitals, and virtual scenes for community and family nursing are constantly being developed. Yvonne l et al. proved that virtual nursing can effectively cultivate students to cross geographical barriers, acquire multiculturalism, and enhance their cultural ability through a prenatal/postpartum virtual simulation experience of African American and Amish patients (33).

In general, the use of virtual nursing in training nursing students shows promise. Many virtual scenes, such as first aid for disaster accidents, invasive operations, and nursing care models that inject cultural differences, need to be developed by staff.

Clusters of References

Highly cited references affect the frontier development of research, mainly in the field of nursing education, which is consistent with the analysis results of hot keywords. The clustering of citations continue until the most recent references can predict the research trends, which are virtual simulation, virtual learning, clinical skills, and dementia. We can find that dementia has become a hot research keyword.

Virtual Clinical Learning Simulation

The largest clustering result of citations contains virtual simulation, virtual learning, and clinical skills. This means that

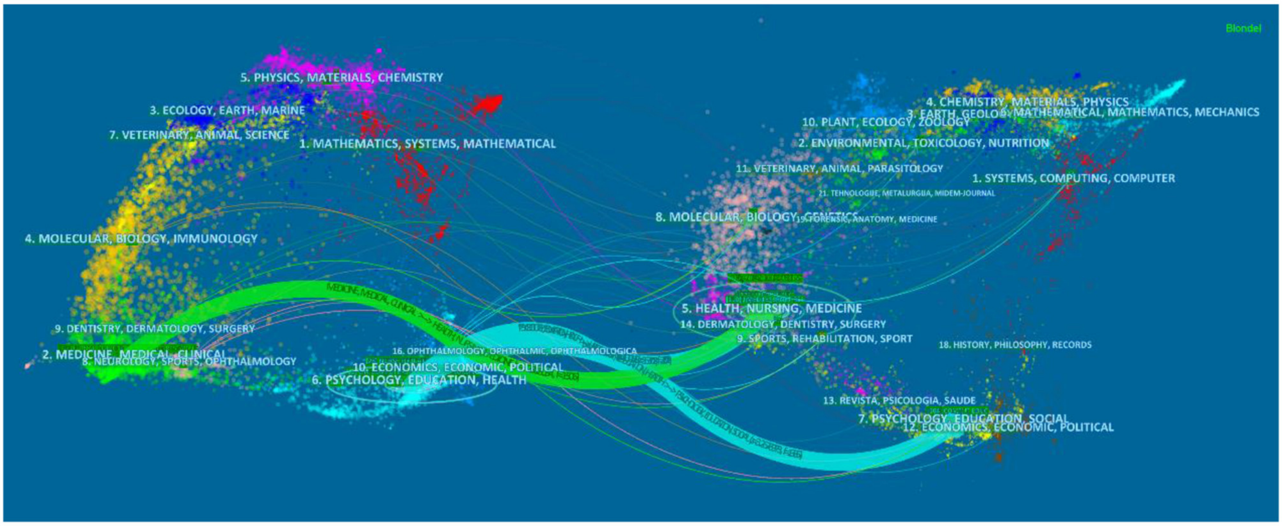

FIGURE 6 | The dual map overlay of journals contributed to publications on the application of VR in Nursing from 2012 to 2021. The green path shows articles in the research fields of MEDICINE / MEDICAL / CLINICAL that are more likely to cite articles in the field of HEALTH / NURSING / MEDICINE. The blue path shows the subject fields of PSYCHOLOGY / EDUCATION / SOCIAL, which are probably cited by PSYCHOLOGY / EDUCATION / HEALTH.

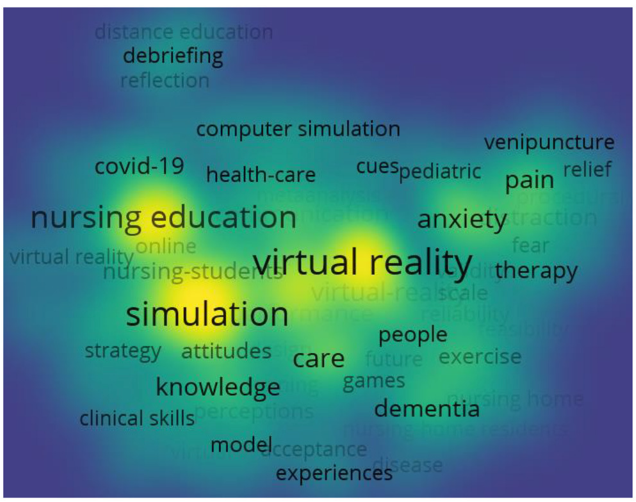

FIGURE 7 | The density visualization of keywords in publications on the application of VR in nursing from 2012 to 2021. A keyword with higher frequency counts forms a yellow region, and those with lower frequency counts form a blue region.

various virtual reality systems suitable for nurse training are being developed.

The use of high fidelity simulation technology has been suggested as a means of providing clinical experience for nursing students (34). The purpose of virtual clinical simulation (VCS) in nursing, which can allow one or more people to participate, is to cultivate students' professional skills (35). Since the behavior intention of interns must be understood in the development of VCS (36), various virtual clinical skill training systems have been continuously developed and improved. The virtual nursing system promoting humanistic care covers, but is not limited to, the following: nursing various organs in the human body, mental and psychological care (37), oral nursing (38) skills in knee arthroplasty (39), hysteroscopic surgery nursing (40), nasogastric tube placement (41), and surgical suture (42). The nurse training program also includes management ability is (43). It is also worth mentioning that VR has helped to realize telemedicine services (44).

Virtual nursing training is not only an optional teaching modality in different nursing operations, but it also breaks down regional and spatial barriers and introduces new ideas to telemedicine service development.

Dementia

Another result of the clustering of citations shows dementia as a research trend. In 2018, 50 million people worldwide suffered from dementia, an increase of 6% from 2015 (45). Due to the aggravation of the aging problem of the global population, dementia is becoming more and more prominent. However, the lack and uneven distribution of existing medical resources has not yet been resolved. This phenomenon forces researchers to develop intervention scenarios for virtual treatment that are more scientific.

Virtual scene training for dementia allows for the participation of both medical staff and patients. In order to improve nurses' empathy for dementia patients and help improve the living environment of dementia patients, Paul Slater et al. and Jennifer Stargatt et al. discussed using a VR project as a tool to help health care professionals sympathize with dementia patients (46–48). Patients with dementia have cognitive impairment and various behavioral and psychological symptoms, such as cognitive disorder, tension, depression, psychosis, shouting, and

TABLE 5 | Keywords with the strongest citation bursts of publications on the application of VR in nursing from 2012 to 2021.

Rank	Keywords	Year	Strength	Begin	End	2012–2021
1	Virtual reality	2012	3.09	2013	2019	
2	Knowledge	2012	3.98	2020	2021	
3	Simulation	2012	2.71	2020	2021	

TABLE 6 | The top 10 references of publications on the application of VR in nursing from 2012 to 2021.

Rank	Title of cited documents	DOI	Count	Interpretation of the findings
1	INACSL Standards of Best Practice: Simulation[SM] Simulation Design	doi: 10.1016/j.ecns.2016.09.005	29	This paper lists 11 standards, which supplement and revise the best practice standards of the International Nursing Association for Clinical Simulation and Learning (INACSL): Simulation[SM].
2	Clinical Virtual Simulation in Nursing Education: Randomized Controlled Trial	doi: 10.2196/11529	20	It is concluded that using the clinical virtual simulator as a resource for the experimental group's education can provide higher learning satisfaction and knowledge improvement than that of the control group after a randomized controlled trial.
3	Virtual vs.Face-to-Face Clinical Simulation in Relation to Student Knowledge, Anxiety, and Self-confidence in Maternal-New Nursing: a Randomized Controlled Trial	doi: 10.1016/j.nedt.2016.08.004	19	This study finds that virtual clinical simulation training may be a promising educational learning tool after assessing the knowledge and self-confidence scores of 56 students who completed a randomized controlled trial.
4	Using Game-Based Virtual Reality with Haptics for Skill Acquisition	doi: 10.1016/j.ecns.2017.09.010	17	The usability score shows that more students are eager to undergo sterile catheterization training using the virtual reality system for skill practice.
5	INACSL Standards of Best Practice: Simulation[SM] Debriefing	doi: 10.1016/j.ecns.2016.09.008	15	This paper lists 5 standards, which supplement and revise the best practice standards of the International Nursing Association for Clinical Simulation and Learning (INACSL): Simulation[SM].
6	Virtual Simulation in Nursing Education: A Systematic Review Spanning 1996 to 2018	doi: 10.1097/SIH.0000000000000411	14	This study systematically reviews the research on the impact of virtual simulation on the learning results of nursing students, and puts forward guiding opinions for future research in the field.
7	Virtually Nursing Emerging Technologies in Nursing Education	doi: 10.1097/NNE.0000000000000295	13	This paper introduces six new augmented reality products and systems that can improve nursing education.
8	Online Virtual Simulation and Diagnostic Reasoning: A Scoping Review	doi: 10.1016/j.ecns.2016.04.001	12	In order to prove the effectiveness of online virtual simulation in teaching diagnostic reasoning to health care providers, this study carried out a survey of online classroom virtual simulation contact.
9	Clinical Virtual Simulation in Nursing Education	doi: 10.1016/j.ecns.2017.09.005	12	This study evaluated the simplicity, usefulness and intention of nursing postgraduates in using clinical virtual simulation in nursing research.
10	Virtual Gaming Simulation for Nursing Education: An Experiment	doi: 10.1016/j.ecns.2017.02.004	12	This paper compares students' use of virtual gaming simulation (VGS) with traditional laboratory simulation and points out that the combination of VGS and effective hands-on simulation can become a part of students' teaching and clinical practice.

violence (49). Wendy Moyle et al. measured and described the effectiveness of participation, indifference and the emotional state of dementia patients through a VR forest, and concluded that virtual technology has a positive impact on them (50). Jorge Oliveira et al. reported a pilot randomized controlled trial involving 17 subjects and explored the effect of cognitive stimulation reproducing several instrumental activities of daily life in VR on patients with dementia caused by mild to moderate Alzheimer's disease. They concluded that VR is helpful in maintaining the cognitive function of patients with Alzheimer's disease. Jung-Hee Kim et al. recruited 10 Korean dementia patients and developed a VR intervention program based on their psychological needs. The scheme was proven to be convenient and safe as the program alleviated the patients' behavioral and psychological symptoms (51).

Developing VR scenes for dementia can help nurses and patients make positive adjustments for abnormal behavior and psychology. The construction of a VR scene should refer to the

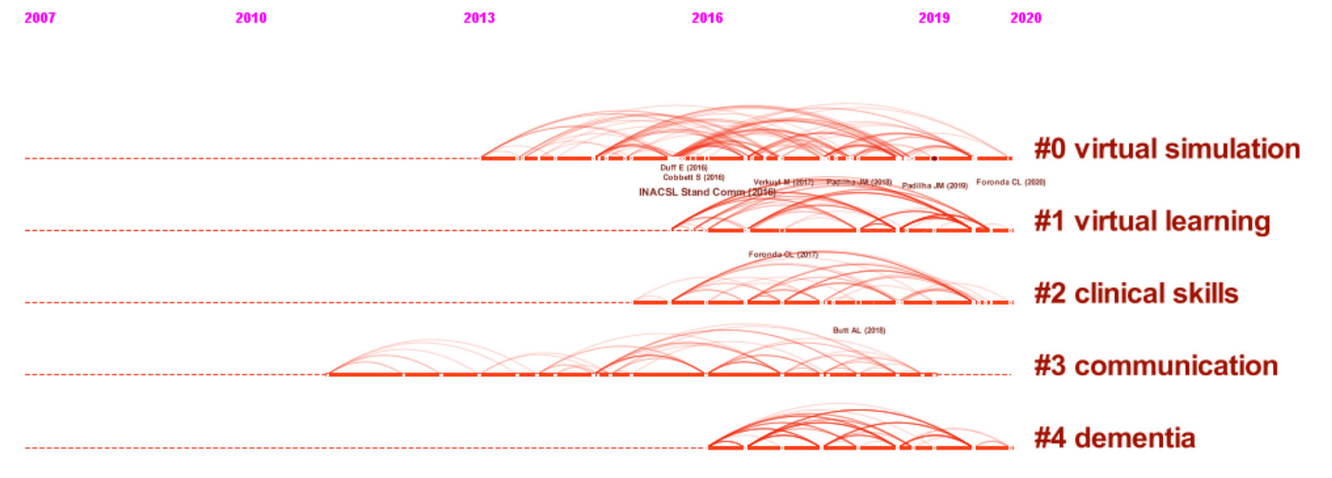

FIGURE 8 | Co-cited references timeline map of publications on the application of VR in nursing from 2012 to 2021. The cited literature is represented by the node on the timeline on the left side of the image. The citation link between documents is represented by curved connecting lines. The clustering label of the co-cited literature may be found on the right side of the image. The stronger the clustering strength, the higher the label position.

physical and psychological needs of different groups, such as different races, genders, and lifestyles, to improve comfort of use. There is still great room for development in this field.

Open Challenges and Future Opportunities in Virtually Nursing

The research fields of citation journals are rich, covering medicine, rehabilitation, neurobiology, psychology, economics, kinematics, computer science, and mathematics. This shows that the development of today's VR in the field of nursing is inseparable from the basic knowledge of various disciplines.

In recent years, there has been a growing demand for geometric problems in emerging application fields, such as VR. Bogucka et al. introduced the modeling and processing of geometric data, which still faces problems that need to be solved (52). In programming, a deep understanding of software code is required. A VR digital gamification method for program code, which applies digital gamification to a multi metaphor VR visualization of software program structure was described and evaluated by Oberhauser et al. The results of their preliminary empirical investigation described and evaluated a VR digital gamification method for program code, which applies digital gamification to multi metaphor VR visualization of software program structure. The results of their preliminary empirical investigation show that it is possible to increase subjects' fun and motivation as well as focus attention, and encourage the exploration of software structure (53). Since the development of the new system requires labor costs, it is necessary to ensure the practicability and effectiveness of the scene. In a study on the use of VR therapy for pain patients in 2018, it was found that VR in a certain range can help patients and hospitals save costs. However, going beyond this range may result in economic burdens to the hospital (54). In a 2021 survey, Roman et al. found that VR provided an alternative tourism model during the COVID-19 pandemic. At the same time, a VR tourism environment can simulate safe travel by allowing users to visit certain destinations despite political restrictions and economic difficulties. Moreover, VR technology can help people meet their spiritual and psychological needs during some special periods. For example, it can reduce the anxiety of mothers during childbirth and the fear of children undergoing surgery (6, 28, 55). In the past 2 years, more personalized and refined VR with neurotic feedback systems have been developed. Tartarisco, G et al. trained 20 nurses to simulate workplace stress situations. A neuro fuzzy model was used to collect the subjects' heart rate, breathing, and activity during training. The model was found to show good performance in the classification of stress level (56).

In summary, there is still a very broad space for the development of VR in the field of nursing. For nurse training, more high-risk or disaster first aid scenes need to be developed. To meet the needs of special groups, a theoretical framework to support the construction of virtual scenes must be used to ensure the effectiveness of the system. The introduction of biological signal feedback model is also a good idea. Economic and political factors deserve to be included in the system design plan.

Limitations

There are some potential limitations to this study. To begin, we only looked at published literature from 2012 to 2021. Some studies are ongoing but have not yet been published. Second, we only searched the literature in the woscc database, a popular academic database. There may be minor differences if you include citations from other databases, such as Google Scholar or PubMed. However, because different database citation counting methods differ, fusing and analyzing at the same time is impossible. Third, even though we read the 408 articles analyzed in this paper at the same time, we cannot rule out the researchers' inherent bias.

CONCLUSION

Nursing VR products have been used or are being used in many countries, but the number of SCI research papers in this area is not very large. As a new field in nursing research, virtual nursing has had an impact on both nurses and clients. It covers a wide range of disciplines and has applications in the full lifecycle. Nursing research tends to focus on nurse education and the elderly. The design of virtual scenes can be edited with reference to the dynamic standards of the International Nursing Association for Clinical Simulation and Learning (INACSL). Virtual scenes need to be tested before they are put to use in order to get a suitable and effective virtual training system.

Today's health care system is complex, and nursing is becoming more and more professional. Nursing students must be prepared for emergency and basic community nursing environment. Based on the above factors, the research and application of nursing VR have become more extensive. Given the COVID-19 pandemic, more VR scenes need to be designed and applied to staff training and home isolation staff care. With the emergence of the concept of the metaverse, the research and application of VR technology in nursing will gradually increase and the links between various disciplines in this field will become closer.

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

JZ, YL, and FZ acquired, analyzed the data, and drafted the manuscript. RM and FF designed the research, acquired the article information, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Digitizing the Informed Consent Process: A Review of the Regulatory Landscape in the European Union

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Background: Rapid technological advancements are reshaping the conduct of clinical research. Electronic informed consent (eIC) is one of these novel advancements, allowing to interactively convey research-related information to participants and obtain their consent. The COVID-19 pandemic highlighted the importance of establishing a digital, long-distance relationship between research participants and researchers. However, the regulatory landscape in the European Union (EU) is diverse, posing a legal challenge to implement eIC in clinical research. Therefore, this study takes the necessary steps forward by providing an overview of the current regulatory framework in the EU, relevant to eIC.

Methods: We reviewed and analyzed the key EU regulations, such as the EU General Data Protection Regulation (GDPR) and the Clinical Trials Regulation (CTR). We investigated the legality of eIC in several EU Member States, Switzerland, and the United Kingdom. To this end, we contacted the medicines agencies of various countries to clarify the national requirements related to the implementation and use of eIC in clinical research. Our research was complemented by comparing the legal acceptance of eIC between the EU and the United States.

Results: In the EU, a distinction must be made between eIC for participation in clinical research and eIC for processing the participants' personal data, complying respectively with requirements laid down by the CTR and the GDPR. On a national level, countries were classified into three groups: (1) countries accepting and regulating the use of eIC, (2) countries accepting the use of eIC without explicitly regulating it, and (3) countries not accepting the use of eIC. As a result, the regulation of eIC through laws and guidelines shows a large variety among EU Member States, while in the United States, it is harmonized through the Code of Federal Regulations.

Conclusion: Various requirements must be considered when implementing eIC in clinical research. Nevertheless, requirements across the EU Member States may differ significantly, whereas, in the United States, efforts have already been made to achieve a harmonized approach.

Keywords: electronic informed consent, ethics, privacy, General Data Protection Regulation, Clinical Trials Regulation, clinical trial

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INTRODUCTION

The principle of obtaining informed consent (IC) from participants as a prerequisite to participate in clinical research has initially been embedded in the Nuremberg Code and Helsinki Declaration (1–3). The practice of IC is also enshrined in guidelines for Good Clinical Practice (GCP). The GCP guideline of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use describes ethical and scientific requirements when designing, conducting, recording, and reporting clinical trials involving human subjects. According to this guideline, IC is "*a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate*" (4). IC may also serve as a legal ground for processing research participants' personal data, according to the basic principles embedded in the European Union (EU) General Data Protection Regulation (GDPR) (5, 6). In the GDPR, IC is one of the legal bases for processing personal data[1].

The IC process has historically always been documented on paper forms. However, digital technologies are reshaping this process, since electronic informed consent (eIC) could offer various advantages compared to paper-based IC forms (7). For instance, eIC could include multimedia components such as audio and video to present information in an interactive and engaging way (8). Moreover, eIC could include a personalized communication interface and facilitate ongoing communication with research participants. Nevertheless, face-to-face contact between the participants and the research team remains crucial to establishing a relationship of trust, and it is necessary for individuals who do not have access to technology or lack digital literacy (8, 9). Various initiatives have already implemented innovative types of consent and reported on the use of dynamic consent, a type of eIC, in biobanking and epidemiological research (10, 11). Dynamic consent is primarily developed to provide participants with more control over the future use of their data and samples (11). It enables participants to interact with the interface to manage their decisions on the use of their personal data or samples in research studies over time and thus, to have more control over their involvement in research (10, 12). Additionally, dynamic consent may increase transparency by providing an overview of participants' data usage or by feeding back study results (13).

In 2021, the European Medicines Agency (EMA) published a draft guideline on computerized systems and electronic data in clinical trials. As described in this guideline, eIC refers to "*the use of any digital media (e.g., text, graphics, audio, video, podcasts, or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document informed consent via an electronic device (e.g., mobile phones, tablets, or computers)*". As the EMA highlighted, investigators need to pay attention when using electronic methods since it might discriminate against people who are not comfortable using this kind of technology, potentially leading to bias in clinical research. Therefore, alternative methods for providing information and documenting IC should be available for those unable or unwilling to use electronic procedures. The EMA emphasized that any sole use of eIC should be justified and described in the protocol (14).

Despite the increasing interest in eIC, its adoption has been hampered due to various reasons. The most critical issue is the legal acceptance of eIC in clinical research (8, 9, 15). Concerns have been raised regarding whether eIC would comply with local regulations (8, 15). Moreover, it was reported that legal requirements, related to eIC, may differ across countries. For example, some countries require participants' wet-ink signature and do not accept the use of electronic signatures to provide IC for study participation (9). To this end, this manuscript aims to analyze the current regulatory framework relevant to (electronic) IC, examining how this framework could be further developed to facilitate eIC implementation in clinical research.

METHODS

We reviewed and analyzed the key EU regulations, such as the GDPR, Clinical Trials Regulation (CTR), and the Regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation). Moreover, we complemented our analysis showcasing national requirements related to the implementation and use of eIC in clinical research. For this purpose, we contacted the medicines agencies of several countries and described the various approaches currently used. This research was complemented by comparing the legal acceptance of eIC in the United States (US). Furthermore, recommendations were suggested to promote the implementation of eIC in clinical research.

RESULTS

Electronic Informed Consent in European Regulations

Informed Consent for Participation in Clinical Research

The CTR, an EU-level binding legislative act, aims to harmonize the conduct of clinical trials throughout the EU and increase transparency in this field (16, 17). IC, which has a central relevance within the CTR, is defined as "*a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the clinical trial*". Pursuant to Article 29 of the CTR, requirements are defined to obtain valid IC. IC must be written, dated and signed by the research participant and a member of the investigating team performing the interview, in which the necessary study-related information is conveyed to the participant (17). As a result, the CTR does not offer specific guidance for the use of eIC for participation in clinical trials.

[1] GDPR Article 6(1)(a).

Informed Consent as a Legal Ground for Processing Personal Data

The GDPR defines personal data as any information that can be directly or indirectly linked to an individual[2]. Special categories of personal data refer to sensitive information, such as health data, and it is restricted to process this type of data. According to the GDPR, data processing must be based on one of the legal grounds described in Article 6 and one of the conditions in Article 9 in the case of sensitive data. IC is one of these legal bases for the lawful processing of personal data. The consent of the data subject is specified as "*any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her*" (6). The GDPR clarifies that consent may be given by an oral or a written statement, including by electronic means[3]. The human subjects' IC related to data processing can be obtained together with their IC for research participation. However, the request for IC related to data processing should be clearly distinguished from IC for research participation (6, 18).

The GDPR aims to foster transparency regarding the way human subjects' data are processed (6, 19). Therefore, clear and plain language must be used when informing human subjects about the purpose and legal basis for data processing, the categories of recipients, the contact details of the controller and the data protection officer and if applicable, the transfer of personal data to a third country or international organization. Additionally, information must be conveyed about other aspects, such as the period of data storage and the data subjects' rights (e.g., the right to be forgotten) (6).

The Interaction Between the General Data Protection Regulation and the Clinical Trials Regulation

The CTR provides that EU Member States shall apply the GDPR to the processing of personal data carried out in the framework of the CTR[4]. Therefore, protecting the participants' privacy is one of the conditions to conduct a clinical trial[5]. The GDPR also refers to the relevant legislation applicable to clinical trials[6]. Therefore, both regulations apply simultaneously, and the CTR constitutes a sectoral law containing specific provisions relevant to data protection. Regarding the legal basis for the processing of personal data during the lifecycle of a clinical trial, the European Data Protection Board (EDPB) considers distinguishing between two main categories of processing activities (20):

(1) *Processing operations related to reliability and safety purposes*: these processing activities do not necessarily have to rely on consent. Processing for reliability and safety can be covered by the legal grounds of "legal obligation"[7] or "public interest" in the case of sensitive data[8]. As noted by the EDPB, several activities envisaged under the CTR satisfy the conditions for the applicability of this legal basis. For instance, archiving of the clinical master file[9] or disclosure of clinical trial data to the competent authorities for an inspection[10].

(2) *Processing operations purely related to research activities* in the context of a clinical trial cannot be based on a "legal obligation". Depending on the trial and the concrete data processing, they may either fall under the data subject's explicit consent,[11] a task carried out in the public interest[12] or the legitimate interest of the controller[13].

Informed Consent in the Clinical Trials Regulation and General Data Protection Regulation: Not the Same

As the EU Commission's Directorate-General for Health and Food Safety highlighted, the IC under the CTR must not be confused with the notion of consent as a legal ground for the processing of personal data under the GDPR (21).

Under the CTR, IC serves as an ethical standard and procedural obligation,[14] addressing the ethical requirements of research involving humans derived from the Helsinki Declaration. The IC under the CTR functions as a measure to protect the right of human dignity and integrity of individuals under the Charter of Fundamental Rights of the EU (22). Therefore, IC under the CTR is not conceived as an instrument to comply with data protection requirements. As the Directorate-General pointed out, IC in the context of the CTR is a safeguard for the participants, and not a legal basis for data processing (21).

Under the GDPR, consent must be specific, informed, unambiguous, and freely given. Moreover, the consent must be explicit when special categories of data, such as health data, are processed[15]. From these requirements, the "*freely given*" may be the most challenging one in the GDPR, since it implies real choice and control for the data subjects (23). Therefore, IC cannot be a valid legal ground for data processing where there is a clear imbalance between the data controller and the data subject[16]. The EDPB clarified that imbalance of power might exist wherever there is "*a risk of deception, intimidation, coercion or significant negative consequences (e.g., substantial extra costs) if the data subject does not consent. Consent will not be free in cases where there is any element of compulsion, pressure, or inability to exercise free will*". The primary examples for these situations are when the employer, public authority, or doctor ask for consent from the

[2]GDPR Article 4(1).
[3]GDPR Recital 32.
[4]CTR Article 93.
[5]CTR Article 28(1)(d).
[6]GDPR Recital 161.
[7]GDPR Article 6(1)(c).

[8]GDPR Article 9(2)(i) allows the processing of personal data when this is "*necessary for reasons of public interest in the area of public health, such as [...] ensuring high standards of quality and safety of healthcare and of medicinal products or medical devices, on the basis of Union or member State law, which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular professional secrecy.*"
[9]CTR Article 58.
[10]CTR Articles 77–79.
[11]GDPR Article 6(1)(a) in conjunction with Article 9(2)(a).
[12]GDPR Article 6(1)(e).
[13]GDPR Article 6(1)(f) in conjunction with Article 9(2)(i) or (j).
[14]CTR Article 28.
[15]GDPR Article 9(2)(a).
[16]GDPR Recital 43.

TABLE 1 | Processing health data in imbalanced/dependent cases.

Imbalanced/dependent situations (e.g., employer-employee, physician-patient, public authority-citizen)	
Clinical Trials Regulation	**General Data Protection Regulation**
Consent might be possible (e.g., with ethics committee review and specific safeguards)	Consent may not be the proper legal ground, since not freely given. Another legal ground is necessary for processing personal data (e.g., public interest)

employee, citizen or patient to process personal data (23). In the case of clinical trials, the imbalance between the investigator and the participant might occur. Therefore, IC may not always be the proper legal ground for processing personal data in clinical trials (**Table 1**). Thus, for processing personal data, other legal bases may be necessary, such as "public interest" or "legitimate interest" (18). The CTR also addresses the issue of imbalance, highlighting "*...whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate*".[17] Additionally, the EDPB considers that this will be the case when a participant is not in good health condition (18). However, ethics committees can allow consent in these imbalanced situations, with specific safeguards, such as supporting the patients' decision-making by discussing their choice with a trusted adult or relative, especially when potentially vulnerable groups are involved (24).

The withdrawal of IC under the CTR and the GDPR should also not be confused. The CTR clarifies that participants may withdraw from a clinical trial at any time by revoking their consent. This withdrawal shall not affect the activities already carried out[18] before the withdrawal[19]. Under the GDPR, there is also a possibility for data subjects to withdraw their consent at any time,[20] and there is no exception from this rule in the case of scientific research (25). The GDPR requires that consent can be withdrawn by the data subject as easily as giving consent; thus, eIC is a convenient method to fulfill this requirement[21]. The GDPR does not imply that giving and withdrawing consent must always be done through the same action. As a result, it is possible to withdraw a paper-based IC electronically. However, when the participant's IC was acquired electronically, he or she should be able to withdraw it as easily as giving it (23). In this case, similarly to the CTR, the withdrawal of consent shall not affect the lawfulness of processing the data based on consent before the withdrawal. Once the consent has been withdrawn, the data controller must stop data processing and ensure that the data are deleted or anonymized, unless the data can be processed on another legal ground (6, 17).

[17] CTR Recital 31.
[18] CTR Recital 76.
[19] CTR Article 28(3).
[20] GDPR Article 7(3).
[21] GDPR Article 7(3).

Signing Informed Consent Electronically

Next to providing study-related information to research participants electronically, eIC also refers to documenting their IC via an electronic device (14). To this end, various types of electronic signatures may be used. The eIDAS Regulation establishes a legal framework for electronic services, including electronic signatures, across the EU Member States. The main objective of this Regulation is to "*remove existing barriers to the cross-border use of electronic identification means used in the Member States to authenticate, for at least public services*". Therefore, the Regulation does not create a general obligation to use electronic signatures. EU Member States "*remain free to use or to introduce means for the purposes of electronic identification for accessing online services*", in particular in the private sector[22]. The Regulation only provides a legal framework for electronic services and encourages the use of them. According to Article 3 of the eIDAS regulation, an electronic signature is defined as "*data in electronic form which is attached to or logically associated with other data in electronic form and which is used by the signatory to sign*" (26). Another signature type defined in this Regulation is an advanced electronic signature. More specifically, an advanced electronic signature is an electronic signature that is "*(a) uniquely linked to the signatory, (b) capable of identifying the signatory, (c) created using electronic signature creation data that the signatory can, with a high level of confidence, use under his sole control, and (d) is linked to the data signed therewith in such a way that any subsequent change in the data is detectable*"[23]. In addition, the eIDAS Regulation sets the standard and criteria for a qualified electronic signature. A qualified electronic signature is defined as "*an advanced electronic signature that is created by a qualified electronic signature creation device, and which is based on a qualified certificate for electronic signatures*", and is the legal equivalent of a handwritten signature (26). One of these three different types of signatures could be used to document IC via an electronic device, considering the requirements set out by this Regulation.

The Acceptance of Electronic Informed Consent

Aside from the requirements of the European legislation that need to be complied with, requirements at the national level need to be considered when implementing eIC in clinical research. Therefore, we shed light on the legal acceptance of eIC in several EU Member States, Switzerland, and the United Kingdom. Generally, three groups of countries were identified. The first and second groups refer to countries that accept the use of eIC (including electronic signatures), with or without explicitly regulating it. The third group includes countries that do not accept the use of eIC (including electronic signatures). We provided examples for each of these groups. In addition, we compared the legal acceptance of eIC in the EU and the US (**Table 2**).

[22] eIDAS Regulation Recitals 13, 17, and 21.
[23] eIDAS Regulation Article 26.

TABLE 2 | The acceptance of electronic informed consent in the European Union and United States.

EU Member States			United States
eIC is allowed		**eIC is not allowed**	**eIC is allowed**
Group 1:	Group 2:	Group 3:	Regulated and clarified by a regulatory body
Explicitly regulated (e.g., Belgium)	Not regulated (e.g., Finland)	Explicitly regulated (e.g., Switzerland)	

eIC, electronic informed consent; EU, European Union.

Across European Union Member States, Switzerland, and the United Kingdom

Group 1: Countries That Regulate and Accept the Use of Electronic Informed Consent (Including Electronic Signatures) in Clinical Research

Austria. According to the Austrian Medicines Act Article 39(2), participants must provide IC in written form to participate in a clinical trial (27). Nevertheless, Article 4(1) of the Federal Act on Electronic Signatures and Trust Services for Electronic Transactions (Signature and Trust Services Act) describes that "*a qualified electronic signature satisfies the legal requirement of written form as defined in §886 of the General Civil Code*", meaning that a qualified electronic signature is allowed to document the participants' eIC (28). Moreover, the Austrian Federal Office for Safety in HealthCare specifies that electronic information, such as audio and video, can be used to inform participants on the condition that it is approved by an ethics committee (29).

Belgium. In Belgium, the conduct of clinical trials is regulated by the Law of May 7, 2004 on experiments on human beings. Pursuant to Article 6(1) of this Law, the participants' consent must be given in writing (30). In addition, the use of electronic signatures is governed by the Law of July 21, 2016 on eIDAS and electronic archiving, which further implements the EU eIDAS Regulation (31). The Clinical Trial College, an independent body within the Federal Public Service Health, Food Chain Safety and Environment issued a guidance on the use of eIC in interventional clinical trials in Belgium. This guidance summarizes the following requirements: informing participants, signing consent forms, access to eIC after signing, the dossier to be submitted to the ethics committee, and the application of the GDPR. For example, this guidance specifies that the electronic method of signing the IC must be adapted to the clinical trial, the context of the IC process as well as the participants' needs. If it concerns a phase 1 trial that requires the participants to show their official identity card at each visit, electronic signatures can be used that "*involve participant's handwritten signature using a finger or a stylus or biometric e-signature under the condition that there is a table trail which makes it possible to demonstrate that the person making the electronic signature was indeed the participant (e.g., the check of the ID document of the person)*". In addition, this guidance sets out that if the participants' identity is not verified, an advanced or a qualified electronic signature must be used (32).

United Kingdom. The United Kingdom Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) issued a joint statement, setting out the ethical and legal requirements when using eIC. In this statement, reference is made to the Medicines for Human Use (Clinical Trials) Regulations 2004 which lay down the requirements on informing and documenting consent in clinical trials. In addition, this statement clarified that electronic methods may be used for seeking, confirming, and documenting IC in research studies (33).

With regard to electronic signatures, the EU eIDAS Regulation is supplemented by the United Kingdom eIDAS Regulations (Statutory Instrument 2016/696) (34). Electronic signatures can be classified as "simple", "advanced" or "qualified". The type of electronic signature that should be used depends on the specific study. In the case of clinical trials of investigational medicinal products involving risks no higher than that of standard medical care, also referred to as type A trials, any simple electronic signature may be used (including typewritten or scanned eSignatures). In the case of type B and C trials involving a somewhat higher or a markedly higher risk compared to standard medical care, respectively, simple electronic signatures "*that involve the participant tracing their handwritten signature using a finger or a stylus or biometric eSignatures should normally be used as these allow for direct comparison with eSignatures and/or wet-ink signatures previously used by the participant for the purpose of audit or where the consent is contested*". However, the HRA and MHRA advise against the use of typewritten or scanned images of handwritten signatures. When clinical trials are conducted remotely, it may not always be possible to verify the participants' identity face-to-face. In these cases, the authorities prefer the use of advanced or qualified electronic signatures. In other types of research, any form of simple electronic signature should be sufficient to document consent. However, the HRA and MHRA emphasized that signatures traced with a finger or a stylus or biometric electronic signatures may be preferable for studies involving more than minimal risk, burden or intrusion (33).

Netherlands. Medical scientific research, involving participants who are subject to procedures or are required to follow rules of behavior, is subject to the Medical Research Involving Human Subjects Act (WMO) (35, 36). In 2020, a legislative procedure was initiated aiming to include the use of electronic signatures for obtaining the participants' IC in the WMO (37). This amendment will enter into force at a time to be determined by Royal Decree. Article 6 of the WMO will be modified and will include that the participants' IC "*can be obtained by electronic means, on the condition that such means are sufficiently reliable and confidential, appropriate to the research, and are set forth in the research protocol*". In addition, Article 6 will lay down that the research participants shall be informed in the same manner, if possible and preferred by the participants, as in which consent can be given. In any case, information must be conveyed in writing and, if desired, in an interview with the research team (38).

Group 2: Countries That Accept the Use of Electronic Informed Consent (Including Electronic Signatures) in Clinical Research Without Explicitly Regulating It

Finland. Although eIC is not mentioned in the national legislation, the use of eIC in clinical research is possible. Cases are assessed individually by the Finnish Medicines Agency (FIMEA), which is the competent national authority for regulating pharmaceuticals (39). According to FIMEA, researchers must describe in their application how they would organize the eIC process. Based on that, applicants may have permission to use eIC.

The National Committee on Medical Research Ethics (TUKIJA) in Finland, an expert group on research ethics, advises regional ethics committees on ethical principles related to medical research (40). The TUKIJA has issued guidance and templates on IC for participation in clinical trials. In these documents, the Committee has clarified that eIC is also accepted: "*Written consent can also be provided electronically. If you intend to use an online system for obtaining consent, please provide a description of the method and your reasons for opting for this alternative in your application to the committee*" (41).

Furthermore, the Finnish National Health Information system (KANTA) allows Finnish citizens to access their electronic prescriptions, medical records and manage their consent online for several purposes (42, 43). These purposes might include secondary use of data for medical research. The Act on the Secondary Use of Health and Social Data (552/2019) allows the further use of health data for medical research through the Social and Health Data Permit Authority (FINDATA) (44, 45). The Authority's jurisdiction on data permits and requests is based on section 44 of the Act on the Secondary Use of Health and Social Data (552/2019) (44). However, this Act applies to registry-based research, not to clinical trials. Register-based research "*utilizes health and social data for other purposes than for which the data was originally saved in the customer register or utilizes national registries*" (46). Although FINDATA and KANTA are not supporting clinical trials yet, the regulation and establishment of complex online health data management systems may help to foster the acceptance and trust in health cloud systems and eIC in the case of clinical trials.

Group 3: Countries That Do Not Accept the Use of Electronic Informed Consent (Including Electronic Signatures) in Clinical Research

Switzerland. The Swiss Ethics Committees on research involving humans issued a guideline on the use of eIC in clinical trials. According to this guideline, information can be conveyed by using electronic media, such as video or podcasts. The Swiss Ethics Committees recommend that "*the investigator, project leader, or the sponsor of the research project discuss plans for using an eIC with the Ethics Committee prior to finalizing the development of the eIC to ensure that the Ethics Committee agrees that the format may be used to convey the information the subjects*". Nevertheless, a hand-written signature of the trial participants is necessary to document their consent. At the time of writing, the legal validity of electronic and/or digital signatures is under review. In addition, other requirements are set out in this guidance that must be taken into account when developing and using eIC. For example, it is required that "*a validated system is in place to ensure subject's privacy, when electronic communication tools are used as part of the eIC interview process*" (47).

In the United States

In the US, there is no comprehensive, national data protection law. However, there are several sector-specific privacy and data security laws at federal, state, and local levels (48). At the federal level, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule aims to strike a balance between limiting the disclosure of personal health information and allowing researchers to access health data to support medical research. The disclosure of protected health information for research is allowed when: (i) the individual provides written consent or (ii) the Privacy Rule requires or permits it in other ways, such as approved by an institutional review board (49, 50). In the US, eIC is allowed and thoroughly regulated. The requirements for eIC are set forth by the US Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). More concretely, the relevant FDA and HHS regulations are outlined in the Code of Federal Regulations (CFR), under titles 21 and 45 (51, 52). Requirements related to IC, including the elements the participants need to be informed about, are presented in 21 CFR part 50 (53). Similarly, requirements related to documentation of IC are described in 45 CFR part 46. This part also addresses the elements that need to be included when broad consent is sought for the storage, maintenance, and secondary research use of identifiable information or samples (54). The use of electronic signatures is subject to 21 CFR part 11. This part sets out the criteria under which electronic signatures are considered equivalent to paper-based signatures. An electronic signature is defined as "*a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature*". The CFR clarifies the criteria of electronic signatures by detailing rules on the components, controls, integrity, and safety of electronic signatures, which are also applicable to clinical trials and biobanking (**Table 3**; 53).

Moreover, in 2016, the FDA and HHS issued a guidance on eIC, intended for institutional review boards, investigators, and sponsors engaged in or responsible for oversight of human

TABLE 3 | The regulation of electronic informed consent in the United States and the European Union.

	US	EU
Presentation of study-related information	HIPAA 21 CFR part 50 45 CFR part 45	CTR/GDPR
Electronic signatures	21 CFR part 11	eIDAS Regulation

CFR, Code of Federal Regulations; CTR, Clinical Trials Regulation; eIC, electronic informed consent; eIDAS, electronic identification and trust services; EU, European Union; GDPR, General Data Protection Regulation; HIPAA, Health Insurance Portability and Accountability Act of 1996; US, United States.

subject research under HHS. The guidance clarifies eIC as *"the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent"* (52). This clarification and further guidance on eIC are crucial for the unified application of rules on electronic signatures and IC. Overall, the requirements of electronic signatures and the IC process are regulated on the federal level in the US, resulting in a harmonized legal environment for acquiring eIC in the fields of healthcare and medical research.

DISCUSSION AND RECOMMENDATIONS

Our manuscript provided an overview of the most important regulatory instruments relevant to eIC in clinical research. Although in the EU several regulations are regulating (parts of) eIC in clinical research, Member States still have room for introducing diverse requirements. The CTR, laying down the principles for IC for trial participation, does not set out requirements specifically related to eIC (17). The GDPR has strict rules on data protection, and allows the use of eIC, but does not require it (6). In addition, the eIDAS Regulation is not necessarily targeting the use of electronic signatures in clinical research (26). Some countries, accepting the use of electronic signatures, refer in their statements to the eIDAS Regulation while others, such as Switzerland, still require a wet-ink signature to document the participants' consent. On the contrary, in the United States, the CFR lays down the requirements for eIC, and the FDA considers electronic signatures equivalent to handwritten, paper-based signatures. Overall, the regulations in the EU on data protection, clinical trials and electronic signatures result in a complex, partially harmonized legal environment, which poses a significant challenge for researchers implementing eIC.

Official position statements on the regulatory acceptance of eIC across EU Member States are highly variable. Some countries such as Austria and the United Kingdom published comprehensive guidance, allowing the use of eIC (including electronic signatures) in clinical research, whereas others such as Switzerland forbid it (29, 33, 47). Since drug development has been globalized to make treatments available to patients around the world, it may be crucial to harmonize the legal requirements across the EU Member States (55–57). Moreover, the EMA published a statement to urge the conduct of large multi-center, multi-arm clinical trials to investigate COVID-19 treatments. This statement stressed the importance of involving all EU Member States in these trials (58). When multi-country clinical trials are conducted, it needs to be ensured that the regulatory requirements in these countries are met. Due to the lack of harmonized eIC requirements, significant costs and additional delays may be added to the process of clinical research (59). Therefore, efforts are required to ensure that requirements have a high level of consistency to facilitate the conduct of multi-country clinical trials. Over the years, progress has been made in drafting guidance documents for eIC. In 2016, the FDA issued a guidance document in the US (52). In the EU, the EMA has taken the necessary steps to foster the adoption of eIC in clinical research by publishing a draft guideline on computerized systems and electronic data in clinical trials (14). These guidelines may contribute to increasing the regulatory convergence at a global level.

Requirements stemming from various regulations need to be considered during the implementation and use of eIC. When participants' eIC is sought for research participation, the rules laid down by the CTR must be met. For instance, the eIC interface must inform participants about the aspects of the research study that are relevant to their decision on participation (17). An eIC system could make use of telemedicine technology to interactively guide participants through the information (8). In addition, the CTR specifies that obtaining participants' written, dated and signed IC is a condition for a valid IC (17). If IC is documented via an electronic device, several electronic signature types could be used, as outlined by the eIDAS Regulation. However, a qualified electronic signature is the only type that has an equivalent value as a wet-ink signature (26). Next to IC for participation in research as an ethical requirement, it can also serve as one of the legal grounds for the processing of personal data. In this case, the eIC system must comply with the multiple obligations imposed by the GDPR. For example, similar to the CTR, the eIC interface must offer participants the possibility to withdraw their consent related to data processing (6).

CONCLUSION

The application of eIC is increasingly becoming part of the clinical trial landscape, due to the COVID-19 outbreak and technological advancements. Therefore, our research outlined the regulatory framework relevant to eIC in clinical research, focusing on the EU. Although eIC has the potential to provide a safe, fast, and reliable tool to expedite research, the regulation of it is lagging behind, pulling back its potential. In the EU, despite the efforts to harmonize the rules on data protection and clinical trials, the legal acceptance of eIC significantly differs among the Member States. As our research highlighted, some Member States allow eIC (including electronic signatures), with or without explicitly regulating it, while other States simply do not allow the application of eIC, resulting in an unharmonized and confusing legal environment for researchers. In the United States, the acceptance and regulation of eIC on the federal level enables researchers to use the full potential of this technological application to enroll participants and have an interactive relationship with them during the research study. However, the sectorial approach and less strict rules on data protection rules are less efficient and result in an unharmonized protection in the US. Alignment of the regulatory requirements on eIC and data protection rules across countries may successfully advance the adoption of eIC, which would be crucial to enhance clinical research and successfully fight against present and future pandemics.

AUTHOR CONTRIBUTIONS

ED and JM designed and conducted this study and produced the first draft. PB and IH was subsequently revised the manuscript. All authors approved the final manuscript.

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Clinical Coders' Perspectives on Pressure Injury Coding in Acute Care Services in Victoria, Australia

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Pressure injuries (PIs) substantively impact quality of care during hospital stays, although only when they are severe or acquired as a result of the hospital stay are they reported as quality indicators. Globally, researchers have repeatedly highlighted the need to invest more in quality improvement, risk assessment, prevention, early detection, and care for PI to avoid the higher costs associated with treatment of PI. Coders' perspectives on quality assurance of the clinical coded PI data have never been investigated. This study aimed to explore challenges that hospital coders face in accurately coding and reporting PI data and subsequently, explore reasons why data sources may vary in their reporting of PI data. This article is based upon data collected as part of a multi-phase collaborative project to build capacity for optimizing PI prevention across Monash Partners health services. We have conducted 16 semi-structured phone interviews with clinical coders recruited from four participating health services located in Melbourne, Australia. One of the main findings was that hospital coders often lacked vital information in clinicians' records needed to code PI and report quality indicators accurately and highlighted the need for quality improvement processes for PI clinical documentation. Nursing documentation improvement is a vital component of the complex capacity building programs on PI prevention in acute care services and is relied on by coders. Coders reported the benefit of inter-professional collaborative workshops, where nurses and coders shared their perspectives. Collaborative workshops had the potential to improve coders' knowledge of PI classification and clinicians' understanding of what information should be included when documenting PI in the medical notes. Our findings identified three methods of quality assurance were important to coders to ensure accuracy of PI reporting: (1) training prior to initiation of coding activity and (2) continued education, and (3) audit and feedback communication about how to handle specific complex cases and complex documentation. From a behavioral perspective, most of the coders reported confidence in their own abilities and were open to changes in coding standards. Transitioning from paper-based to electronic records highlighted the need to improve training of both clinicians and coders.

Keywords: clinical coders, quality assurance–healthcare, clinical records documentation, pressure injury (ulcer), pressure injury documenting, acute care services, electronic medical record (EMR), coding standard

INTRODUCTION

Pressure injuries (PIs) substantively impact quality of care during hospital stays, although only when they are severe or acquired as a result of the hospital stay are they reported as quality indicators. The three main Australian sources of PI data include: (1) incident reporting systems, (2) clinical coded data derived from medical records and discharge summaries, and (c) data generated from Pressure Ulcer/Injury Point Prevalence Surveys (PUPPS/PIPPS) (1). Australian researchers (1–4) have repeatedly highlighted the lack of consistency and uniformity in the reporting of hospital-acquired pressure injury (HAPI), which leads to inaccurate data interpretation. Furthermore, these researchers have suggested that there is a need for greater uniformity of reporting and data standardization before providers can benchmark performance across hospitals and evaluate time trends in PI incidence. This study examines challenges that hospital coders face in accurately coding and reporting PI data and subsequently, explores reasons why data sources may vary in their reporting of PI data.

A PI is defined as “localized damage to the skin and/or underlying tissue, as a result of pressure or pressure in combination with shear” (5). The National Pressure Ulcer Advisory Panel (NPUAP), the European Pressure Advisory Panel (EPUAP) and Pan Pacific Pressure Injury Alliance (PPPIA) (5) identify four stages of increasing severity in PIs: stage I—non-blanchable erythema, stage II—partial thickness skin loss, stage III—full thickness skin loss, and stage IV—partial thickness tissue loss. In addition, a PI is classified as either an unstageable PI, when eschar or slough obscure the assessor’s ability to determine the true depth of the injury, or suspected deep tissue injury (SDTI), when a localized area is of discolored purple or maroon colors (5). The depth of tissue damage may vary, which is related to anatomical location (5).

PIs may be present and detected at hospital admission, or they can occur at any point during the patients’ admission in acute care. A PI acquired during a hospital stay is referred to as a hospital-acquired pressure injury (HAPI). Multiple factors on various levels may increase the risk of HAPIs occurring. For individual patients, key contributing factors are whether the patient is advanced in age, or has multiple comorbidities or high functional and mobility dependency upon admission. Physiologically, necessary factors include whether there is high skin perfusion and low oxygen saturation levels. Hospital-episode specific factors, such as whether the hospital stay is prolonged and the presence of suboptimal nurse-to-patient ratios, also have been reported to increase PI incidence (6–8).

Globally, intensive care unit (ICU)-acquired prevalence of PI was reported at 16.2% (95% CI 15.6–16.8); the study included 1117 ICUs in 90 countries (9). However, countries vary in the reported ICU-acquired prevalence of PIs, which is attributed to the organizational and workforce factors, including HAPI prevention protocols, the use of preventive measures, staffing levels, and the quality of care (8). A 2019 Australian study conducted at eight tertiary hospitals included 1,047 patients aged ≥65 years with limited mobility, the authors reported 10.8% of participants developed a PI within the first 36 h of hospital admission (6).

The incidence and prevalence of PI are projected to increase in upcoming years due to global population aging, increasing incidence of chronic illness, and increasing dependency levels, and particularly of concern is the potential for increases in HAPI, which hospitals have long sought to reduce. For example, incidence of HAPI during COVID-19 has been linked to the prone positioning needed for COVID-19 patients with acute respiratory distress syndrome (7, 10–15). HAPI are associated with poor health outcomes (16), reduced quality of life, and significant healthcare costs (17), particularly for those with stages III and IV PIs, which may represent approximately one third of the total costs for HAPI (18). Accurate PI staging and early prevention are important to monitoring and benchmarking hospital quality of care and associated care costs.

Globally, researchers (16, 19) have repeatedly highlighted the need to invest more in quality improvement, risk assessment, prevention, early detection, and care for PI to avoid the higher costs associated with treatment of deep tissue injuries. Quality improvement requires complex but sustainable approaches (20–22) based in a capacity building framework (19, 23) that includes use of high quality data. Quality of PI data can be impacted by various challenges related to PI identification, classification, measurement, and reporting (2, 24), including the accuracy of clinical documentation (25) and factors related to work of coders.

Australian inpatient hospital admissions receive a single Diagnosis-Related Group (DRG) code that is subsequently used by payers to process healthcare providers’ claims and is used for hospital-based outcome indicators. The appropriate DRG for an inpatient admission is determined from patient records manually and standardized to ICD format (26). DRGs are then assigned using the current edition of the International Classification of Disease ICD-10-AM/ACHI/ACS Eleventh Edition (https://www.ihpa.gov.au/what-we-do/icd-10-am-achi-acs-current-edition). The Australian Commission on Safety and Quality in Health Care promotes improved documentation leading to DRGs in the National Safety and Quality Health Service Standards, which are the basis for the country’s hospital-based outcome indicators (25). Within the Australian healthcare system, inpatient episodes assigned to PI treatment can receive optimal funding from payers.

To understand clinical coders’ behavior related to PI coding, we used the Theoretical Domains Framework or TDF (27) to frame a study into the challenges that hospital coders face as they seek to accurately and consistently reporting PIs and PI staging. The TDF is widely utilized by researchers as a theory-informed approach to analyzing behavioral determinants when process implementation is problematic. This study applies Atkins et al. (28) version (28) of the TDF with 14 domains of challenges: (1) Knowledge of the process, (2) Individual skills with the process, (3) Beliefs about one’s own capabilities, (4) Beliefs about consequences, (5) Environmental context and resources, (6) Social influences, (7) Behavioral regulation, (8) Optimism, (9) Emotions, (10) Goals, (11) Social/professional role and identity, (12) Reinforcement, (13) Intentions, and (14) Memory, attention and decision-making capability. Originally, Michie et al. (27) developed the TDF to explain who follows evidence-based guidelines, but Atkins et al. (28) have generalized the framework for use across implementation issues.

Coders' perspectives on quality assurance of the clinical coded PI data have never been investigated. However, a number of previous studies suggest that the TDF will be a useful framework for understanding the complexity of coding PIs and what factors impact how coders engage in PI coding. For example, recent Canadian studies (29, 30) of coders' perspectives on quality assurance reported the following barriers to producing high-quality medical coding data: (1) clinicians' notes can be incomplete and nonspecific; (2) errors and discrepancies can be present in patients' charts; (3) discrepancies in clinicians' and coders' terminology are present; (4) coders have a limited role in questioning, interpreting and modifying a diagnosis; (5) coder-clinician communication issues are present; and 6) staffing issues can occur. The identified barriers are well linked with the TDF domains and the related constructs. Quality assurance research examines the process used to meet optimal standards (31); and the past studies mentioned have identified a number of barriers that could make it difficult for medical coders to provide optimal coding of PI cases. Conducting this study, we aimed to identify individual, organizational and health system level barriers to the optimal PI coding process.

MATERIALS AND METHODS

Aim/s and Objectives

This article is based upon data collected as part of a multi-phase collaborative project to build capacity for optimizing PI prevention across Monash Partners health services (23). One of the project objectives was to identify individual, organizational and health system level barriers to the optimal PI coding process. Other objectives are presented in **Table 1**. The detailed description of Monash Partners Capacity Building Framework has been discussed elsewhere (23).

Methods

This qualitative study uses data from 16 semi-structured phone interviews with clinical coders and was part of a larger study including 48 total semi-structured phone interviews also including nurses from four acute care hospitals in Melbourne Australia. All interviews were audio-recorded using a handheld mobile recording device. Participant verbal consent to both the interview and audio recording was obtained prior to each interview.

Recruitment Strategy

Participants were recruited with the support of the project Advisory Committee, which had representatives from the University, four major acute care hospitals participating in this project, Wounds Australia – the National peak body for wound prevention and management, and Monash Partners – a partnership between leading health services, teaching and research organizations, and consumer support group. Representatives of the Advisory Committee from the participating health services verbally explained and provided a brief summary of our project to the clinical coders in each of their health services. Clinical coders wishing to participate then contacted the interviewer (LT) to schedule their interview.

Data Collection

Data were collected, using an interview guide developed by VT based on the TDF, and refined by LT, CW, JBH, and approved by the Project Advisory Committee. The interview guide (**Supplementary File 1**) included open-ended questions related to PI coding experience and was guided by the Theoretical Domains Framework (TDF) domains (2017 version). Open-ended questions were followed by prompts that probed the barriers and enablers to optimal PI coding and identified coders' needs and suggestions for improving the process of PI coding. Interview questions were modified by the interviewer (LT) depending on the interview flow. The interview guide was not piloted, because the TDF framework and questions are well supported in previous research.

Phone interviews were conducted by an experienced wound research nurse (LT) between December 2020 and March 2021. LT was employed by Monash University; and had no work-related relationship with the clinical coders recruited from health services. There was no unequal relationship between the interviewer and the participants. The average interview lasted 45 min, ranging between 29 and 64 min, depending on the participant's availability. All audio files were verbatim transcribed using professional transcription, and the first four transcripts were compared to audio-recordings by LT and VT to ensure the accuracy of the transcribed text. Interview transcripts were not sent back to participants for verification. All participants were reimbursed with a $25 Coles Myer gift card for participation, which was posted to their preferred address upon completion of the interview.

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. The main project was approved by the Alfred Hospital Ethics Committee (Project No: 66/17). Site-specific approvals were received from the participating health services ethics committees.

Data Analysis

The data were analyzed using the qualitative data analysis software, NVivo Version 12, later upgraded to Version 20.3. We adopted a theory-driven conceptual analysis (32, 33) as the data analysis method. We utilized the TDF (28) to guide analyses, using a coding framework that included all TDF constructs and the 14 TDF domains. VT initially coded the first three transcripts to develop the coding framework. The coding framework was then reviewed by CW and JBH.

We manually created the first and the second level nodes using a deductive approach that matched to the TDF domains (first level) and the TDF constructs (second level). The third level or child nodes were then created inductively to identify specific barriers and enablers to the optimal PI coding

TABLE 1 | Monash partners capacity building project: project objectives.

Project Phase	Project objectives
Phase 1	1. Map and compare existing PI data across four MP health services (Alfred Health, Cabrini, Monash and Peninsula Health). 2. Develop and pilot PI data harmonization approach across Alfred Health, Cabrini, and Peninsula Health. 3. Identify alignment of PI assessment tool/s and PI coding definitions. 4. Standardize risk adjustment procedures to account for differences in risk of PI development. 5. Establish and evaluate the cost effectiveness of pilot PI clinical registry.
Phase 2	1. Identify individual, organizational and health system level barriers to integrate PI assessment and care across the continuum. 2. Interview and develop training modules for nurses and clinical coders, based on interviews to ensure accurate PI assessment, documentation and coding across Monash Partners hospitals.

process, as well as, current needs and suggestions for coding improvement. Technically, utterances were linked with the particular barrier/enabler or need related to PI coding process, and mapped across the developed coding framework based on the TDF domains and related constructs. Although we were mindful of potential additional themes, we did not find any that were outside of this framework.

We interviewed 16 participants. Data saturation was reached by the 12th interview, when the remaining four voice files were with the transcription agency. We reached saturation when subsequent analysis did not generate any new barriers/enablers and needs/suggestions related to PI coding process within the TDF constructs. We then informed the remaining two coders who had agreed to be interviewed to thank them for their interest and stopped recruitment.

RESULTS

Participant Characteristics

Sixteen participants were recruited, including 11 clinical coders from three public health services and five coders from a private health service in Victoria Australia. All participants were female, which reflects the national profile of clinical coders, where 93% of them are female (34). Three participants were in the 25–34 years age group, six in – 35–44, six in – 45–54, and one in – 55–65. Further details on their education and years in clinical practice are provided in **Table 2**.

Summary of the TDF Domains

Eleven theoretical domains were mentioned in relation to the PI coding process, including barriers, enablers and suggestions for improvement (**Table 3**). The domains judged to be most important were those referred to most frequently by all participants: Environmental Context and Resources (referred 304 times), Social/professional Role and Identity (referred 167 times), Knowledge (referred 163 times), and Behavioral Regulation (referred 109 times). Other important domains included Intentions (referred 61 times by 12 of participants), Skills (referred 57 times by 13 participants), Beliefs about Capabilities (referred 54 times by 14 participants), and Memory, Attention and Decision Making (referred 12 times by 4 participants) (**Figure 1**). Less common domains included: Emotions (referred 3 times by 2 participants), Reinforcement (referred 2 times by 2 participants), and Beliefs about Consequences (referred once by 1 participant). Optimism and Goals domains did not emerge. We did not ask specific questions related to coders' goals and their optimism and during interviews, coders did not provide any relevant information related to these domains. Social influences domain was combined with Social/professional Role and Identity domain given that in the hospital setting in which the coders work, their identity and social influences were shaped largely by the clinicians and other professionals with which they interacted. Our decision to combine both domains was based on similarity of what the participants said across these domains.

Environmental Context and Resources

All 16 coders discussed the accuracy of hospital record documents as the main factor that ensures the accuracy of PI coding. The following information needs to be included in the nurses' notes: (1) definitive PI diagnosis; (2) PI stage; (3) PI location; (4) if PI detected on admission or acquired in hospital; (5) PI assessment conducted; and (6) the PI care plan. If this information was included in the discharge summary, coders were expected to confirm this from nurses' notes. However, sometimes nurses used incorrect terminology or incomplete description; for example, the patient record may indicate "injury," but it would be difficult to determine if it was a PI, thermal injury, or injury to skin sustained as a result of radiation therapy. Sometimes, clinicians used terminology such as "skin lesion," "blister," and "wound" instead of "pressure injury," which required further clarification. Nursing notes with correct terminology was particularly important for complex cases associated with chronic wounds, including venous leg ulcers, diabetic foot ulcers, and PIs. The main suggestion for improvement of the coding process provided by all participants was "to improve the accuracy of documentation."

At the time of the interviews, three public health care services had transitioned to the electronic medical record system (EMR), while the private health service was using paper-based records. The coders identified that the transition to EMR might have impacted quality of coding. For example, if nurses used an incorrect terminology for PI, this may not even appear to coders in the EMR. Also, from the coders' perspective, the EMR made it difficult for people documenting a PI to find how other clinicians had documented the PI during the patient's stay. One coder (C302) reported clinicians "had more freedom" using the paper-based form and were able to include drawings; whereas,

TABLE 2 | Participant characteristics ($n = 16$).

Participating health services		
Public health service 1	4	25%
Public health service 2	3	19%
Public health service 3	4	25%
Private health service	5	31%
Gender		
Male	0	
Female	16	100%
Age		
25–34	3	19%
35–44	6	37%
45–54	6	37%
55–65	1	6%
Education		
Bachelor of Nursing and HIMAA* clinical coder course	1	6%
Bachelor of Education and HIMAA clinical coder course	1	6%
HIMAA clinical coder course	2	13%
Bachelor Nutrition and Dietetics and Masters of Health Information Management	1	6%
Bachelor of Applied Sciences and HIMAA clinical coder course	1	6%
Bachelor of Health Sciences and Masters of Health Information Management	1	6%
Bachelor of Health Sciences and Bachelor of Health Information Management	2	13%
Bachelor of Health Information Management	7	44%
Current position title		
Clinical coder	3	19%
Health Information Manager	7	44%
Health Information Manager/coding educator	2	13%
Health Information Manager/coding auditor	3	19%
Health Information Manager/coding educator and auditor	1	6%
Current involvement in coding-related activities		
2 days/week	1	6%
3 days/week	4	25%
4 days/week	4	25%
5 days/week	7	44%
Duration of clinical practice		
<10 years	7	44%
11–20 years	5	31%
21–30 years	3	19%
>30 years	1	6%
Coding experience		
<5 years	3	19%
6–10 years	4	25%
11–20 years	5	31%
>20 years	4	25%
Completion of course on pressure injury coding		
Completed	1	6%
Not completed	15	94%

**HIMAA, The Health Information Management Association of Australia Ltd. is the peak professional body for health information management professionals in Australia.*

electronic entry of PI information was more structured and did not allow for this "freedom."

Social/Professional Role and Identity

Coders reported internal and external audits are the main facilitators of high-quality coding. Participants acknowledged that internal audits are conducted by coding auditors primarily for revenue purposes, but also help to improve the quality of coding. There are also reconciliation audits; and some health services have PI-specific reconciliation audits to double check that "the prefixes are correct," that is PI detected at admission and HAPI were accurately reported. These audits are usually followed by an education session for the coding team.

External audits are conducted by the Department of Human Services and by private health funds. The private health funds conduct two types of auditing. Pre-verification auditing is conducted to check the codes and related evidence prior to a health fund paying the hospital for that admission. The other type of auditing is conducted yearly and includes external auditors coming onsite and selecting about 200 records for review, as participant C202 explained.

All participating health services have coding educators/advisors, available up to 5 days a week, to provide support and training for coders. A request can be made via the Coding Advisor software; and the required guidance and standard recommendations will be provided upon request. Further, coding educators run intensive training programs for interns and new staff. Coding educators also inform the coding team about all recent changes to standards and monitor if these changes have been implemented.

In pre-COVID time, internal meetings were used to answer frequently asked questions and to discuss changes in coding standards. The internal meetings also provided an opportunity for coders to communicate shortcomings in medical notes. However, at the time of the COVID-19 outbreak, most coders moved to working from home and did not have the opportunity for face-to-face internal meetings.

Interprofessional collaboration also impacted data quality and subsequently the quality of PI coding. Regular meetings of coders with wound nurses improved nurses' understanding of what needed to be documented. Coders explained to wound nurses that it was easier to work when they had well-documented cases, which reduced the number of queries and saved time. Most coders reported that the quality of coding impacted on data, funding and decision making, and that this ultimately improves quality of PI data and therefore improves patient care. For example, coder C203 said: "We have done some education with the nursing staff in order to help empower them to really know how the documentation is going to affect the patient's coding and ultimately care in the hospital, how much the hospital can provide care, and that has resulted in some improvement here in [healthcare service]." The participants acknowledged that when clinicians say that they are too busy to meet with them, coders always try to convince clinicians that better explanation of what should be documented will save clinicians a lot of time, they would spend answering coders' queries.

TABLE 3 | Main domains, constructs and sample quotes.

Domains	Main constructs	Main sub-themes	Sample quotes
Environmental Context and Resources	Barriers and Facilitators	Accuracy of documentation	Often, you'll get, say, a leg ulcer with peripheral vascular disease with gangrene, with a diabetic foot ulcer, with a pressure injury stage 3... You want to make sure that you've reflected all those conditions in the correct amount of coding, so you're not double-coding and you're coding it correctly…That's what I find quite interesting and that's the challenge. Some cases are so simple and, therefore, like pressure injury stage 3, no problem, code that. It's the ones that are the diabetic feet with pressure injury or is that a blister, is that a wound? And that's what becomes quite challenging… C403 I personally will only code it if it's documented in the notes, and when it is beyond routine care. So, say if it just says a patient has a pressure injury, given air mattress, then I wouldn't code it. I would code it when there's a care plan. C303 Q: Is there any things you'd like changed or – would improve things for your end? A: From a coding point of view, I guess – I've probably said it a million times, just getting the best documentation that we can. Because that will reduce the time we spend trying to dissect all that information and then having to send a query, getting it back, changing the codes, finalizing the codes and then repeating that for the next case. C101
		Electronic medical record (EMR) and coding	Nurses used to write down 'sacral', or 'pressure area on sacrum', but now, if they haven't put this thing into the skin incision thing, it doesn't even appear in front of us. When something doesn't appear in front of you – other coders don't even know that exists. And there are hundreds and hundreds of things like that all over the EMR. It really has been – I know it's all designed for safety of the patient, but for us it's been truly quite mega. C302 I think the electronic medical record has added complexity because when the nurses documenting it in their view they can't necessarily see what other nurses have documented along the way, or other clinicians have documented along the way. For example, if they're documenting, because these go into the result section now, whereas before it was a clinical note and it would be a note that would be added to and built on by nurses during the stay. Whereas now it's all this discreet data entry where they might not have the context and the awareness of what else is being input. And so, we find that that perpetuates bad data because they never happen across a note, like they would have when it was paper and go, 'Oh actually our wound care nurses said it's a stage two, not a stage one, I better from now on document it as a stage two'. So, we do find this EMR discreet data sometimes perpetuates bad data entry, particularly in long stays. C102 Now everything has gone to electronic. So, it is more difficult, I suppose, to know where to look and to remember to look in the electronic system, than maybe what it was in the scan system. But it would be there in your face and the form would pop up, whereas the electronic system, unless I go searching for it, well then you don't see it quite so easily. So maybe more are being missed. C402
Social/professional Role and Identity	Organizational Commitment	Auditing	The internal auditing that happens is more for revenue purposes, so it's not so much quality, but you'll improve the quality, I guess, if something gets flagged. So, we have an algorithm actually that runs over the data and prioritizes what is most likely to change and for the biggest revenue change So that's also run over data each day and probably on average five records a day are flagged for auditing. C202 We audit DRGs [Diagnosis Related Groups] and we audit to make sure that they're at the correct DRG and we also have some quality audits. So, we've actually introduced a pressure injury quality audit at my organization. So, anything that is unspecified will get seen by the CNC [Clinical Nurse Consultant] and they do their own research in the record to ascertain whether or not it is a pressure injury. It's like a reconciliation audit. C103
		Support from coding educators	We do have a coding educator who's available 5 days a week who provides significant support and extended training for people in the areas that they're not familiar with. The hospital really does invest in our training quite a lot, and resources. C203 We have a senior coder on duty every day, and you can write to them, put it in the Coding Advisor's box, about anything or anyone. So, it could be: "Do I cancel this? Do you think this can meet 0002?" And you will get your answer back within the day from someone who's highly educated in coding. And that will give you guidance. And then it'll come back with all the reasons, and all the standards that they've looked at. C302 When a coder first starts we do a training program with them of the coding specialty which includes pressure injuries and also access to coding books, the online software. We do run the education program so it's a combination of face-to-face presentations, self-directed learning which we've had a lot of last year with PowerPoint presentations and also quizzes. C201
		Internal meetings	We also have the coding meetings, where we have an option for people to raise coding queries like, "I coded this and I'm not exactly sure. Has anyone come across a situation like this?" C401

(Continued)

TABLE 3 | Continued

Domains	Main constructs	Main sub-themes	Sample quotes
		Interprofessional collaboration with clinical staff	Because we've worked with the wound nurses, it becomes a lot easier, but prior to that, there was a lot of confusion and a lot of time taken in terms of writing the documentation queries, sending it out, getting it answered, getting it back, changing it. But now we've got a good relationship with the wound nurses and they understand what we need. So, it's become a lot easier. C101 I think we have to work collaboratively together. We really do need to have a larger voice because it impacts on data, it impacts on funding, it impacts on decision making across everywhere. We want to ultimately improve patient care, that's the end goal. So, we need to really work together. Data is important. I think if there was one message, data is so important, so let's try and get it right. C103
		Following the coding standards and coding guidelines	We use the Australian coding standard; the standard reference number is 1221 and also Victoria have their own set of rules that go with that as well so using a combination of the two. From that there must be documentation by a clinician or a nurse with evidence of assessment of the pressure injury and commencement of a treatment plan. C201 I don't think I code it as often as you perhaps want to code it. Yeah, because the documentation is probably as such that it's only showcasing routine skin pressure area – care, rather than something then that the documentation meets the standards that I use to code. So that is a standard principal and the additional diagnosis standard. There're certain parameters that we need to make sure are documented before we can code a principal diagnosis and then so often if the pressure injury is more than not an additional diagnosis, there's quite a few checks that you've got to make sure are documented before that diagnosis actually meets coding criteria and that's where the difficulty lays. C403 There're the Australian coding standards; and then adding to that, the Victorian – Victoria decided to create additional diagnoses criteria, so that's like an add-on to the coding standards. And then we also have the [Vic] coding committee, which people can write in coding queries, and then they're answered, and they essentially become rules that you can – advice you can follow. And then there's the national body, which are the national coding rules. Which again is the same sort of principle, people can write in coding scenarios and they will give advice on how best to code them, and then they're considered advice that you need to follow as well. So, if there's a particular coding rule that says, "In this situation you need to code it like this," you have to follow those rules, you can't just then change your mind and do something else. C401 So, the Australian Coding Standards is quite clear about the coding of pressure injuries. And together with the ACS 0002, which describes what is necessary for the standard of increased clinical care, which allows you to code it as an additional diagnosis, it's really very clear. There's no ambiguity about the coding of pressure injuries. Ambiguity comes in the clarity of the clinical documentation. C203 For example, sometimes a patient will come in with a pressure injury and it can change some stages. So, from a stage 1 to a 3 to a 2, but we always code to the highest stage. C101 I've got to be extra careful with the prefix, whether that was a pre-existing condition, or developed while the patient was in hospital, because that's one of the Australian Commission on Safety and Quality in Health Care hospital acquired complications. C303
		Professional development	I'm always interested in anything that will help me improve my coding and my knowledge. Whether that's a pressure injury or another condition. C101 Each time there's a coding update we all do it; and it's been online now, so we all do anything that's mandatory, for sure. C205 Twice a year there's a whole day coding workshop. And then we have a coding quiz every month. And then, you're supposed to have an hour a month to read all the new advices. C302 I have done a workshop a few years ago when the grades of the pressure injuries were first introduced into the coding system. C404
		Involvement in health professionals' education	Sometimes, it is about just educating people on the type of code that we use, the definition behind it, what the code is, if the definition has changed over time. So, we definitely do educate them on that. C103 I don't have a title. It's just part of being a clinical coder. Almost everyone has additional jobs in reporting or education. C203
Knowledge	Knowledge	Procedural knowledge	So, we get the electronic medical record and usually to look for a pressure injury. We look at the wound nurse notes and then we extract from their notes in the software that we use at the [health service] … In contacts, we look at the whole medical record or the admission notes. So, sometimes pressure injuries can be documented by nurses, medical staff, podiatry, but we usually code in to the wound nurses, because that's their specialty. So, we have to extract the location of the pressure injury, the level, so the stages. Also, whether it was acquired in care or hospital-acquired or whether it was present on admission. Then we go into software called 3M Coder and we code based on that information that we've got. C101

(Continued)

TABLE 3 | Continued

Domains	Main constructs	Main sub-themes	Sample quotes
		Knowledge of the ICD-10-AM classification	The company that actually produced ICD 10, the Independent Hospital Pricing Authority, IHPA… they release coding advice and education on a quarterly basis... So, we make sure that we read through all of those when they come out, or at least all of the information that's relevant to the coding that we do. C404 Q: How would you rate your knowledge on the information contained within the ICD-10-AM, the International Classification of Diseases? A: I'd say it's pretty good. Again, I've had a fair bit of experience, so yeah. I still have to refer to the standards and review things every now and then, but yeah. C201
		Knowledge of pressure injury classification	But we do have some coders who have a nursing background and then done their studies and become a health information manager. So, my team leader was actually a nurse, so she's got a lot of background knowledge and she understands a lot of the concepts a little bit better than I do. C101 Australian Coding Standards, ACS… So, we use those definitions. And they also – not only have clinical information in how to classify pressure injuries, they have a section called pressure injuries. They also have a section about condition onset flags. So that's determining if it's present on admission or occurs after admission. So, we use those definitions as well. Our ACS is pretty good explaining the pressure injury staging. And we've had in-house education sessions. So, again, [I could rate] my knowledge of probably a nine [out of ten] for me and our educators maybe a seven or eight [out of ten] generally. C102 Q: And how would you rate your knowledge on pressure injury classification and staging and skin changes terminology? A: Well, our wound care chart has lovely pictures on it. So, really that's my education about it. The more ugly the wound – usually the higher the stage. But yeah, I certainly – I'm not off the top of my head, I wouldn't know what the definition of a stage 1 vs. a stage 2 vs. a stage 3 is. I don't have to know that to decide what code. I just need the stage documented and then I'll go with that. C202 When I became more involved [in coding] through the years, it's [the pressure injury classification] certainly changed a lot, the coding of it; and when it changed, I really went into reading the descriptions. And, where I've worked, at various places, the wound chart really goes into describing the level. So, I've read a lot, looked at photos as well, if I can, because that really helps to understand the severity of it [pressure injury]. C205
		Impact of COVID-19 on training	We were a bit restricted last year with group meetings with COVID, but we did more online, so she'd [the coding educator] send out quizzes on a regular basis that everybody had to complete. And she records their answers on a PowerPoint presentation on a topic. So, a bit of a mixture of approaches. C202 The manager has done education sessions with the consulting physicians here, but again that was before COVID, which it hasn't really happened in the last year, but that is something that they talk about, how critical the accurate documentation is and a documented plan of care. C203 So back pre-COVID days, we'd actually get, say, the skin integrity nurse to come and we would – they would talk to us about their process and we would talk to them about our process as well to try and bridge that gap between understanding the care delivery process and the documentation process and then the coding process, so - and linking those three areas together. C403
		Knowledge: suggestions for improvement	Q: Is there any improvements that could be made to ensure accuracy of coding? A: I think it comes down to documentation and just continuing to educate [clinicians] when we can. It's kind of hard if you don't know what to do or why it's needed, then you never do it. But if we can get it out there, like we have with the pressure injuries and with the wound nurses then we can see the improvements and get better documentation and better data and coding. C101 I like learning the anatomy about the different [pressure injury stages], like what makes a stage one a stage one and the definitions from a clinical perspective. But also, I would really love some ideas to take back to our CNCs on other organizations that have an electronic record and their data flow sheets, all their wound charts and etcetera, so we can see what else is out there and potentially improve what's in our system. C103 I think apart from the documentation the other thing and you were asking about before with our knowledge of pressure injury terminology and things like the skin changes and what the staging actually means and the progression of the injuries. C201 I think webinar's good, and it would be great to get a variety of different scenarios, or different people, different treating clinicians perhaps, and maybe different sites so that we can see how different sites do code and find the documentation, or any issues that they've come across or resolved. C401 Although you watch the presentation and you're actually on board and you listen, sometimes, you don't catch everything or you don't understand everything. So, what I've done is, on my own time, I've gone back in and just re-watched the presentation, just sit and taking a few of my own notes. C104 I like face-to-face workshops, but online webinars and things well we've seen a rise of that kind of thing in the last year due to pandemic. So that is a good way of being able to capture everyone at a time that's convenient for them to do it. Whereas face-to-face workshops are more difficult when you have part-time staff, etc. Yeah, so I guess webinars are a good way. C202

(Continued)

TABLE 3 | Continued

Domains	Main constructs	Main sub-themes	Sample quotes
Behavioral Regulation	Action planning	Ensuring accuracy of coding	Q: How do you ensure the accuracy of the code? You touched on it a bit before… A: Yeah, the description in the code or the codes for say the area and the stage, I would not just click on the code, I would go into the tabular list which gives you more detail of the area because the most common ones are probably on the heel or the sacrum but, sometimes, you'll get the malleolus or something like that and I think oh gosh, I'd really better click on the tabular list to really look at the whole definition of this code, just to check I've got the right stage and body area. C205 Q: Now, we're just looking at the accuracy of coding. How do you ensure that the patient episode is allocated to the correct DRG with pressure injuries? A: Obviously, the first thing you have to do is you have to make sure that the principle diagnosis is correct, and then that will usually determine what DRG it falls into. And then if they have a procedure, the procedure may change the DRG, or if they were admitted for a particular procedure like a hip replacement, or an appendicectomy or something like that, that will determine what the DRG is. And then, in terms of the DRG split, so C, B, and then A DRG, that will depend on the complexity. So, for example, if they do have a pressure injury that's treated, that might impact the DRG. C401 A: So, we read podiatry in-patients notes, especially for pressure injuries of the foot or toes. Q: The wound chart? Would you double-check that? A: Wound chart, yes. Wound chart, nursing notes, podiatry and obviously the medical in-patient notes as well. C101 We do have a hybrid model here at [private healthcare], where we use the PAS, the Patient Administration System, in conjunction with a paper record. But all the nursing notes and the doctors' notes are handwritten, which obviously takes more time to decipher. There are often doctors letters, which come up on PAS or in the correspondence section, which aren't typed. We do need to do significant work on getting discharge summaries because the rate is very low, which also is an excellent source of information when it's there. And our wound charts… the way that they're set up is very difficult because we cannot code pressure injuries off the wound charts because they don't provide sufficient space for a written assessment and a plan of care because they're basically tick charts and body shapes with diagrams that they fill in to indicate the place of the injury or a device and don't meet the coding standards to allow us to code from those charts. And then often it's not backed up in the notes; and that's where we come into problems with the documentation. C202
		Documentation query	If there wasn't all the information that I wanted and there was a DRG impact to that particular admission, then I potentially would need to send a query. So, a documentation query is when we send a question to the clinician with all of the available documentation that is in the record and we ask them. For example, when I say clinician I might send a pressure injury query to our pressure injury CNC nurses. C103 But we've had a policy here in – well an instruction to the coders here in the past that we generally don't query things that won't make a difference to revenue. So, if you've already got that episode of care into maximum revenue then there may be no need to query the pressure injury. If that was the diagnoses that was going to make a difference to revenue then yes, you'd definitely be querying it. C202 [In relation to pressure injury] And you can see that I haven't got quite the full picture here, and I need to put a doctor query in, and the funding will be improved, then you would go ahead and put a doctor query in. If I've got a patient admission that I'm coding and I can see perhaps there is a pressure injury in there, but coding it doesn't increase the funding, I wouldn't then ask the doctor for more information or skin integrity specialist for more information because it's not going to cause any difference. And that's where the gap is because it's public health, and you would only do that to help optimize your funding, so you can make sure that you're reimbursed for that episode of care, but if you are not going to optimize the funding, you wouldn't put the query in, so – yeah, that is a bit of a gap. C403
	Self-Monitoring	Double-checking codes	When I open a record or an episode, I write down anything that would meet the criteria for coding; and then I signal out anything I need to check and I would put the codes in the 3M Codefinder [health information system] and then I'd go and do that whole process again just to double-check and then I check the DRG before finalizing it just to ensure that say it's not an ear, nose and throat DRG with a completely laparoscopic cholecystectomy. So just check that it's relevant, the DRG matches the case mix and the codes. C203 So, I might pull it up myself and go, "oh my God, that one wasn't an endoscopic one, it was a non-endoscopic one, so it's coded wrongly." So, yes, I do little things like that for my own purposes, so that I can get the coding quality correct. So yeah, there are a few simple audits yes that I do pull, but the research and epidemiology tool, is somebody else's portfolio. C402 So, you do, definitely do a check before you hit enter. C403

(Continued)

TABLE 3 | Continued

Domains	Main constructs	Main sub-themes	Sample quotes
		Using systems to ensure the quality of coding	So, we ran a program called PICQ, which is a Performance Indicator of Coding Quality, so that software – well actually we upload a file, an extract file, each day to [the name of the company], which is the private company that owns that software. So, all our coding every day gets run through that; and then each coder gets an email the next morning if they've generated an error that's been picked up that way. So that's probably more quality check. C202 We use a PICQ error program which picks up our errors and gives you a report every day if you have a warning or an error from the previous day and you can go and clarify the record immediately while it's still fresh in your mind. And besides with correcting the record, it also helps you learn about what triggered that warning in the first place and how you may avoid that in the future. C203 We also can run our own reports using Quick View software. So, on a monthly basis I'll run a report on that to see how many HACs [hospital-acquired complications] we had; and so, if it looks like an unreasonable number, we'll pull records out and check the coding. If it looks reasonable, do a quick desktop audit to make sure it makes sense. I guess that's the main way, monthly reports. C202
Intentions	Stability of intentions	Direct impact on the patient's episode of care	But I mean, the reason why we're coding is for a summation of that person's journey. A person can have a variety of issues which weren't treated; so, we shouldn't be coding them, and it hasn't impacted that person's stay. I think that the discharge summary, if done correctly, have the most important diagnosis available. C103 You have to look at each episode on merit, you can't really go back to previous – If you've got a patient who's been admitted 30, 40 times with the same things, you still have to take each episode on its own merit. C401
		Optimizing patient's funding	Q: And would a pressure injury capture and coding make a bit of revenue? A: Depends what the patient's in for originally. Sometimes, it will make no difference. And it just depends what DRG [Diagnosis. Related Group] the episode's in the care. I mean, sometimes, the diagnosis can make the difference of $10,000 between if something's coded or not, but it's not always a pressure injury to make a difference and it depends on the DRG. Sometimes, you can have the same code and it will affect one DRG, but it won't affect another DRG. Depends on the complexity level that's been assigned to it for that visit. C202 Q: So, you'll come across information that might say it looks like a pressure injury. Do you then have to send out a query about that? A: It depends on the funding that that patient is having. If it's going to make a difference to the funding, then we would send out a coding query about it. But if it's not going to affect the DRG, the diagnostic related group, then we don't spend time on sending a query. That's only appropriate for the funds that use DRG funding. Some funds are funded by diagnostic related groups, and the more detailed documentation, the higher the split. And of course, we want to reflect as accurately as possible everything that happened with that patient because it will change the amount of funding that the hospital receives. So, another patient that's on a per diem rate and we receive the same amount per day regardless of what's wrong with them, we would spend less time following up and chasing documentation to accurately reflect what is already written in the record. Q: Because you've already got them under a daily funding. C203
Skills	Practice	Supervised practice	You do a year training so where your records are being checked, your coding's being checked and you're learning the different specialties of the hospital. I'd probably say [it takes] maybe about 4 years to be really confident. C201 We do have an extensive training program, but we don't have new coders at the moment, because it does, it takes a fulltime person to train them and things. And I think every hospital in the state though, really, they get – if you're not experienced, it's very difficult at the moment to get a job, because none of the hospitals will put on a trainee. But just because you finished Uni, does not mean that you are set forth on coding – it's another 2 years of being on the frontline. C402 And, I think, that's why the training goes for a year because – I might be coding a respiratory case, but they've also got cardiology and renal as well. So, you've got to really be trained in every area before you can [code on your own] – "Okay, you're off training now, out you go, you go code on your own," and not every case of mine was then checked then because I had then proved a certain level of ability in that year, yeah, as you cover everything. And as you get signed off on one, then if you do, do some live coding, it's only for those renal episodes. So, it's – they're quite careful that they don't release you until they're confident that you've been upskilled in all the areas. So, it's nothing like having theory. Theory's great, but in actual practice, it's knowing the inhouse systems, it's a completely different kettle of fish. C403 And once you – you do lots of practice coding, so you're coding ones – cases that have been previously coded, so like shadow coding them. Then you start coding some live ones and all of your ones that you've – say, I've just freshly learnt about renal, then I start coding my own renal and they're all checked themselves and then you have to pass – the trainer has to review and you have to pass that unit before you can move on, so you have to be able to prove some ability in making sure that your code is matching their coding and they're quite confident that you can go ahead and keep coding that unit. C403

(Continued)

TABLE 3 | Continued

Domains	Main constructs	Main sub-themes	Sample quotes
Beliefs about Capabilities	Perceived competence	Perceived competence	Q: How would you rate your knowledge and skills related to pressure injury coding? A: On a scale of one to 10, 10 being brilliant…Coding, I would hope to be a 10 out of 10. C103 I've been coding for over 20 years. I am a coding advisor at where I work, so I actually am a point of call for other coders to ask questions of. I have coded consistently across that 20 years. I have worked at a number of different places. So, fairly familiar with all different types of documentation, always stay on top of the education, and always reading new queries that come out. C301
	Self-confidence	Self-confidence	Q: How confident do you feel allocating pressure injury codes to patients' period of care? A: Depends on the admission. Again, I guess going back to just the scenario of that patient's stay and the way it's documented so sometimes it's quite easy, and I feel very confident, other times it might be a bit harder to try and work out whether it's appropriate to assign it. In that case, I'd then discuss it with another coder and then from that discussion feel pretty confident once I've had a second opinion. C201 If I've got that sufficient documentation, then I'm confident to code it. There are times where sometimes I have to think really, really hard whether or not it meets additional diagnosis in that particular case. So actually, maybe I would say 70% of the time I would be comfortable with assigning that code. C103 I'm pretty confident when there's information or when there's even the word 'wound', I feel like I'm confident in finding out more and what they mean and a 'wound' doesn't necessarily mean acute trauma. I like to look deeper to see what is that wound, so I feel quite confident in my own practice. C403 We're very confident. We all have our senior staff who we report to, as in senior educators. If I find something that is inaccurate or I'm querying it or I'm not sure about, I'll just ask her. And I will just send her an email. And we always give feedback. And therefore, our educators tend to have meetings and discuss anything that comes up, or anything that's new, or anything that we find that it's unusual. C104
Memory, Attention and Decision Making	Memory	Memory	Sometimes it's worse the longer you've been coding because you remember five/ten years ago how we used to code it and that kind of got stuck in your brain, but the more recent stuff didn't. The newer coders might refer to the standards are bit more often because they're used to doing that in their training and they're kind of aware, whereas one that's been coding in years or so might think oh yeah, I know that and not go back to it as frequently, so may still be depending on memory. C202 People would go shortcuts because they start remembering codes off the top of their head, people will always find shortcuts, but it's that self-checking that you need to make sure that, "Okay, I've coded this." C403.

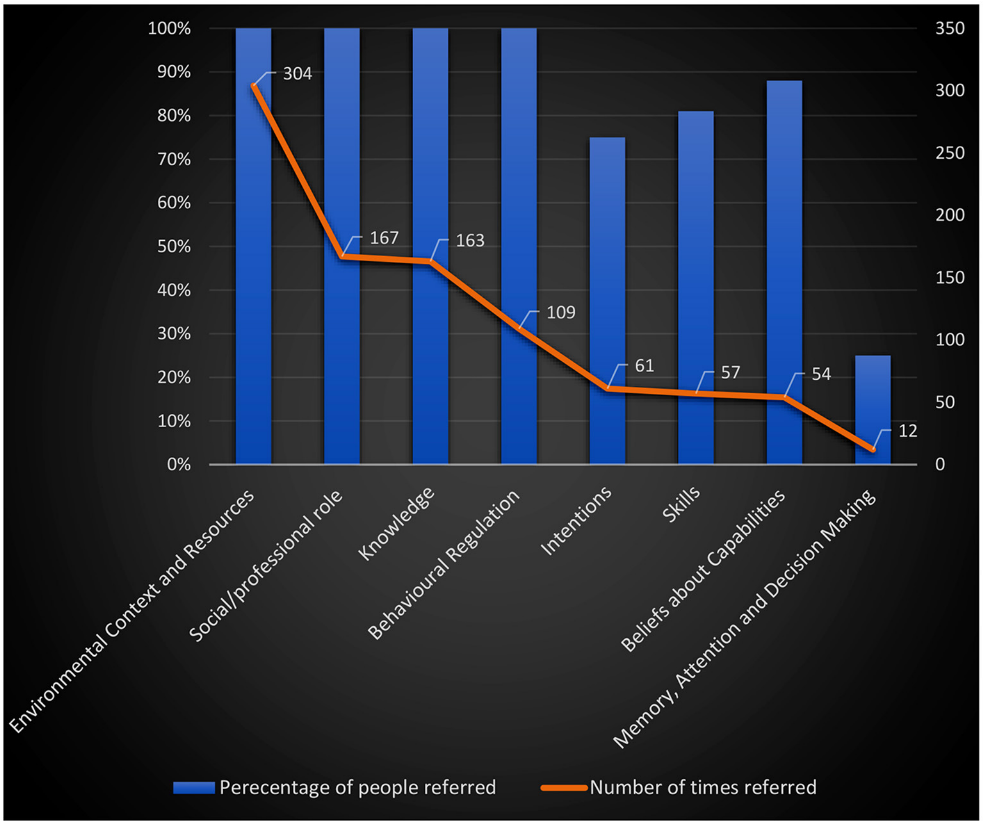

FIGURE 1 | The summary of the TDF domains: percentage of the participants referred and the number of times referred.

Following the coding standards and professional guidelines, ongoing professional development, and involvement in health professionals' education were the main professional roles discussed by all coders. They acknowledged following national and state coding standards and reported that coding standards were clear on how to code PI; for example, coding standards specified clearly how and when to code principal and additional PI diagnosis. In addition to these standards, there were coding scenarios developed by the coding committee, which also provided advice on how to code scenarios. For example, coders reported they always coded the highest stage of PI and all parts of the body if more than one PI were identified. Coders reported they paid specific attention distinguishing a PI on admission and HAPI.

Moreover, participants acknowledged the need to be up-to-date on the changes in coding standards in order to successfully implement standards into practice. They also acknowledged the need for researchers to interpret statistical information in light of the coding requirements for a particular year and to compare data across different periods of time with caution. They provided an example on how changes in coding standards affected the availability of statistical information on HAPI over time, which could easily be misinterpreted as improved quality of care:

> "They change the goalposts regularly, and it's very hard for us to keep on our toes. As far as you're concerned with pressure injuries is that you may have found a period of time from when ACS 0002 [Australian Coding Standards 0002], which was not this edition, it was the previous edition... There would have been a period of time where pressure injuries weren't– appeared to be coded less because we were looking to documentation of a care plan being carried out, not just the documentation of a care plan. So, there probably would have been a drop in pressure injury coding, a significant drop from when ACS 0002 came in, you will have noticed. So, if you looked at data from maybe 8 years ago, you would have seen pressure injuries going nuts, like people just coding them left, right and center. I've got to look at the years on my books." C301

The need for ongoing professional development was another professional activity identified by all coders who reported it was mandatory on a yearly basis. Regular face-to-face workshops were attended pre-COVID. As part of professional development, the coders reported completing online quizzes on a monthly basis. They also had specific online training on the ICD-10-AM classification every 2 years, to review new editions of the PI classification. In addition to mandatory training, coders attended workshops related to specific health conditions, including PI. Coders acknowledged that the COVID-19 outbreak impacted educational sessions. Some coders reported regular face-to-face group meetings were replaced with online meetings during the pandemic. In some healthcare services, online quizzes were developed for coders to be completed online; and answers were summarized and distributed to all coders via PowerPoint presentations, with correct answers and explanations. Some coders reported that their collaborative sessions with consulting physicians and skin integrity nurses ceased during COVID-19 outbreak because clinical work was prioritized during the pandemic period.

Six coders, who indicated their current position as coding educators/auditors, and some regular coders discussed their involvement in coders' and clinicians' education as their professional activity. One of the coders, C203, explained: "I don't have a title. It's just part of being a clinical coder. Almost everyone has additional jobs in reporting or education."

Knowledge

The participants discussed their procedural knowledge of the coding process, knowledge of the ICD-10-AM classification, and knowledge of PI classification. They also provided suggestions on how to improve their knowledge, including the topics of interest and preferred learning methods. When probed regarding their need to develop knowledge further, most coders suggested that coders from a non-clinical background and less experienced coders benefited from webinars on PI classification. Other suggestions were to improve coders' knowledge on how and where PI was documented in the electronic medical record and to have various clinical case scenarios with reflection on coding – 'it would be great to get a variety of different scenarios, or different people, different treating clinicians perhaps, and maybe different sites; so, that we can see how different sites do code and find the documentation, or any issues that they've come across or resolved' (C401).

Considering that most coders interviewed had extensive coding experience, they had excellent knowledge of PI classification. They discussed the following steps of the coding process, including (1) accessing the EMR/or paper-based record and reading the wound nurse's/other clinicians' notes to confirm the diagnosis of PI; (2) accessing the whole medical record or the admission notes; (3) extracting the location and the stage of the PI; (4) referring to the Australian Coding Standards to confirm that the PI documentation obtained meets criteria for coding; (5) determining whether a PI was present on admission or acquired in care; and (6) coding PI based on the acquired information using 3M Coder software. Most coders described their knowledge of the ICD-10-AM classification as "good" and "above average" because they are proficient and regularly follow the two-yearly classification updates.

Clinical coders from a nursing background with clinical care experience reported they have excellent knowledge of PI classification. Clinical coders from the private health service, who had worked with paper-based records, reported they took information from the wound care chart, which included photographs clearly depicting different stages of PI. Other coders reported they used the PI classification provided in the Australian Coding Standards, which they found to be clear and informative. A few coders rated their knowledge of PI stages as "not so good," particularly when differentiating unstageable and suspected deep tissue injury. Also, they said that they "don't have to know" the classification of PI to decide "what to code," and just need to code "the stage documented" in the notes because "coders are not allowed to diagnose" and use stage of PI as documented by clinicians.

Various suggestions regarding the modes of delivery were shared by participants. Some coders preferred face-to-face workshops because of the ability to ask questions, but also acknowledged that this mode of delivery would be impractical during COVID-19 and post-COVID-19 periods. Many coders agreed that online modules and webinars would be their preferred mode of delivery because the online module and the webinar recording could be accessed at any time. The participants also preferred clear, concise and straight to the point content, and coding training sessions no longer than 30–60 min.

> I like face-to-face workshops, but online webinars well we've seen a rise of that kind of thing in the last year due to pandemic. So that is a good way of being able to capture everyone at a time that's convenient for them to do it. Whereas face-to-face workshops are more difficult when you have part-time staff, etc. Yeah, so I guess webinars are a good way. C202

Coders reported the benefit of inter-professional collaborative workshops, where nurses and coders shared their perspectives. Collaborative workshops had the potential to improve coders' knowledge of PI classification and clinicians' understanding of what information should be included when documenting PI in the medical notes. Specific emphasis was placed on the care plan – 'there has to be some sort of a care plan for it [PI], for us to code it. There has to be a specific care plan, to see that it's been assessed. And a care plan's been put in place, and that care plan has been implemented… but a bit of cream on a red bottom doesn't cut it anymore' (C402).

Behavioral Regulation

To ensure the accuracy of coding of PI stage and the body area in which the PI occurred, some participants said that they would always "go into the tabular list which gives you more detail of the area" rather just simply "clicking on the code." Accessing complete set of details allowed them to ensure that the right PI stage and the right body area was selected. To ensure the accuracy the Diagnosis-Related Groups (DRG) assigned during coding, coders ensured that the principal diagnosis was correct, which determined the DRG. So, for example, if the patients "do have a pressure injury that's treated, that might impact the DRG" (C401).

Coders used multiple sources of information to ensure that the reported PI met the coding standard to improve coding accuracy. This included checking the wound chart, discharge summary, nurses' notes, podiatrist notes, and the medical in-patient notes. As one of the coders (C202) reported: "we cannot code pressure injuries off the wound charts because they don't provide sufficient space for a written assessment and a plan… and don't meet the coding standards to allow us to code from those charts." They also pointed out that if the wound chart information is not backed up in the nurses notes and discharge summaries, coders would need to initiate a documentation query.

If there was incomplete or inaccurate documentation, coders initiated a documentation query to a clinician. They would usually send coding queries with all available documentation either to the unit doctor/specialist or to a clinical nurse specialist. This process usually took the coder about 15 min, although it could take longer depending on the case complexity. Clarification then would take a couple of days depending on clinician availability. All of the participants affirmed that they only initiated documentation query when it impacted whether funding would be improved. They reported that querying the clinical doctor regarding documentation was mainly used for optimizing funding. Often coding a PI would not optimize funding and, therefore, they would not initiate a clinician query "because it's not worth the time and effort of the clinician, it's not going to bring any more money back to the hospital, but you're then making a gap with the quality side of things" (C403).

The participants discussed ensuring quality of the coding they did through simple "self-audits" that double-checked the codes before data were entered. As one of the coders (C203) discussed, she repeated the whole process of coding at least once to double check the codes that she used in the 3M Codefinder health information software, and she checked the DRG matched the case mix and codes in patient information. Another coder (C402) said that, from time-to-time, she realized that incorrect codes were allocated, and she would "pull up" the case and check if the codes were correct.

In addition to simple checks, coders also used the computerized systems to ensure quality of coding. They said that an extract file of their coding for the day would run through the Performance Indicator of Coding Quality (PICQ) error-picking software. If an error was picked up by the system, the coders would receive an error notification message. The record would need to be clarified, and the coder would then deal with.

Coders also said that they can run their own reports using Quick View software on a monthly basis. They would usually run a report on the number of hospital-acquired complications they had over that month. If they found an unreasonable number of hospital-acquired complications, they would pull records out and check accuracy of coding: "If it looks reasonable, do a quick desktop audit to make sure it makes sense. I guess that's the main way, monthly reports" (C202).

Intentions

Coders further explained that they coded only health issues that had a direct impact on patients' episode of care. Patients usually presented with a variety of health issues, not all of which would be the focus of treatment. Health issues that had no direct impact on the patient's episode of care were not coded. If the coders had incomplete information on PI upon admission and the PI did not progress during hospital stay, coders would not initiate the coding query process because the PI should not be coded.

> The reason why we're coding is for a summation of that person's journey. A person can have a variety of issues which weren't treated; so, we shouldn't be coding them, and it hasn't impacted that person's stay. I think that the discharge summary, if done correctly, have the most important diagnosis available. C103

The participants said that their intention to code PI and initiate a coding query was also dependent on the financial outcome—the ability to optimize patient's funding. They reported that, sometimes, "the diagnosis can make the difference of $10,000, if something's coded or not" (C202), depending on the level of complexity assigned for a particular admission. They said that they "want to reflect as accurately as possible everything that happened with that patient because it will change the amount of funding that the hospital receives" (C202). However, if it is not going to optimize patient's funding, they would not "spend time on sending query" (C203). As the coders further explained, this is only appropriate when funds require use of the Diagnosis Related Group (DRG).

Skills

Years in practice and importance of the supervised practice were discussed as main factors that influence the quality of coding. Some participants openly said that university training alone is insufficient to start independent coding, and it takes from 2–4 years for a graduate to develop the necessary coding skills. They discussed the importance of in-service training program for graduate coders and supervised practice for developing their skills and learning the coding process of the different hospital specialties, including PI.

> So, at uni [university] there was a unit based on medical terminology. But you learn on the job as you go. C101
>
> Okay, someone completely green from uni [university], I would say would potentially take about 18 months to train. I have to reiterate also that seems like a long time but we have a very complex case mix at the organization that I work with. C103
>
> You do a year training, where your records are being checked, your coding's being checked and you're learning the different specialties of the hospital. I'd probably say [it takes] maybe about 4 years to be really confident. C201

Some participants used the terminology of "live" and "shadow" coding. Shadow coding was described as coding cases that were already coded as part of the supervised practice program, while live coding was described as independent coding of live cases. They explained how each coder was required to complete and pass a particular specialty unit before being allowed to independently code that specialty. Ongoing skills development has already been discussed as part of "professional role" in the Social/professional Role and Identity Domain.

Beliefs About Capabilities

Most coders we interviewed perceived themselves as competent. Some were experienced coders who had worked as medical coders for decades at various health services. They were confident in allocating PI codes, sending queries, and supporting junior coders.

> I've got a lot of coding experience and as soon as I see the word it's like a beacon goes off in my brain and I make sure I find out as much information as I can about pressure injuries because they can be catastrophic to patients. It's important to capture the data. C205

> I've been coding for over 20 years. I am a coding advisor at where I work, so I actually am a point of call for other coders to ask questions of. I have coded consistently across that 20 years. I have worked at a number of different places. So, fairly familiar with all different types of documentation, always stay on top of the education, and always reading new queries that come out. C301

They linked their confidence to knowledge of the process of coding and ICD-10-AM classification. Some coders came from nursing backgrounds and were confident in their own evaluation of PI staging. Junior coders explained their own confidence in themselves as coming from the support available to them from coding advisers. Most coders acknowledged that if they had sufficient documentation, they were confident to allocate a PI code.

> I've worked in aged care for such a long time. I feel like I've got that bridge understanding between delivering care and understanding what we need to document to make sure that we can keep delivering that quality care because if you're not documenting what you've undertaken and done, there's no way you can assess and re-assess and then create practices moving forward to make sure optimal care and person-centered care are delivered. C403

Memory, Attention and Decision Making

Coders discussed that, with time, they memorized the codes and used them "off the top of their head," as C403 explained. In this case, they said it is important to double-check that back in the index to ensure the quality of coding: "But there is a standard on pressure injuries. So, if I needed to refresh my memory, I could certainly read the standard in the book, if I was a bit studious about something" (C402).

Some coders acknowledged that it could be difficult to reconstruct their procedural memory when new changes were implemented. This is particularly problematic for coders who were in service for a prolonged period of time, while recently graduated coders would frequently consult the Standard and the guidelines. In general, if they needed to refresh their memory of codes, the ICD-10-AM classification, and the PI stage, coders said that they would either use a search engine or book a workshop.

DISCUSSION

National Safety and Quality Health Service Standards use coded clinical data for monitoring patient safety through its hospital-based outcome indicators (25); HAPI has been identified as an important indicator of the quality of care (35).

One of the main findings was that hospital coders often lacked vital information in clinicians' records needed to code PIs and report quality indicators accurately. Coders identified frequent need for additional information on (1) whether a PI had been diagnosed; (2) the PI stage; (3) PI location; (4) if the PI had been detected on admission or acquired in the hospital; (5) how the PI assessment was conducted; and (6) the subsequent PI care plan. If this information was included in the discharge summary, it was also expected to be confirmed in the body of the nurses' notes. The described efforts to "improve the accuracy of clinical documentation" are consistent with other studies conducted in Australia (25) and specifically on PI (1, 2). Studies conducted in Canada (29, 30, 36), Portugal (37), UK (38), and USA (39) also highlighted the need for quality improvement processes for PI clinical documentation. Nursing documentation improvement is a vital component of the complex capacity building programs on PI prevention in acute care services and is relied on by coders (40, 41). Educational interventions on the quality improvement designed for nurses have the potential to improve the quality of PI documentation (42). Studies in other medical fields suggest that both paper-based (43) and electronic records (44, 45) need to be improved. However, PI reporting was found to be more accurate and complete in the electronic health records compared with paper-based records (46).

Our findings identified three methods of quality assurance were important to coders to ensure accuracy of PI reporting: (1) training prior to initiation of coding activity and (2) continued education, and (3) audit and feedback communication about how to handle specific complex cases and complex documentation. From a behavioral perspective, most of the coders reported confidence in their own abilities and were open to changes in coding standards. In general, coders expressed their greatest frustrations in identifying, from documentation, the appropriate information needed to apply coding standards. To assure the accuracy of clinical documentation, the proposed interprofessional collaborative educational sessions, which are in place in some health services were reported to be beneficial. Previous studies also reported that improved clinician-coder collaboration is beneficial (30) as it can improve the quality of coding (47).

Transitioning from paper-based to electronic records highlighted the need to improve training of both clinicians and coders. EMR implementation is a complex process, and clinicians have a critical role in successful EMR implementation (48). Documentation-related benefits of EMR implementation include timeliness, better quality and quantity of nursing documentation and improved quality of the documentation process (48). However, it may increase documentation time (49), particularly during transitional periods, when nurses have insufficient skills and knowledge of where to enter their notes on PI assessment. Moreover, services transitioning from paper-based to electronic records should ensure coders have full access and know where to access clinicians' notes on PI, and that they have appropriate training to access PI documentation on the EMR system.

Internal and external audits were identified as main enablers to ensure optimal coding, which is important for both the revenue generation and benchmarking of quality of care. This finding aligns with studies conducted internationally (50–52). NHS UK (51) developed a 10-points checklist to improve the quality of clinical-coded data, which includes (1) manageable levels of medical documentation and improved quality of medical documentation and easy to use EMR; (2) consistent and complete discharge summaries; (3) availability of the coding updating process; (4) regular engagement with clinicians; (5) regular analysis and routine audits; (6) attention to staffing issues, including the skill mix and the number of coders; (7) training and guidance; (8) the IT system used for coding are fit for purpose; (9) assessment units should be formalized to ensure all patient information is captured completely and accurately; and (10) broader uses, when clinical coded information underpins all aspects of health care management. In our study, coders identified the following personal approaches and institutional support systems to assure the quality of coding: (1) accessing the EMR/or paper-based record and reading the wound nurse's/other clinicians' notes to confirm the diagnosis of PI; (2) accessing the whole medical record or the admission notes; (3) extracting the location and the stage of the PI; (4) determining whether a PI was present on admission or acquired in care; and (5) coding PI based on the acquired information using 3M Coder software.

A few coders rated their knowledge of PI stages as "not so good," particularly when differentiating unstageable and suspected deep tissue injury (DTI) because these two stages are more challenging to assess. The lack of PI stage differentiation skills is a common pitfall in PI staging and reporting that is discussed in literature (2). This finding aligns with the previous research on PI data conducted in Australia (1). Australian Coding Standards update to focus on unstageable and DTI PI two stages helpful as the coders reported using the standards to guide their classification, and they found the standards to be both clear and informative.

Implications for Practice and Research

The Theoretical Domains Framework offers a comprehensive approach to studying the factors that influence routine use of professional practice. For hospital coders, whose work includes identifying and reporting PI data collected from hospital sources, the TDF provides a method for evaluating the barriers and enablers to ensuring quality PI reporting on a daily basis. Our results from interviewing coders in Melbourne hospitals identified both educational and feedback approaches that would lead to better quality reporting of PI. In particular, professional education in an interdisciplinary setting could help coders understand better how to apply clinicians' notes to inform the coding process. While, from a feedback perspective, improvement and tailoring of internal and external auditing processes would continue to improve PI quality. Coders were relatively confident in their own ability to apply PI standards, particularly if they had complete and accurate information in clinicians' notes, but expressed concerns about how to most effectively and efficiently communicate with the hospital staff on the importance of quality PI reporting. An in-depth exploration of clinicians' perspectives on documenting PI would offer a valuable insight into a collaborative practice that improves the documentation quality and consequently the quality of coded data. Coded data extracted from documentation in the patient's medical record is a vital source of PI data; and further research is needed to identify quality improvement strategies across countries and to facilitate an international consensus on PI data collection and reporting (53).

Study Limitations

While we attempted to recruit clinical coders with different experience levels, most of our participants were experienced coders, who had worked in the field for 6 years and over and were in senior positions. Less experienced coders might, therefore, have a different experience of the process of PI coding. Our interview guide was loosely based on the TDF, and some domains and constructs might not have emerged for this reason. That is, we actively asked the participants to prioritize the domains of interest and did not prompt participants for less important domains, for example Emotions. We did not pilot the interview guide, although we did seek coders' input during the interview guide development. The transcripts were not sent back to the coders to verify the content. Although the opportunity to read the transcripts were offered to all participants, only one requested their interview transcript. In regards to transferability, our findings would be of interest to all countries that have adopted the ICD-11 and may be of interest to developing countries that have adopted a simplified version (54) of disease classification.

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 Alfred Hospital Ethics Committee (Project No: 66/17) and the participating health services ethics committees. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CW, VT, and JB-H designed this research project and secured the grant. VT and CW designed the questionnaire. LT conducted the interviews. VT, LT, and CW developed coding framework. VT coded the transcripts, analyzed data and drafted the manuscript with support, and guidance from CW and JB-H. All authors critically reviewed the manuscript and approved the final 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/fpubh.2022.893482/full#supplementary-material

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Temporal and Spatiotemporal Arboviruses Forecasting by Machine Learning: A Systematic Review

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Arboviruses are a group of diseases that are transmitted by an arthropod vector. Since they are part of the Neglected Tropical Diseases that pose several public health challenges for countries around the world. The arboviruses' dynamics are governed by a combination of climatic, environmental, and human mobility factors. Arboviruses prediction models can be a support tool for decision-making by public health agents. In this study, we propose a systematic literature review to identify arboviruses prediction models, as well as models for their transmitter vector dynamics. To carry out this review, we searched reputable scientific bases such as IEE Xplore, PubMed, Science Direct, Springer Link, and Scopus. We search for studies published between the years 2015 and 2020, using a search string. A total of 429 articles were returned, however, after filtering by exclusion and inclusion criteria, 139 were included. Through this systematic review, it was possible to identify the challenges present in the construction of arboviruses prediction models, as well as the existing gap in the construction of spatiotemporal models.

Keywords: digital epidemiology, computational intelligence, arboviruses forecast, machine learning, systematic review, dengue, chikungunya, Zika virus

1. INTRODUCTION

Vector-borne diseases present a major public health challenge for many countries around the world (1–3). Arboviral diseases are diseases caused by arthropod-borne viruses which are viruses that need a vertebrate host and a hematophagus arthropod (the transmitting vector) in order to maintain themselves in nature (4–6). Arboviruses transmitted by *Aedes aegypti*, e.g., manage to maintain themselves in nature through a human-mosquito cycle. In other words, for the transmission of one of these diseases, it is only necessary for the hematophagous arthropod to inject its infectious saliva into the blood of a non-viremic individual at the time of the bite.

However, non-vertical transmission is also possible, such as during sexual intercourse, from mother to child during pregnancy or childbirth, in addition to transmission of blood, bone marrow, and organ transplantation (6).

Since arboviruses are part of the Neglected Tropical Diseases (NTDs) group, they impact directly and indirectly the countries wherein they are endemic (7). The direct impact is related to the number of people infected and the number of deaths caused by arboviruses. On the other hand, the indirect impact is more associated with socioeconomic impacts (7). Dengue, Zika, and chikungunya fever, transmitted by Aedes mosquitoes, are examples of diseases that belong to the group of NTDs. According to the World Health Organization, dengue fever is present in more than 100 countries around the world. Furthermore, in the last decade, there has been an increase of around 300% in the number of cases of the disease (2). Chikungunya, in turn, has been identified in more than 60 countries since 2004, when it first spread to countries in Europe and the Americas (8), whereas the Zika virus is currently present in a total of 86 territories around the world (9). Thus, the arboviral diseases rapid global spread amplified the challenges faced by the scientific and governmental communities (10).

The arboviruses dynamics are associated with several heterogeneous factors that involve demographic, climatic, and environmental aspects of a region. Demographic changes arising from intense migratory flows from rural to urban areas have led cities to grow inordinately. The swelling of urban populations along with urban population mobility associated with other factors, such as poor sanitation, also plays an important role in transmission vector proliferation. In addition, the lack of water distribution, as well as the difficult access to health systems, also bring barriers to controlling the vector (3, 11, 12). Another aspect associated with arbovirus dynamics is the local climatic and environmental conditions. Luminosity, rainfall, relative humidity, and temperature, act directly on the mosquitoes' development and interfere with the eggs' hatch, as well as their lifetime and dispersion (3, 11, 13).

With climate change and the increase in the number and frequency of international flights, two new arboviruses transmitted by the *A. aegypti* mosquito have emerged in Brazil: Chikungunya and the Zika virus. Raising, in this way, new challenges regarding the control and monitoring of the vector (14–19).

Hence, considering the impact caused by the vector-borne diseases, several research groups have directed their efforts to understand the dynamics of arboviruses through mathematical and computational models for the creation of prediction models (3, 20, 21). We believe that prediction models can be a good tool for health authorities to implement public policies for rapid monitoring and control of the arboviruses spread. Therefore, this document proposes a systematic review of the literature to identify models for predicting arboviruses cases transmitted by the *A. aegypti*—dengue fever, Zika virus disease, and chikungunya—as well as the mosquito dynamics. In particular, this review seeks to answer the following research questions. In particular, this systematic review seeks to analyze what are the biggest challenges when it comes to implementing arboviruses prediction models. In addition, we sought to identify the main techniques for predicting mosquito cases or foci and which are the main variables that interfere in the dynamics of disease transmission and the dynamics of the transmission vector.

2. METHOD

The strategy for conducting this systematic review is detailed in **Figure 1**. First, we performed an automatic search in scientific databases, such as IEE Xplore, PubMed, Science Direct, Springer Link, and Scopus. We searched for articles published between 2015 and 2020 wherein the metadata, titled or abstract contained the terms defined in the following search string: ["Arboviruses" **OR** "arthropod-borne virus" **OR** "dengue" **OR** "chikungunya" **OR** "mosquito-borne disease"] **AND** ["Machine Learning" **OR** "Deep Learning" **OR** "neural network" **OR** "artificial intelligence"] **AND** ["forecast" **OR** "prediction"].

In the following step, we identified the number of articles that were retrieved from each scientific database. We then checked if the articles met the exclusion criteria. In this review, we excluded works that were not in English, works that were not completed, and documents classified as posters, tutorials, editorials, or calls for articles. We also excluded works that did not include arbovirus or breeding site prediction and works that did not include computational techniques.

After filtering according to the exclusion criteria, we briefly read the article's abstract, introduction, and conclusion. This step was essential in order to select the articles according to the inclusion criteria. The works selected in that phase were those which met at least one of the following criteria:

1. Works with computational intelligence methods to predict arboviruses cases.
2. Works with computational intelligence methods to predict mosquito breeding sites.
3. Works with computational intelligence methods to predict the mosquitos' dynamics.
4. Works with statistical learning (Bayesian and other probabilistic methods).
5. Works involving forecasting with differential equations.

The remaining articles after filtering by the inclusion criteria were fully read and evaluated according to the quality criteria described in **Table 1**. We used a 0-1 scale to assess study quality, where Yes (Y) = 1; Partially (P) = 0.5, and No (N) = 0. Three reviewers performed articles assessment, independently, and the disagreements were resolved by discussion among the reviewers.

From the articles selected by the inclusion criteria, we extract the following information: the title of the article, the name of the authors, the institution, the application of the study, the methodology applied to the study, the prediction model, results, the advantages, and the disadvantages of the method.

3. RESULTS AND DISCUSSION

The search process returned 51 articles from IEEE Xplore, 95 articles from PubMed, 238 from Scopus, 20 from Science Direct,

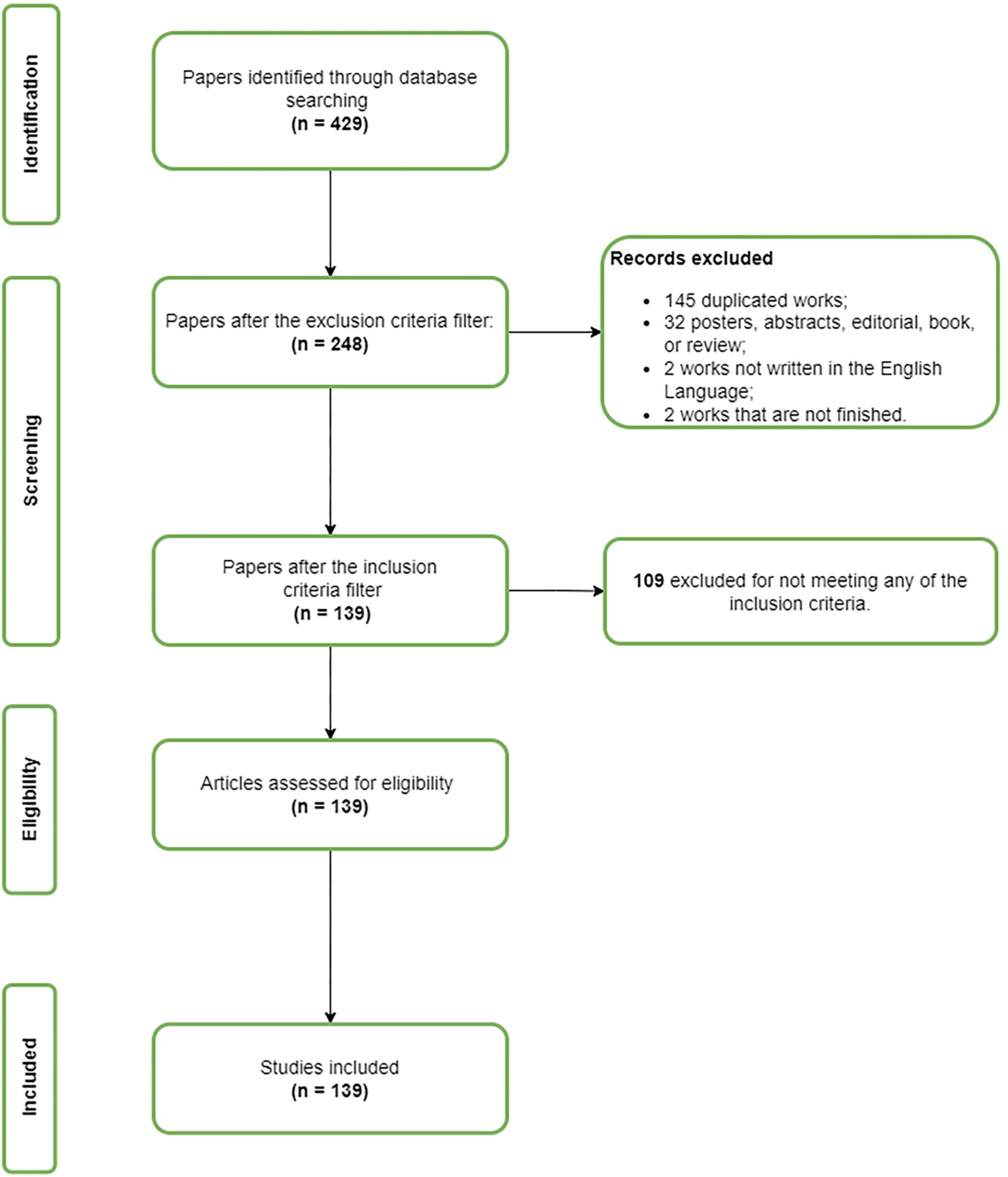

FIGURE 1 | This system consisted of the following steps: (1) First, we performed a search of scientific databases (IEEE Xplore, PubMed, Scopus, Science Direct, and Springer Link). (2) We then filtered the returned articles according to the exclusion criteria. (3) In the next step, we selected the article that remained from the previous stage according to the inclusion criteria. (4) After completing the previous step, we read, evaluated, and summarized the studies included in the review. (5) In the last step of this review, we grouped the studies considering their common characteristics.

TABLE 1 | Quality criteria used to evaluate the selected studies.

ID	Quality criteria	Answer
QC1	Are the objectives clearly stated?	Y/P/N
QC2	Are the data sources clearly described?	Y/P/N
QC3	Do the authors present the variables to build their models?	Y/P/N
QC4	Do the author explicitly defined which computational techniques or prediction model they used as well as their architectures and parameters?	Y/P/N
QC5	Do the authors report which metrics they used in order to evaluate their models?	Y/P/N
QC6	Are the conclusions coherent to the study findings and also with the set objectives?	Y/P/N
QC7	Do the authors detail the weakness of their work?	Y/P/N

TABLE 2 | Number of studies per group, considering the following stratification: Group 1: prediction of arboviruses by counting; Group 2: detection of arboviruses; Group 3: prediction of risk and epidemiological outbreaks of arboviruses; Group 4: modeling the dynamics of mosquitoes and breeding sites; Group 5: spatio-temporal modeling; Group 6: other approaches.

Group	Description	Number of studies
Group 1	Arboviruses (count) prediction	80
Group 2	Arboviruses detection	15
Group 3	Arboviruses Outbreaks and Risk prediction	18
Group 4	Models of mosquitoes dynamics, breeding sites models	10
Group 5	Clustering, spatiotemporal modeling	9
Group 6	Other approaches	7

and 25 from Springer Link. It is important to emphasize that, for the Science Direct database, the search string had to be reduced. For this database, the number of Boolean operators in the original string search was not supported. In this case, we used the terms: ("dengue" **OR** "zika" **OR** "chikungunya") **AND** ("Machine Learning" **OR** "artificial intelligence" **OR** "regression") **AND** ("forecast" **OR** "prediction"). From the 429 works collected, 181 were excluded in the filtering by the exclusion criteria stage. Among these 181 articles, 145 were duplicated studies, 32 were posters, abstracts, books, proceedings, or systematic literature review. In addition, two of them were excluded because they were not in English, and two articles were unfinished. We then screened the remaining 248 studies by reading the title, abstract, and conclusion. After the inclusion criteria stage, 109 were removed from this study for not meeting any of the inclusion criteria. Hence, 139 articles were included in this systematic review.

In the last step of the systematic review, we grouped the 139 selected articles according to their common characteristics (**Table 2**). The studies were divided into six groups: Arboviruses (counts) prediction (Group 1), Arboviruses detection (Group 2), Outbreaks and Risk prediction (Group 3), Models of mosquitoes dynamics, breeding sites models (Group 4), Clustering, modeling, and spatiotemporal prediction of arboviruses (Group 5), and Other Approaches (Group 6). In Group 1, we considered only the studies that presented models for counting arboviruses. In Group 2, we only included the studies that involved arboviruses detection. Group 3, in turn, is composed of studies that present models for predicting arbovirus outbreaks, as well as predicting the risk of an outbreak. The studies that presented vector monitoring and prediction models were included in Group 4. Those articles that investigated arboviruses prediction models with a spatiotemporal approach were included in Group 5. Finally, the studies that presented more than one of the approaches mentioned above—or that did not fit into any of the previous groups—were included in Group 6.

3.1. Arboviruses (Counts) Prediction

Among the 139 selected studies, about 80 studies are related to the prediction of the incidence of arboviruses cases (**Table 2**). Considering the year of publication, we observed that most of the studies in this group were published in 2018 and 2019. The number of articles published in 2018 and 2019 was 19 and 22, respectively, with a drop in the number of publications related to this topic in the year 2020 (**Figure 2**). Regarding the scores referring to quality criteria, we noticed that most scores were high, with the exception of QC7. For this criterion, the average score achieved by the studies was 0.33 (**Figure 3**).

The *A. aegypti* is the transmitter vector of three different type arboviral diseases. Taking into account the types of arboviruses transmitted by this mosquito, we found a significant amount of work focused on the construction of dengue fever transmission models. In these studies, the authors, in most cases, do not distinguish the serotype of the disease. In other words, dengue cases are generally considered as: dengue fever, dengue hemorrhagic fever and dengue shock syndrome, including local and imported cases. However, the studies of (22–27) are only focused on prediction models for dengue hemorrhagic fever. Regarding the other two diseases transmitted by the *Ae. aegypti*, we found a small number of articles addressing Zika virus disease and chikungunya's numeric prediction models (28–33).

The returned studies also brought a great variety related to the attributes used to build arboviruses prediction models. It is noted that, in several studies, prediction models are built taking into account only past values of disease cases (17, 25, 29–31, 34–38). However, arboviruses are diseases that need a transmitting vector for the arbovirus cycle in nature to complete. Furthermore, climatic factors directly affect the life cycle of the transmitting mosquito. In this context, several studies have investigated prediction models considering the effect of climatic and environmental variables on arbovirus transmission. Therefore, we observed a wide variety of studies that used at least one of the following variables as model attributes: temperature, rain, and relative humidity. However, some studies included other parameters in their models such as the number of rainy days (39–41), number of stormy days, and wind speed (41).

Furthermore, environmental variables obtained through remote sensing were also explored in a relevant number of studies. The most common were normalized difference vegetation index (NDVI) (42–44), vegetation index (45),

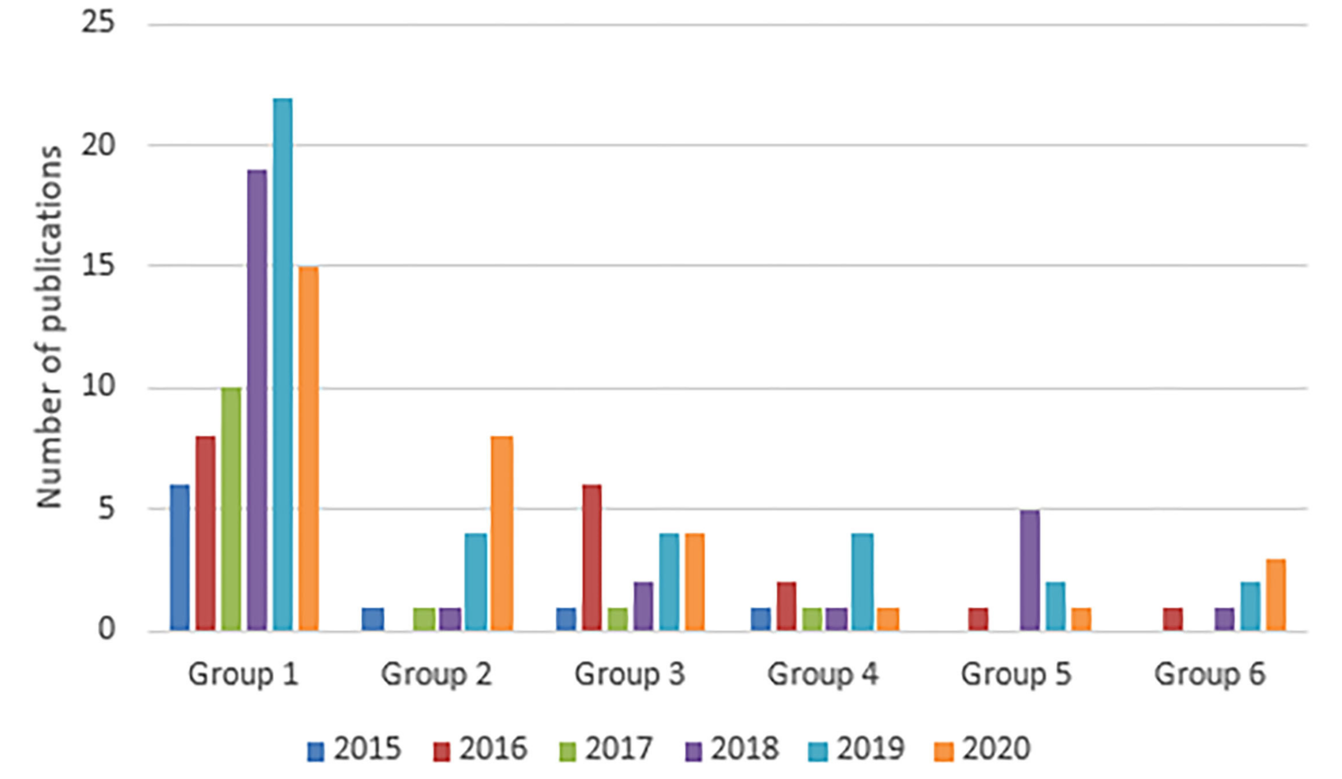

FIGURE 2 | Distribution of the number of articles according to the year of publication for each group.

enhanced vegetation index (46), smoothed vegetation index, smoothed brightness temperature index, vegetation condition index, vegetation health index (44), land surface temperature (43, 46, 47), Southern Oscillation Index (SOI), and Sea Surface Temperature Anomaly (SSTA) (48). In the studies of (47) and (44), the authors included information on the EL Ninõ phenomenon as well as (47)—that included variables related to the El Niño Southern Oscillation Index—and (44)—that included the Oceanic Niño Index variable in their model.

The research groups also explored attributes other than climate variables, such as epidemiological surveillance variables and sociodemographic variables. Among the epidemiological surveillance variables, the most used were: the number of larva-free, house index (39, 49), weekly breeding percentage (50), container (49), breteau index (49, 51, 52), standard space index, adult mosquito density, *Ae. aegypti* larvae infection, and female mosquito infection rate (52). Mosquito dynamics interfere with arbovirus dynamics. Including this information in predictive models can be an outlet for the search for more robust models that can understand the arboviruses' dynamics in a given region. Sociodemographic aspects also influence the arboviruses dynamics. Considering this fact, Dharmawardana et al. (45) also implemented in their model a mobility model in order to predict the dengue cases's incidence curve. Still considering sociodemographic information, other researchers included in their models' population density (32, 40), poverty percentage (32), population (41, 46, 53), Gini Index—a measure of income inequality—, education coverage (24), and unavailability of the garbage dump. In the model developed by (50), the population size attribute was considered for both the resident population and non-resident foreign population. Models considering sociodemographic factors can help us to understand how population dynamics are related to arboviruses cases. In this way, it can help to guide socio-educational actions and to direct the implementation of basic sanitation and infrastructure policies.

Continuing the analysis regarding the variables included in the prediction models, we observed that data from social media and search volume reported by search engines can be a powerful tool in monitoring arbovirus-borne diseases. In the study of (54), data from Baidu (a popular search tool in China) and social media are used to model the incidence of dengue in Guangzhou, China. Data referring to the number of comments, number of likes, and number of forwarding that are associated with dengue as a primary keyword are captured. In the studies of (30) and (27), the authors use Google Trends data to generate models for predicting Zika and dengue hemorrhagic fever, respectively. Espina and Estuar (36), in turn, use Twitter data to identify infodemiological content to be used in predicting dengue. In a world where information is gaining speed at every moment, the implementation of arbovirus models using social media can be an alternative for monitoring, surveillance, and disease prediction.

Taking into account the datasources used by the authors, we identified that in a vast majority of the returned studies,

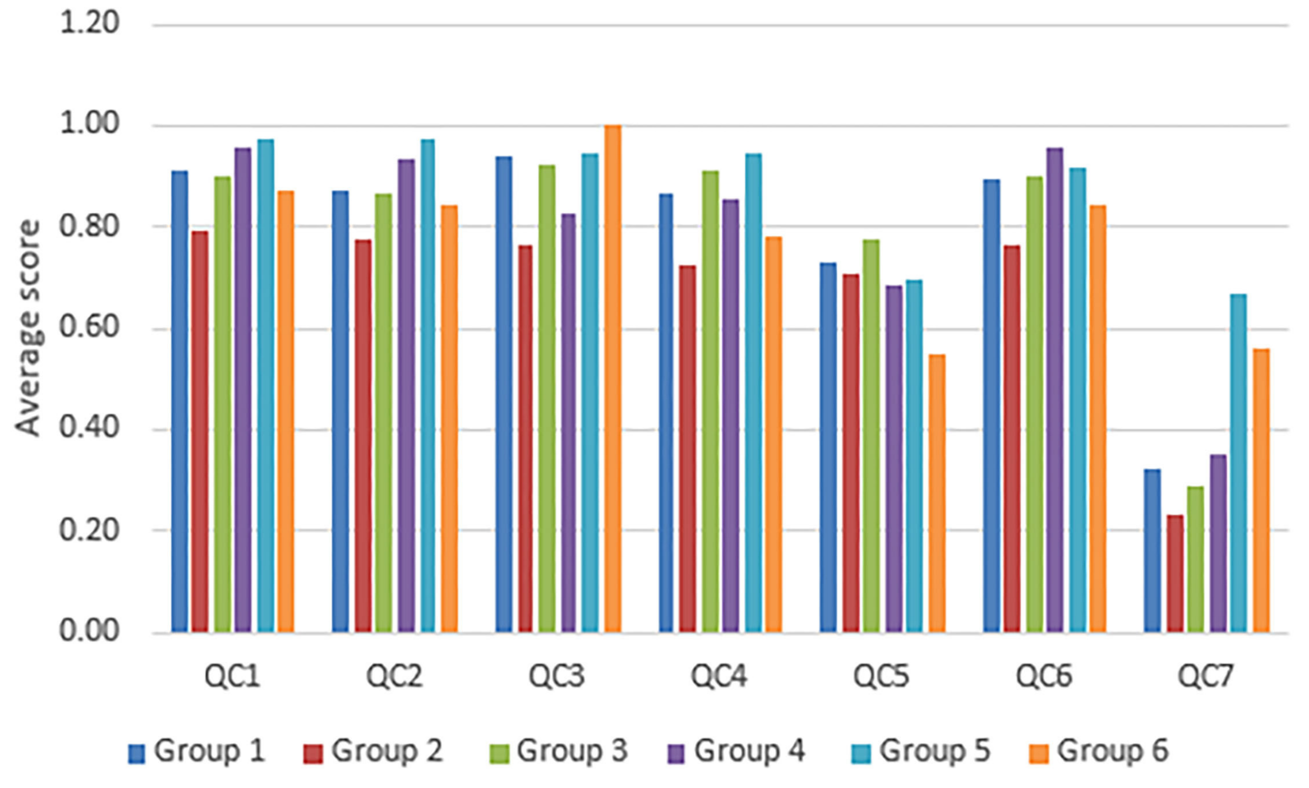

FIGURE 3 | Average score for each quality criteria for the studies from each group.

the data were obtained through government institutions. These institutions were responsible for either epidemiological surveillance or meteorological monitoring of the study area. One of the limitations presented in studies that use government data is the underreporting cases (55). Usually, when the individuals do not have the most severe form of the disease, they do not seek health services. Hence, under these conditions, those individuals are not included in the statistics. Moreover, health data usually have other limitations such as missing values, e.g., (55). However, some works use alternative sources to obtain data. Data can also be obtained through social media and search engines (27, 29, 30, 36, 54) and through data from the WHO (29, 31). On the other hand, we observed that in some studies, the authors do not explicit the origins of the collected data (37, 39, 43, 44, 56–60). The lack of information regarding the datasources can affect the study's reproducibility since the databases' original conditions to generate the models are not clear.

When we evaluated the studies regarding the types of models used in the predictions, we observed that the vast majority of authors investigated moving average models (27), such as the Autoregressive Integrated Moving Average (ARIMA) (17, 23, 29, 35, 41, 43, 46, 56, 61–63), Seasonal Autoregressive Integrated Moving Average (SARIMA) (55, 63–66), Autoregressive Integrated Moving Average with Explanatory Variable (ARIMAX) (67). Several works have also presented a wide variety of models using artificial neural networks, mainly the LSTM (59, 68–70). But models using backpropagation neural networks (BPNN), GANN networks (60), Elman Recurrent Neural Network Levenberg Marquardt Algorithm (ERMN/LMA) (22), and Deep feed-forward neural networks (28) were also investigated. Although neural networks have been extensively explored, in many studies, the authors did not explain the type of network they were investigating (23, 45, 46, 61, 66, 71, 72).

When working with prediction, we also prioritize the computational cost associated with the implemented technique. In this sense, optimization algorithms can help us to reduce the computational cost by reducing model training time. Optimization algorithms do this by looking for attributes that represent the dataset being studied. Therefore, some studies in this group investigated some optimization techniques. In the study of (57), the authors investigated several optimization algorithms associated with the Least Square Support Vector Machine (LSSVM). The investigated algorithms were: Moth Flame Optimization (MFO), Gray Wolf Optimizer (GWO), Firefly Algorithm (FA), and Artificial Bee Colony (ABC) algorithm. Saptarini et al. (22), in turn, used Genetic Algorithm, as well as (68). Finally, we notice that, when it comes to predicting the count or incidence of arboviruses, there are a wide variety of model applications.

In the articles evaluated by this group, we observed that among the main diseases transmitted by *A. aegypti*, the models for predicting dengue cases are the most explored by research groups. As the diseases transmitted by this vector present similar symptoms in their milder forms, in regions where dengue, zika, and chikungunya viruses circulate, the models may present errors related to the low distinction between the diseases. The models that included climatic variables and/or variables of sociodemographic aspects performed better than those that only took into account the historical series of confirmed cases of the disease.

As for the origin of the data sources, we observed that the data obtained by governmental institutions provide greater reliability to the models. However, these models have limitations, mainly in relation to the underreporting of cases. Underreporting can impair the performance of case prediction models. The data that are obtained through the analysis of user behavior in social networks can act as an important tool in the prediction of arboviruses. Since, in some regions, the public system may take a long time to update notifications, alternative data sources can be a good solution in the development of robust models, especially in critical situations such as during arbovirus outbreaks. On the other hand, models generated using data solely from social networks may not be applied in regions where access to the Internet and mobile devices are scarce. That is, in some peripheral regions, the model may not be able to identify disease cases in that region.

Regarding the prediction models selected, we observed that most of the studies that used Artificial Intelligence opted for deep learning models. Despite the promising results that were obtained, the use of deep networks, such as LSTM, is linked to large memory consumption. In other words, it takes a lot of training time and resources to create applications for the real world. Moving average models, in turn, are good tools for capturing trends, periodic changes, and random distortions in historical series. In addition, they are simple and quick to apply.

Thus, the models of the historical series are very relevant and can be a very useful tool in the planning of public policies to combat arboviruses. However, these models are not able to provide information regarding the spatial distribution of diseases. That is, they are not able to point out which areas are being more or less affected by diseases transmitted by *A. aegypti*.

3.2. Arboviruses Detection

For this group, 15 studies were selected from the 139 included in this review (**Table 2**). The publication years for this group varied between 2015 and 2020, wherein the majority of the studies were published in 2019 and 2020 (4 and 8 articles, respectively). For the years 2015, 2017, and 2018, there was only one publication on this topic (**Figure 2**). Considering the quality criteria evaluated, the vast majority reached a low score in QC7 as presented in **Figure 3**.

Among these 15 articles in this group, we noticed that they focus on two of the three arboviral diseases transmitted by the *A. aegypti*. That is, 12 articles focused on dengue fever prediction models, whereas three of them focused on Zika virus disease. It is also important to highlight that, in all articles, the authors used machine learning algorithms in order to build their prediction model.

For Zika virus disease prediction, we noticed that the authors investigated different algorithms to predict positive cases of the disease. Jarrin et al. (73) evaluated support vector machines (SVM) and logistic regression to build their models, whereas Jarrin et al. (74) and Mahalakshmi and Suseendran (75) investigated Random Forest and Multilayer Percetron (MLP) algorithms, respectively.

Jarrin et al. (73) investigated SVM and RL algorithms—implemented in Python 3.7—to classify individual samples into “infected” or “uninfected” with the Zika virus. According to the author’s results, the classifier showed a better accuracy for the “infected” class. The method presented by (73) can be used for the early diagnosis of ZIKV infection. Jarrin et al. (74), on the other hand, used mass spectrometry approaches to detect ZIKV by RT-PCR using RNA samples extracted from serum and urine to classify the diagnosis. The problem presented by (74) was modeled using Random Forest using MATLAB R2017a. The model presented by the authors is a robust platform that can be implemented in routine laboratories in order to help to support the diagnosis. Mahalakshmi and Suseendran (75) used the Multilayer Perceptron (MLP) artificial neural networks classifier. The data used is synthetic and was collected from the Internet. For prediction, the Weka software (version 3.8) was used. As the study was carried out with synthetic data, it is essential that tests be carried out with data from real databases. Having been trained only with artificial instances, when coming into contact with a real-world dataset, the accuracy of the generated model can drop significantly.

To predict dengue, the selected studies used different predictors. Mello-Román et al. (76) have developed a system in which data collection is based on the symptoms of the disease. The dataset is composed of cases registered by the Paraguayan health system, e.g., patients admitted due to fever and complete dengue diagnosis. Mello-Román et al. (76) carried out their tests using the IBM SPSS Modeler software in order to train their MLP and SVM algorithms. According to the author’s results, the MLP showed better accuracy over the SVM classifiers.

(77) provide a prediction of the types of dengue cases. In order to investigate the best classifier, the authors evaluated the Decision Tree (DT) and Random Forest (RF) algorithms. Ho et al. (78) group explored a different method to speed up dengue diagnoses in the laboratory. The authors analyzed the decision tree (DT), deep neural network (DNN), and logistic algorithms. In this way, through the clinical parameters identified in the study, it is possible to help with the burden of laboratories for the diagnosis of dengue. Alam et al. (79) in their approach bring a prototype of a new framework for analyzing biomedical data called biocloud. The data gathered on this framework is modeled with a support vector machined to classify the disease’s cases. This type of technology can provide services at a low cost and can be used in remote areas.

Ganthimathi et al. (80) developed an early dengue diagnosis system using Artificial Intelligence. In their research, Ganthimathi et al. (80) investigated two separate machine learning algorithms: support vector machine as well as k-nearest neighborhood. According to Ganthimathi et al. (80)’s findings, both algorithms presented good performances, however, the SVM showed superior performance compared to KNN’s performance. Kapoor et al. (81) also treated the dengue prediction problem as a classification problem. Thus, in the study, Kapoor et al. (81) investigated four different classifiers, namely Random Tree, Random Forest, Support Vector Machine (SVM), and artificial neural networks. An interesting aspect of (81)'s model is that they used as their model's not only demographic information but also symptomatological data and clinical trial reports. Ariffin and Aris (82), in turn, created a system to help individuals in the self-diagnosis of dengue cases. As a classifier, the authors used artificial neural networks. As shown by the results obtained by (82), the model developed achieved high reliability for detecting the disease. Despite being a disease that helps in self-diagnosis, it is important to emphasize that medical guidelines are not dispensed with using the tool. Dharap and Raimbault (83) brought a different approach from the others studies commented so far. In their approach, Dharap and Raimbault (83) assessed the effectiveness of medical hematology analyzers that flags arboviruses' presence in blood samples. The machine learning algorithms used in their study were regression and Random Forest. With their results, they demonstrated that it is possible to screen arboviruses infection using a low cost, but also an effective predictor.

Srivastava et al. (84) bring a classification of dengue using online learning. Thus, learning takes place with just a few training examples. No retraining of the model or redeployment of the prediction engine is required. The following algorithms were used: Adaptive Regularization of Weights (AROW) and its Variants, Gradient Descent Online (OGD), Confidence Weighted Learning (CW) and Soft Variants (SCW 1 and Scw 2), Normalized HERD (NHERD), Passive Aggressive (PA) and its variants PA1 and PA2, Improved Ellipsoid Method (IELLIP), Approximate Large Margin Algorithm (ALMA), Second Order Perceptron and Perceptron (SOP), Relaxed Online Maximum Margin Algorithm (ROMMA), and Aggressive Romma (AROMMA). The evaluation of the classifiers was done offline in the Weka software with SVM and RF, and later, the classifiers were evaluated online. Additionally, this system is a health system helping to signal patients with a high probability of being diagnosed with dengue. Sasongko et al. (85) focused on finding the best backpropagation algorithms for early detection of dengue with the addition of multilayer perceptron (MLP) optimization through five algorithms. The backpropagation algorithms used were Gradient Descent (GD), BFGS Quasi-Newton (BQN), Conjugate Gradient Descent—Powel (CGD), Resilient Backpropagation (RB), and Levenberg Marquardt (LM). Additionally, the Levenberg Marquardt algorithm proved to be the best for detecting dengue. In other words, this algorithm solves the data outlier problem well.

Iqbal and Islam (86)'s group performed a performance evaluation of different dengue outbreak prediction classifiers. The methods were evaluated by eight different performance parameters. Iqbal and Islam (86) evaluated K-nearest neighbor (kNN), Support vector machine (SVM), Artificial neural network (ANN), Naive Bayes classifier, Decision tree, and Logistic regression classifier (LogitBoost) algorithms. The experiments were carried out with the Weka learning software. Among the trained algorithms, according to the authors, the one with the best performance was LogitBoost. This classifier had the best classification accuracy, sensitivity, and specificity metrics.

Balamurugan et al. (87) created a classifier for detecting dengue cases based on combinatorial characteristics based on weighted entropy scores based on ideal classification. The algorithms used to extract the most important attributes were Correlation based Feature Selection (CFS), Genetic Algorithms (AG) and Particle Swarm Optimization (PSO), in addition to the Optimized Classification Algorithm based on Weighted Entropy Score (EWSORA). Finally, the data were submitted to conventional classifiers such as Naïve Bayes, J48, Multilayer Perceptron (MLP), and Support Vector Machine (SVM). For evaluation, the Weka software was used. As metrics to evaluate the best models for predicting dengue, accuracy, true positive rate, precision, Recall, F Measure, and ROC were used. After applying the Genetic Algorithm (GA), Particle Swarm Algorithm (PSO), and Correlation-Based Resource Selector (CFS) algorithms for resource selection, the J48 and MLP classifiers proved to be better. EWSORA has greatly improved the accuracy performance for several classifiers, mainly for Genetic Algorithm (GA), Particle Swarm Algorithm (PSO), and Correlation Based Resource Selector (CFS).

3.3. Arboviruses Outbreaks and Risk Prediction

Among the studies evaluated in this systematic review, we observed that 18 articles were related to the prediction of the occurrence of arboviruses outbreaks, or the prediction of the risk of the occurrence of disease outbreaks (**Table 2**). Taking into account the years of publication of the articles, it is observed that most were published in 2016, as shown in **Figure 2**. Regarding the quality criteria, the studies achieved scores above 0.7, as shown in the graph in **Figure 3**. On the other hand, it is important to highlight that among the evaluated studies, the average QC7 score was quite low. In other words, most of the studies did not explicitly state the limitations of the investigated models.

Considering the types of arboviruses, we observe that the vast majority of the studies evaluated focused on the prediction of outbreaks or risk of dengue fever (18, 88–99). Two of the studies involving dengue risk prediction or dengue outbreak were focused on only one dengue serotype (dengue hemorrhagic fever) (89, 90). However, Brett and Rohani (95) show in their study an approach using each serotype for their prediction. In the study of (100) and (101), the authors investigated models for predicting the risk of Zika virus outbreaks, while (102) took into account all cases of arboviruses (dengue, Zika virus, and chikungunya) in their model.

As for the variables used to generate the prediction models, we observed that several studies included the climatic variables (90) where the most common are temperature (18, 91–94, 96, 98, 100, 102), rainfall (18, 91–94, 96–98, 100). Other climatic variables appear less frequently, such as wind speed (90, 91), vapor pressure (100), sunshine (91), atmospheric, and SST predictors (97). Regarding the predictors used for model generation, we observe a greater variety of predictors that are not associated with climate variables, when compared to the predictors used in Section 3.1. The population density, number of travelers, temperature, health expenditure per capita, gross domestic product per capita, water coverage, ZIKV transmission in nearby countries were examples of predictors used in the study of (100). In contrast, Akhtar et al. (101) used gross domestic product per capita, physicians per 1,000 people, and beds per 1,000 people, population densities, in addition to Zika cases. Predictors based on transmitter vector monitoring data have been extensively explored, such as mosquito occurrence (100), breteau index, and ovitrap index (98). It is important to highlight that two of the studies evaluated did not clarify which variables were used in the investigated prediction models.

Regarding the data sources, in a considerate amount of works, the authors usually obtained their databases through local government data sources (90–94, 96, 98, 99, 102). However, some works obtained their databases through other international sources, such as the US National Oceanic and Atmospheric Administration (95), Pan Amerian World Health Organization (PAHO), International Air Transport Associate, World Bank, US Bureau of Economic Analysis (101), and World Health Organization (WHO) (103). Two of the works included in this group did not present information related to the origins of the data sources obtained. In addition, no works were found that used alternative sources such as data originated by means of search engines, as well as data generated through social networks.

Finally, for risk predictions or prediction of arbovirus outbreaks, we found several approaches. Models were investigated using artificial neural networks (89, 101, 102, 104), decision trees (89, 99), gradient boosting regression tree (GBRT) (100), naïve Bayes (89), extreme learning machines (90), Least Absolute Shrinkage and Selection Operators (LASSO) and Ridge (92), support vector machines (SVM) (18, 91, 93). Moreover, early warning signals (EWs) derived from the theory of critical slowing down (95), the Shewhart model (98), population loss value at risk model (103) were also investigated.

In the articles evaluated for this group, we also observed that dengue was the arbovirus that received the most attention in terms of creating models for predicting outbreaks or disease risk. In the models of the studies, the climatic variables of temperature and precipitation are the predictors that appear most frequently in the prediction models. However, regarding predictors that are not related to climate variables, there is no assessment of which factors most impact the performance of the prediction model. That is, none of the studies presented the performance of models with different predictor configurations in a comparative way.

As for the types of models used, we observed that most studies used non-deep machine learning algorithms to generate the prediction models. Despite the promising results, it is difficult to indicate which algorithms had the best performances. The authors used different predictor configurations for the different models, which made it difficult to carry out a more in-depth analysis of the types of models used.

3.4. Models of Mosquitoes Dynamics, Breeding Sites Models

Of the 139 selected articles, 10 were predicted with vector control (**Table 2**). The years of publication range from 2015 to 2020. For the years 2015, 2016, 2017, 2018, 2019, and 2020, 1, 2, 1, 1, 4, and 1 were selected, in this order (**Figure 2**). Analyzing **Figure 3**, we found that the articles scored relatively low on quality criteria 5 and 7. Among these, 7 developed models based on machine learning and 5 based on statistical methods.

Haddawy et al. (105) featured a pipeline design to detect mosquitos' breeding sites using geotagged images with a machine learning approach. In Haddawy et al. (105)'s model, they use container count with resultant in order to create container density maps. The relationship between the densities of the eight types of recipients and the larval survey data was calculated using multivariate linear regression and obtained good precision. For object recognition, Haddawy et al. (105)'s group evaluated a convolutional neural network (R-CNN). Thus, creating geo-tagged container density maps is favorable for providing large-scale detailed hazard maps.

Raja et al. (106) developed early *Aedes* outbreaks prediction models using a machine learning approach. In order to build the prediction models, they used temperature, precipitation, start date notification, and notification date, as well as vector indices such as *Aedes albopictus*, *A. aegypti*, and larvae count.

Raja et al. (106) ran experiments using Bayesian Network Models method in order to create the prediction models. The system interface was implemented in C++ (backend) and the frontend implemented in JapaScript, CSS, and HTML5. The system is able to make predictions considering a 7 days horizon.

Asmai et al. (107)'s proposal was to create a Mobile Application for the Intelligent Detection of Mosquito Larvae (iMOLAP). The mobile app uses the convolutional neural networks (CNN) method, which is the Inception V3 model. The image that is captured is compared to a collection of predefined images to measure accuracy. Therefore, iMOLAP can classify Aedes and larvae species by imaging, and detecting the affected area of the site. This application can be a very important tool to assist in the surveillance and combat of mosquitoes. Lee et al. (108)'s, on the other hand, focused on developing a model to predict mosquito abundance. Thus, they considered climatic variables such as temperature, air humidity, wind speed, and precipitation as model predictors. The authors evaluated different approaches in order to build their model. They investigated using multiple linear regression (MLR), and artificial neural networks (ANN) algorithms. The correlation between climatic variables was assessed using the cross-correlation function. The metrics used were the correlation coefficients, the RMSE, and the agreement index. The results of models made with ANN were better than the MLR in all metrics. The approach brought by this study is interesting and can be very useful in mosquito monitoring. However, the authors did not describe well the apparatus necessary for collecting data on the number of mosquitoes. They did not describe the ANN configurations evaluated. In addition to not being described the number of tests to obtain a result with statistical significance.

In the study of (109), the authors developed a mosquito washing prediction system for *Aedes* in Recife, Brazil. The authors evaluated several types of regressors to build models to predict the number of properties with the presence of mosquitoes in Recife. Among the regressors, Extreme Learning Machines are Single Layer Feedforward Networks (SLFNs), Fuzzy Extreme

Learning Machine, Bayesian Extreme Learning Machine, Interval Type-2 Radial Basis Function, Neural Network (IT2-RBFNN), and Online Extreme Learning Machine (OLEM). First, the spatial distribution of the number of properties that contained water containers contaminated with *Aedes* mosquito larvae was performed. Then, the spatial distribution of properties with mosquito larvae was performed and stratified by the type of water reservoir. Finally, the models are implemented on the real-time surveillance data. As metrics, percentage RMSE and training time were used. In this way, the prediction system shows the mosquito's hotspots. This study takes a spatiotemporal approach, so research can help managers by giving direction to location-based mosquito population control policies, helping to limit transmission to humans.

Bennett et al. (110) brought a mosquito classification to detect *A. aegypti*. The database was created by the authors themselves. They collected samples of larvae present in garages that traded used tires in Panama. Additionally, with mass spectrometry, the types of larvae are identified. Finally, using the Supervised Neural Network (SNN) a classifier is built to identify the type of mosquito present. The model created had a very high capacity for recognizing and classifying training data. This study brings a look at the garages, which can be a strategic point for epidemiological surveillance policies.

Considering the statistical models, we highlight the study of (111). Their group has developed time prediction models for *A. aegypti* oviposition. Both model validation and application were applied in the dengue outbreak in 2016. For this purpose, time series of MODIS (moderate resolution image spectroradiometer sensor) products of normalized difference vegetation index and daytime surface temperature were created. The MODIS model consists of: (1) linear regression modeling and (2) the creation of two models, one with and one without lag times on the independent environmental variables. The environmental variables were standardized and the developed models were compared using the Akaike Information Criteria (AIC) to determine the ideal model in terms of goodness of fit and number of parameters. The model without latency was the best. Both models developed in this article showed that MODIS environmental variables (NDVI and LST) are good predictors because both environmental variables are present in both models, providing acceptable fit and validation results. We can understand that the NDVI increment may be due to precipitation in the near past followed by an increment in the vector activity which is verified by the increments of the oviposition activity. Furthermore, a model based on MODIS has the possibility to envision an operational forecast program at national level.

Estallo et al. (112) created a prediction model evaluating the weather variability associated with the seasonal fluctuation of the oviposition dynamics of *A. aegypti* in a City of Orán, Argentina. To create the model, precipitation data, photoperiod, water vapor pressure, temperature and relative humidity (maximum and minimum) and ovitrap sampling were used. A multiple linear regression analysis was performed with the set of meteorological variables considering the time lag that correlates with oviposition. And the model is validated. The prediction model created allows the prediction of the growth or decrease of the ovitraps activities of *A. aegypti* based on meteorological data. The prediction of these activities can be predicted three or 4 weeks in advance. Because this model brings a more localized and comprehensive assessment with site-specific data that can be used in disease prevention policies.

Hettiarachchige et al. (113) built a data transmission risk prediction model based on high resolution meteorological data. Additionally, this risk is predicted through vector prediction. Routine entomological surveillance data for dengue and meteorological data from a prediction system with high spatial and temporal resolution were used. The risk prediction system was divided into two stages to assess dengue transmission *via A. aegypti*. In the first, logistic regression was used to determine the presence or absence of larvae in the sites of interest using climatic attributes as explanatory variables, and then used a bootstrap approach in an administrative division. In the second, with the negative binomial model inflated to zero, an estimate of the larvae count of the positive division predicted in the first stage is made, and then positive larvae sites are identified and the number of larvae is predicted. Splitting the model into two stages increases the accuracy of identifying positive larval locations. A benefit for risk prediction in non-homogeneous regions.

da Cruz Ferreira et al. (19) developed a temporal prediction of mosquito infestation based on climatic data and monitoring data from *Aedes*. The climatic variables used were daily rain, temperature (minimum, average, and maximum), and relative humidity, and dengue data were obtained from the Health Department of Porto Alegre. The Generalized Additive Model (GAM) and Logistic Regression methods were used. The first method was used for two models, one was fitted with climatic variables, and the other with climatic variables and mosquito abundance as an explanatory variable. Additionally, the second method was used to assess the effect of adult mosquito infestation on the probability of dengue incidence. The second GAM model predicted the data better than the first. The researchers stated that if the population of *Aedes* is continuously monitored the predictions of the infestation rate will be more reliable. And monitoring this population is important for dengue control in Brazilian cities.

The studies presented here brought several different perspectives to control the *A. albopictus* and *A. aegypti* mosquitoes. Some of the variables considered in these studies were: stratification by type of water reservoir; neglected environments, such as garages that contain tires and other potential breeding sites; local and comprehensive assessment of breeding sites; evaluation of mosquito larvae stages; and the seasonality of the mosquito cycle dynamics. Furthermore, in the construction of the prediction models, different machine learning techniques and statistical methods were used. The models with a broad and more restricted evaluation of the study regions proved to be good and robust in terms of evaluation metrics. Many of these works present scalability and reproducibility for prediction at the national level, relating the magnitude of the population of Aedes mosquitoes, the incidence of arboviruses, and the monitoring of this vector. Thus, these approaches can be used to support the implementation of epidemiological surveillance policies. However, some of these studies had limitations, the lack of clarity and uniformity regarding the evaluation metrics and the number of tests, in order to obtain results with statistical significance. Some of these studies also omitted the complete description of the configurations of the adopted classifiers.

3.5. Clustering, Spatiotemporal Modeling

Prediction models involving clustering and spatiotemporal prediction presented relatively few studies when compared to the other approaches presented in this systematic review (**Table 2**). For studies with only these types of approaches, the year with the highest production was 2015, when 5 articles were published on the theme (**Figure 2**). An important point to highlight is the fact that, in the studies included in this group, the authors achieved the highest scores regarding the quality criterion involving the discussion about the limitations presented by the models (**Figure 3**).

Mathur et al. (114) brought a spatiotemporal prediction of dengue. This study also discussed and implemented dengue modeling with clustered incidence map visualization in Selangor, Malaysia. The spatiotemporal mapping was performed using the clustering technique with the k-mean algorithm. Thus were generated the incidence clusters. Then, the Gaussian mixture model was applied, finding the incidence density of dengue. Next, the K-means (K-NN algorithm) was used to find the centroid of the incidence. The Expectation-Maximization (EM) Algorithm was used to relate the clusters. The Bayesian Information Criteria (BIC) is then used to optimize the EM. Finally, with the Geographic Information System (GIS) technique, it is possible to accurately visualize the mapping of dengue incidence vulnerability in Selangor. The latter was used in the prediction. To create the proposed model, the R studio software was used, and to measure the vulnerability index, the K-means grouping was used. This study brings a spatiotemporal approach that can be used to implement health promotion policies. Another study that brought the spatiotemporal approach was the work of (115). In his study, Andersson et al. (115) made use of street images (Google Street) to implement a model to predict dengue hemorrhagic rates in the city of Rio de Janeiro, Brazil. In order to create this model, a siamese convolutional neural network technique was used. First, to create the models, dengue data in Rio de Janeiro were obtained and normalized. Next, street images were labeled according to latitude and longitude. The capacity of convolutional neural networks was analyzed with two approaches Simple-4CSCNN and ResNet-4CSCNN. The proposed models were implemented in the PyTorch framework. Simple-4CSCNN proved faster, with better loss of rating, but exhibited worse results in the validation test set. ResNet-4CSCNN generalized the training data well and reasonable results in the test set. The advantage of this approach is the use of street images to predict dengue cases, and the lack of work on the same line makes comparisons difficult.

The study of (116) was aimed at mapping the probability of an epidemic outbreak of Zika in the world. For this, three models were implemented, reverse propagation neural network (BPNN) (with sigmoid activation function), gradient increase machine (GBM), and random forest (RF). High-dimensional multidisciplinary covariate layers were combined with comprehensive localization data on Zika virus infection in humans. In addition to the demographic distribution data of the *Aedes* mosquitoes, global climate data, socioeconomic data, night light data, and human movement data were used. To create the models, the R language (version 3.3.3) was used. Models were trained with cross-validation 10 times. To assess the performance of the prediction models, the ROC curve was used. The models created were robust and capable of simulating the global probability of transmission risk of ZIKV and also quantified the uncertainty of the accuracy of the prediction models. The models created provided reference information for model selection in the area of epidemiological cartography. However, the study only uses the AUC as a metric for evaluating the models.

In the study of (117), the authors developed a model for clustering and mapping dengue risk susceptibility. In his model, Ghosh et al. (117) used as variables epidemiological data, temperature (maximum and minimum), precipitation, relative humidity and Earth Surface Temperature (LST) images, demographic, socioeconomic, vegetation, and water index data. Two statistical methods were used to create the models: Poisson Models (to form the clusters) and Multiple Logistic Regression. This first was used to estimate the incidence of dengue. Moran location and weighting function I based on the specific spatial distance of the outlier were also used. This second function was used to estimate the probability of dengue occurrence using climatic variables as attributes. The researchers observed a strong association between monthly dengue cases and monthly mean rainfall and an association between monthly mean air humidity and disease cases. The model takes into account a spatiotemporal approach for predicting dengue risk. In addition, it considers the social and demographic aspects of predicting dengue.

In (118)'s approach, the authors created spatiotemporal prediction models for dengue cases taking into account population density. As variables, dengue cases in the city of Khyber Pakhtunkhwa, transmission vector records (*A. aegypti* and *A. albopictus)*, population density and distance to roads and rivers were considered. As methods, logistic regression, variogram function, and binomial kriging with a binary logistic drift were used. Logistic regression was used to assess the correlation between dengue cases and other variables (covariants). Then the variogram function (spherical, Gaussian, circular, and Matém) is calculated for the city under study and its subregions. Additionally, at the end, the estimation of the weights of the kriging equations is done using the weights of the variogram model. The researchers claim that the "presence" of the mosquito and population density affect the dynamics of the disease. And the models performed well in cities with high population density. However, the study did not make clear the databases used as well as the periods chosen for modeling, testing, and validation.

Phanitchat et al. (119) developed an identification of sub-district level dengue clusters in Thailand. For this purpose, data on weekly dengue cases (by gender), population density per Km^2 temperature, and rain in the same period for Khon Kaem province were used. The models used were Bayesian Poisson Regression and Local Indicators of Spatial Association

(LISA). The first was to assess the relationship between the number of monthly dengue cases in the 199 sub-districts. The metric for evaluating the fit of the model was the Wantabe-Akaike Information Criterion (WAIC). Finally, LISA was used to identify hot and cold spots and outliers in the incidence of dengue. The article concludes that dengue outbreaks are more frequent in the rainy season. With the analysis by hotposts, it is observed that there is a cluster of cases around the urban areas of Khon Kaem and in rural areas in the southwest of the region. The spatiotemporal approach is useful for application in health promotion strategies. However, there is an inherent limitation regarding the collection of public data, such as underreporting of cases, errors in reporting symptomatic cases, and absence of asymptomatic cases. In addition, the use of data is a little out of date.

Chen et al. (120) developed a new framework for producing spatiotemporal prediction at the neighborhood level. Various data were used, such as dengue incidence data (with home address data and start date), movement patterns, construction age of buildings in a neighborhood, meteorological data (maximum and minimum temperature and average relative humidity), number of national weekly cases, index by Normalized Difference (NDVI) among others. The separate prediction models and submodels created were based on LASSO for each prediction window. Climatic variables and their effects have a greater effect when analyzing longer time intervals. The fact of having less vegetation, older buildings, greater connectivity to other areas, and more travelers arriving in the area causes the number of cases to increase. The proposed model brings a spatiotemporal approach at the neighborhood level up to 3 months in advance. The system proved to be robust to changes in baseline incidence over time.

Jat and Mala (121), in turn, brought an approach to the use of digital geospatial technologies to identify potential sources of dengue incidence. For this purpose, the spatiotemporal grouping of dengue incidences was performed using the Kulldorff scanning method. With the help of Getis-OrdGi statistics, high-risk areas were identified and then implemented in the GIS. And the data obtained was correlated with meteorological parameters, such as wind speed, humidity and demographic factors, such as age and gender. This work shows that the occurrence of dengue is not random, it is directly linked to meteorological phenomena. Thus, this study serves as a warning and to use actions to group regions that may be focuses on dengue spread.

The studies cited here brought interesting approaches to dengue and Zika, considering both epidemiological and climatic data (such as precipitation and temperature), as well as population density, age of construction of buildings, socioeconomic and demographic data, and cases of the disease by patient gender. One of the works is the first, as far as is known, to use street view images to predict dengue cases, something quite innovative. The models created had good results regarding their evaluation metrics. Both machine learning models and statistical models were used. These surveys also rely on algorithms that do not have a great computational weight, which makes their use by the public service viable. The models made were both at the sub-district level and the global level. The spatio-temporal approach brought by the studies in this section helps health managers in directing public resources to areas that need more attention.

3.6. Other Approaches

The articles included in group 6 are articles that combined more than one approach in their predictions, or that had a very different approach from the rest of the articles evaluated in this review. According to **Figure 2**, three of the studies were published in the year 2019. In the years 2016, 2017, and 2020, 1, 1, and 2 studies were published, respectively (**Figure 2**). Analyzing the scores referring to the quality criteria, the average scores in most QC were above 0.7, except QC5 and QC6 (**Figure 3**).

Among the seven articles, three of them simultaneously addressed numerical prediction models of arboviruses cases and also prediction of the risk of epidemiological outbreaks (122–124). In the study of (125), the authors addressed risk production models as well as clustering models to identify regions with similar patterns of disease transmission. Harumy et al. (126), on the other hand, the authors investigated prediction models of the area as the greatest potential to suspend arboviruses and case prediction. Yamamoto et al. (127), in turn, brought an approach to detecting the importation of arboviruses into a country. As for arboviruses groups, the publications were mostly concentrated on dengue (122, 124, 125). Only Yamamoto et al. (127) brought a study considering Zika virus disease cases.

It is important to highlight the variety of models that were covered. Among them, we can mention Random Forest, RF-USA, Logistic Regression (124), and Naïve Bayes (125) for the classification steps. Both (123) and (122) considered a threshold value for identifying an epidemic or outbreak. In the steps involving regression, probabilistic models (127), LASSO, ARIMA, SARIMA (124), Generalized Linear Regression (123), Artificial Neural Network (122, 126), SEIR model (122), and multiple variate regression (125) models were used.

For studies that presented a mixed approach, models for the numerical prediction of cases are essential for the analysis of the epidemiological curve of the disease. In this way, health authorities may have indications that combat policies are or are not effective in combating arboviruses. On the other hand, predictions with spatial approaches can indicate regions with more or less intensity of cases, which can help the distribution of financial and human resources to the most critical regions. Therefore, a mixed approach to the prediction of arboviruses is shown to be robust to assist in decision-making on arbovirus prevention policies.

4. CONCLUSION

Arboviruses have a major impact on populations affected by seasonal outbreaks of these diseases. In addition to the impact caused by the number of deaths and infections, the socioeconomic impacts tend to remain until the next outbreak. The prevention and control of the occurrence of these diseases are directly associated with the monitoring/control of their transmitting vector.

In this sense, this systematic review aimed to identify predictive models of diseases transmitted by *A. aegypti*, as well as identify existing models for modeling vector dynamics. For this, we defined a review protocol that was followed throughout the process. We obtained 429 publications retrieved from scientific databases using a predefined search string. After filtering through the exclusion and inclusion criteria, 139 studies remained in the review for analysis and evaluation of quality criteria.

The remaining studies after the entire analysis process were grouped according to their similar characteristics. Arboviruses' prediction studies are mostly linked to the numerical prediction of cases. According to the results obtained, we observed that among the arboviruses transmitted by *A. aegypti*, most of the studies are aimed at predicting dengue. Both in numerical prediction models, as a prediction of outbreaks, epidemics, and disease diagnosis. Studies regarding predictions with a spatiotemporal approach are also more focused on dengue rather than on Zika and chikungunya. An important point to highlight is the fact that few studies were focused on the spatiotemporal prediction of diseases, as well as the prediction of models related to mosquito dynamics.

Another point that can be highlighted in the studies in this review is in relation to the variables selected for the generation of arbovirus models. In the case of modeling taking into account numerical prediction, prediction of outbreaks and epidemics, and spatiotemporal prediction, we observed that most studies consider climatic variables as model parameters. Among them, the most common are the historical series temperature, rain and relative humidity. However, parameters related to natural phenomena and also variables obtained by remote sensing also gained prominence, as well as data from social networks and search queries. Furthermore, data related to vector monitoring have also been included both in numerical prediction models of arboviruses and in models related to the dynamics of the *A. aegypti* itself. On the other hand, in arbovirus models that prioritize the detection of infection in the individual, we note that the most used parameters are symptomatological parameters. The use of models based only on symptomatological parameters can cause fever-like diseases to be confused with dengue, Zika, and chikungunya. However, we also found studies that use hematological parameters to detect infection.

In this study, we analyzed that, for prediction problems involving arboviruses and also involving mosquito dynamics, a large part of the data is obtained through local health and climatology agencies. Missing data and cases of underreporting by health agencies are one of the most reported problems in the studies evaluated.

Furthermore, this systematic review also demonstrated that there is a range of models that are widely used in prediction problems. Poisson models and moving average models (ARIMA, SARIMA) are widely used to predict historical series. However, we observe that artificial neural networks, support vector machines, and decision tree-based models are widely explored by the studies in this review. It is important to highlight that in many of the works that use Artificial Intelligence models, the authors often do not describe the configurations of the evaluated models and how the models were validated. In other words, although the models have good evaluation metrics, there is no way to guarantee their statistical relevance.

Finally, the arboviruses dynamics is a very heterogeneous problem that involves the interaction of various factors such as climatic and environmental factors, mosquitoes, and human beings. The heterogeneity of arbovirus dynamics is precisely what makes the prediction problem a very complex problem. Therefore, from this systematic review, we hope to provide a theoretical foundation regarding the state-of-the-art of dengue, Zika, and chikungunya prediction models, as well as the breeding sites of its main urban transmitter vector. Hence, we believe that there is great potential for exploring models with a spatiotemporal approach. These models can be an important tool in the fight against arbovirus-borne diseases, as they contain spatial information of epidemiological interest that will be able to more effectively direct human and financial resources, especially in more vulnerable countries.

DATA AVAILABILITY STATEMENT

The data and materials for all experiments reviewed in this study are publicly available as open datasets and are cited in the body of the text.

AUTHOR CONTRIBUTIONS

CL, AnS, GM, CC, AbS, and WS designed the research protocol. CL, AnS, GM, and CC wrote the document review. AM, AA, LD, IB, MT, EB, and SB supported the research. AbS, TM, TA, LC, OY, PK, KJ, and WS supervised and supported all the work. All authors contributed to the article and approved the submitted version.

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Knowledge Structure and Emerging Trends of Telerehabilitation in Recent 20 Years: A Bibliometric Analysis *via* CiteSpace

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Purpose: Telerehabilitation, as an effective means of treatment, is not inferior to traditional rehabilitation, and solves the problem of many patients who do not have access to hospital-based training due to costs and distance. So far, the knowledge structure of the global use of telerehabilitation has not been formed. This study aimed to demonstrate the state of emerging trends and frontiers concerning the studies of telerehabilitation through bibliometric software.

Methods: Literature about telerehabilitation from 2000 to 2021 was retrieved from the Web of Science Core Collection. We used CiteSpace 5.8.R3 to analyze the publication years, journals/cited journals, countries, institutions, authors/cited authors, references, and keywords. Based on the analysis results, we plotted the co-citation map to more intuitively observe the research hotspots and knowledge structure.

Results: A total of 1,986 records were obtained. The number of annual publications gradually increased over the investigated period. The largest increase occurred between 2019 and 2020. J TELEMED TELECARE was the most prolific and the most cited journal. The United States was the most influential country, with the highest number of publications and centrality. The University of Queensland was the most productive institution. The author Tousignant M ranked the highest in the number of publications and Russell TG ranked the first in the cited authors. Respectively, the articles published by Cottrell MA and Russell TG ranked the first in the frequency and centrality of cited references. The four hot topics in telerehabilitation were "care","stroke", "telemedicine" and "exercise". The keyword "stroke" showed the strongest citation burst. The two frontier keywords were "physical therapy" and "participation" . The keywords were clustered to form 21 labels.

Conclusion: This study uses visualization software CiteSpace to provide the current status and trends in clinical research of telerehabilitation over the past 20 years, which may help researchers identify new perspectives concerning potential collaborators

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and cooperative institutions, hot topics, and research frontiers in the research field. Bibliometric analysis of telerehabilitation supplements and improves the knowledge field of telemedicine from the concept of rehabilitation medicine and provides new insights into therapists during the COVID-19 pandemic.

Keywords: telerehabilitation, CiteSpace, bibliometric analysis, Web of Science, co-citation

INTRODUCTION

During the past two decades, the growing availability of communication technologies (ICTs) has created the opportunity to provide technology-based health care in the hospital or after discharge (1). This way, broadly referred to as telemedicine, may ensure the provision of approachable, cost-effective, and particular health care services in disparate times and areas. ICTs have also shown incredible promise in rehabilitation, encouraging the birth of a fresh branch of telemedicine, known as telerehabilitation. Telerehabilitation is attracting considerable critical attention. Extensive research has shown that telerehabilitation is equal or more effective and less costly compared with traditional face-to-face rehabilitation in motor impairments, postoperative recovery, pulmonary function, cardiovascular disease, and other health-related problems (2–4). Especially during the COVID-19 pandemic, under the circumstance of impacting residents' travel and imposing social distance, telerehabilitation may seem to resemble a feasible alternative to face-to-face delivery of rehabilitation services during and after the enhanced quarantine period (5). Thus, telerehabilitation is an increasingly important area nowadays in society. However, few studies are concerned with the comprehensive knowledge structure of telerehabilitation.

Bibliometrics refers to the quantitative analysis of all knowledge carriers, mainly published literature by mathematical and statistical methods, which can be used to assess the impact of authors, institutions, countries, and keywords on the growth of specific fields according to the number of and citation frequency of publications (6). It helps find the trends and hotspots to form the knowledge structure (7). Gu et al. (8) used bibliometrics to explore the trends in the development of e-health and telemedicine research on the retrieved 3,085 papers from the Web of Science Core Collection in 1992–2017. Ahmed Waqas et al. presented an overview of scholarly work in the field of telemedicine based on CiteSpace in 2010–2019 (9). Thus, Telemedicine has become a hot topic and telerehabilitation research is a branch derived from it. No one visualizes the comprehensive knowledge structure, evolutionary path, and research hotspots of telerehabilitation from the perspective of bibliometrics. The above two articles were published before the COVID-19 outbreak. Since the COVID-19 outbreak in 2019, the demand for telemedicine, especially telerehabilitation, has been increasing, and many researchers have been involved in the study of telerehabilitation. Bibliometrics research on telerehabilitation can be used as a complement to telemedicine knowledge and provide new inspiration for rehabilitation medicine, to promote the further development of remote technology. CiteSpace has been a common tool for bibliometrics analysis, which can provide intuitive information and potential research directions for researchers intuitively. Therefore, this study aimed to use CiteSpace to analyze retrieved records from the Web of Science Core Collection in the past 20 years to provide a better understanding of the development trends and current research status of telerehabilitation for researchers and new people in this field, thereby, guiding future research.

MATERIALS AND METHODS

Data Acquisition

The data of this study were collected from the Web of Science (WOS) including SCI-E, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-E, and IC in January 2022. The data search strategy was as follows: Topic=("telerehabilitation") OR Topic=("remote rehabilitation"). The retrieval period time was from January 2000 to December 2021. If there were no restrictions on language and literature type, 2,166 records were generated in the first query ("telerehabilitation") and 99 records in the second query ("remote rehabilitation"). Subsequently, we processed the retrieved records. The first step was to merge the records retrieved from the two search terms and remove the duplicates. The second step was to retain articles, proceedings papers, and reviews, which were formally published and had comprehensive research data, then removed the document type of letter, meeting abstract, editorial material, etc. Finally, a total of 1,986 records were obtained.

CiteSpace

CiteSpace is a Java-based application, developed by Professor Chaomei Chen, which visualizes interrelationships between scientific articles according to their co-citation patterns (10). Visualization knowledge maps show networks as the commonly seen types of node-and-link diagrams. Nodes in different networks can represent different elements, such as country, author, institution, and keyword. The size of the node, which generally indicates the frequency of citation or appearance, and the different colors of nodes show the different years. The warmer the color, the more recent the year, and the colder the color, the more distant the year. Links between nodes signify relationships of collaboration or cooccurrence or co-citation. The purple ring represents centrality. Nodes with high centrality (>0.1) are commonly regarded as pivotal points or turning points in a specific field. The version of this software is constantly being updated. In addition, CiteSpace provides two indicators, module value (Q value) and average contour value (S value), according to the network structure and clustering clarity, which can be used as the basis for judging

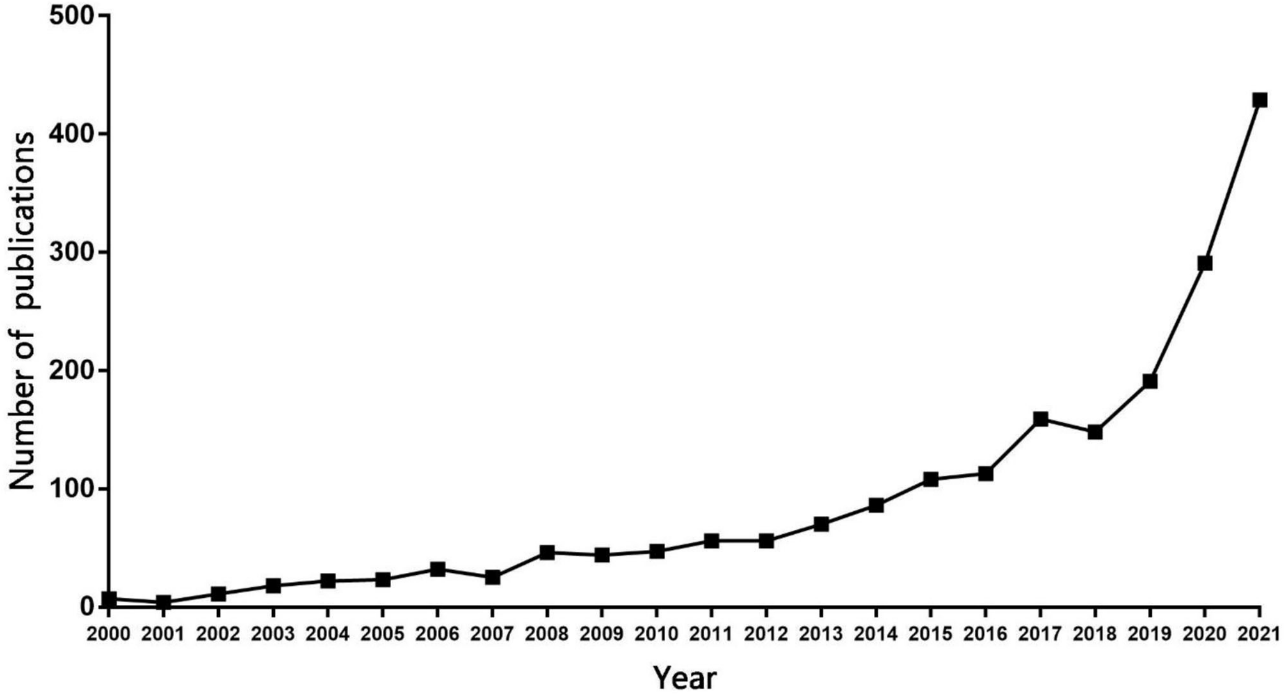


FIGURE 1 | Annual number of published articles from 2000 to 2021.

the mapping effect. Generally speaking, Q value >0.3 means that the community structure is significant, while S value >0.5 means that the clustering is generally considered reasonable. The version used in this research was 5.8.R3 (64-bit). The parameters of CiteSpace were as follows: time slicing (2000–2021), years per slice (1), term source (all selection), node type (choose one at a time), selection criteria (top 50 objects), pruning (pruning sliced networks), and visualization (cluster view-static). We used CiteSpace to identify the time, frequencies, and centralities of the cooccurrence networks, which involved annual publications, journals, countries, institutions, authors, references, and keywords.

RESULTS

Analysis of Annual Publications

In total, 1,986 records were included. The number of publications by years is shown in **Figure 1**. From the figure, we can see the number of publications increased with some fluctuations over 20 years. The number of publications was only 7 in 2000. There were fewer in 2001. It may support that the study and application of telerehabilitation started around the 21st century. Since 2002, the number had risen slowly during 5 years, and declined to 25 in 2007, and then went up again. In 2011 and 2012, the number was the same, 56. The period from 2013 to 2017 was a continued development period; the number exceeded 100 in 2015. Although it fell in 2018, there was substantial growth from 2019 to 2021. The publication outputs were 191 records in 2019. In 2021, the number of articles published was about four times that in 2019 with 429, probably because the impact of the COVID-19 pandemic caused more attention to telerehabilitation.

These results indicated that telerehabilitation, as a medical technology conceived in a new era, is receiving increased attention and more related research is being performed.

TABLE 1 | Top five most productive journals related to telerehabilitation.

Rank	Publications	Journal/IF[a]
1	101	J Telemed Telecare/6.184
2	67	Int J Telerehbilita
3	47	Telemed e-Health/3.536
4	34	FRONT NEUROL/4.003
5	33	Sensors/3.576

[a] *IF, impact factor; IF in category according to Journal Citation Reports (2021).*

Analysis of Journals and Cited Journals

The top five journals with the largest number of published telerehabilitation studies are listed in **Table 1**. Of the five journals, the top three are telemedicine-related journals. FRONT NEUROL and SENSORS show an emphasis on telerehabilitation. Except for INT J TELEREHABILITA, which did not have the most recent JCR journal citation report, the average IF of the remaining four journals was 4.325.

In addition, a cited journal map was generated by CiteSpace (**Figure 2**), resulting in 960 nodes and 7,601 links. The nodes in the map represented journals, and links between the nodes

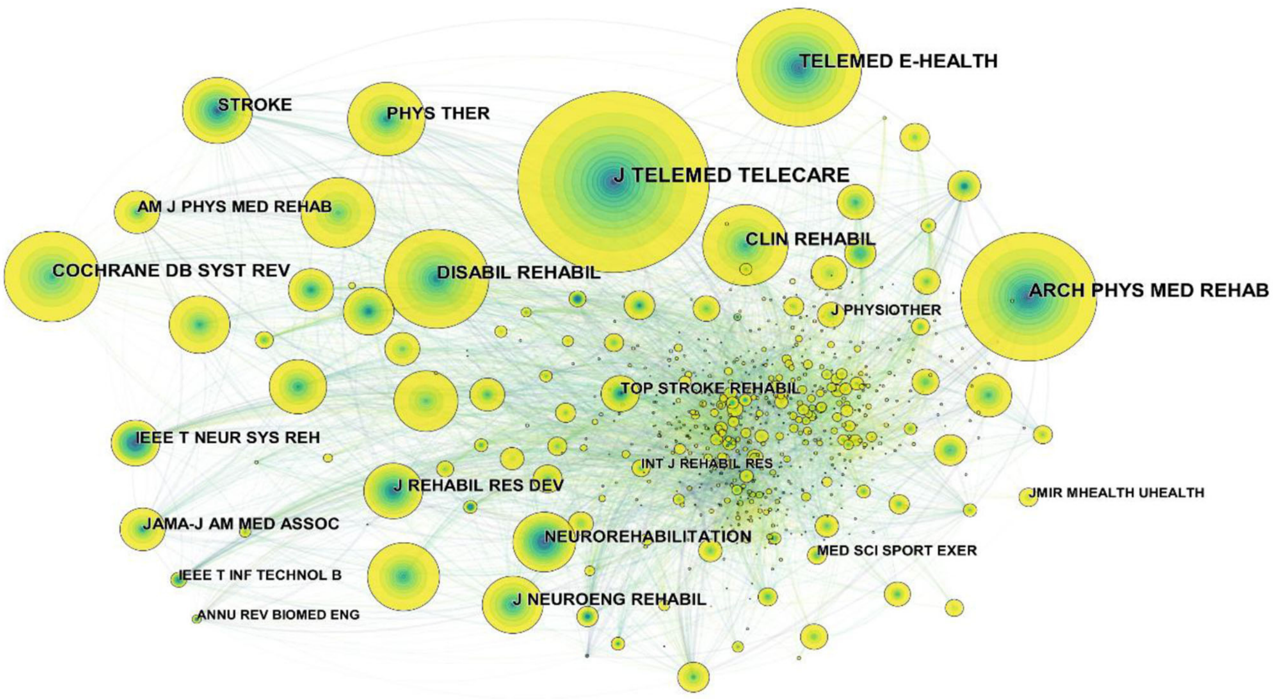


FIGURE 2 | Map of cited journals for telerehabilitation from 2000 to 2021.

TABLE 2 | Top 10 cited journals related to telerehabilitation.

Rank	Frequency	Cited Journal	Rank	Frequency	Cited journal
1	997	J TELEMED TELECARE	6	458	Clin Rehabil
2	727	ARCH PHYS MED REHAB	7	437	Phys Ther
3	669	TELEMED E-HEALTH	8	390	Stroke
4	556	DISABIL REHABIL	9	390	J Med Internet Res
5	490	COCHRANE DB SYST REV	10	381	Int J Telerehabilita

TABLE 3 | Descriptive statistics of the bibliometrics from the top-10 cited journals.

Bibliometrics	Median	25	75	IQR
IF	4.666	3.030	6.617	3.587
Eigenfactor	0.0381	0.0065	0.0615	0.0550
CiteScore	5.750	3.900	7.100	3.200
SNIP	1.280	0.905	1.350	0.446
SJR	1.710	1.458	2.079	0.620

meant co-citation relationships. It can be seen from the figure that these nodes had no purple rings, indicating that the centrality of these journals was not high, the highest was 0.09 from ANNU REV BIOMED ENG. The top 10 cited journals related to telerehabilitation are shown in **Table 2**. We analyzed the bibliometric information of these ten journals (**Table 3**). Because the five selected bibliometrics depicted non-normal distribution, we reported the median, quartiles, and IQR. Most of the journals belonged to Q1, and more than half of the cited journals had an IF above 4.666. The median for the Eigenfactor was 0.0381 and for the CiteScore was 5.750. The median of SNIP and SJR was 1.280 and 1.710, respectively. The impact factor had a range between one and ten; the Eigenfactor score for most of the journals remained below 0.0615. The CiteScore for most journals remained between 3.9 and 7.1. The values of SNIP were primarily concentrated between 0.905 and 1.350. The SJR had a widespread between 0 and 2.5.

Analysis of Countries

We used CiteSpace to generate a country map, 142 nodes and 627 links were generated (**Figure 3**). Telerehabilitation was a concern in many countries. The included 1,986 articles were published by researchers in 142 countries. The top five countries of publications are displayed in **Table 4**. The United States was the main contributor, accounting for a third of the total articles (663), and it was published earlier than any other country. Australia and Italy were ranked in the second and third positions, respectively. Canada and Spain followed with more than 100 articles, while the rest of the country remained below. Except for the United States, the top five countries published their first articles on telerehabilitation around 2006.

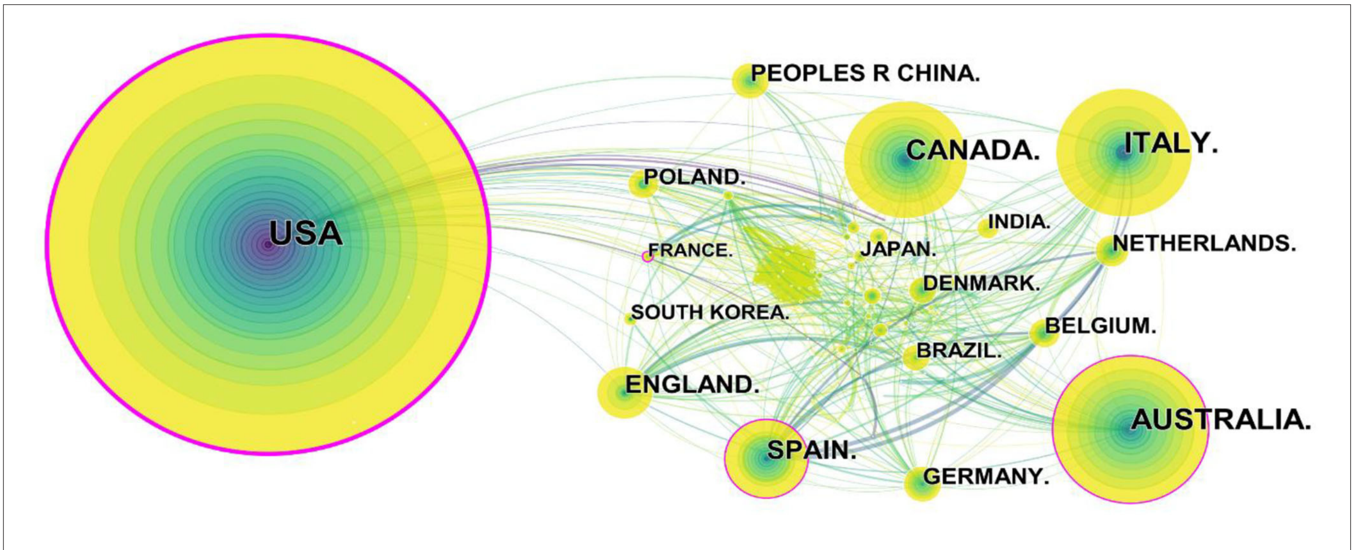


FIGURE 3 | Map of countries researching telerehabilitation from 2000 to 2021.

TABLE 4 | Top 5 countries in number of publications related to telerehabilitation.

Rank	Publications	Countries	Year
1	663	United States	2000
2	241	Australia	2007
3	213	Italy	2006
4	196	Canada	2006
5	135	Spain	2006

We can find that the top five countries are all developed countries with high economic and technological levels, which is conducive to the promotion and development of remote services. Additionally, China (including Taiwan) was the most productive country in Asia with 83 articles. China is the birthplace of traditional kung fu. The study applied the qigong exercise (Liu Zi Jue) under the guidance of remote video combined with acupuncture therapy to the treatment of severe COVID-19 patients and found that patients' symptoms, such as dyspnea and cough, were significantly improved, and their hospital stay was shortened (11).

From **Figure 3**, the nodes represented the country, the purple ring indicated the centrality of literature, and the top five countries in terms of centrality were the United States (0.40), Spain (0.15), Australia (0.13), France (0.13), and Belgium (0.09). The United States had an advantage in terms of volume and importance. North America and Europe took the lead in conducting telerehabilitation research in the world. Telerehabilitation was gaining popularity in Asia after 2019, such as in Japan, India, China, and South Korea, which was reflected in the sharp rise in the number of articles.

Distribution of Institutions

Of the 580 institutions which paid close notice in the field of telerehabilitation, the top 5 institutions were all universities (**Figure 4**). They were Univ Queensland, Univ Pittsburgh, Univ Melbourne, Univ Sherbrooke, and Univ Sydney. Moreover, the top five institutions in terms of centrality were Univ Maastricht (0.14), Univ Duke (0.12), Univ Amsterdam (0.12), Univ Toronto (0.11), and Harvard Med Sch (0.11). Analysis in terms of publication and centrality indicated that the main research institutions were Univ Queensland (Australia) and Duke Univ (United States). They were the cores that formed a complex cooperative network. Univ Queensland's research on telerehabilitation involved Parkinson's disease, heart failure, speech rehabilitation, and so on. The Duke Univ focused more on the telerehabilitation of stroke in the early years but shifted its focus to telerehabilitation of heart failure in recent years.

Analysis of Authors and Cited Authors

The authors of the 1,986 publications were analyzed and resulted in 765 nodes and 1,285 links (**Figure 5**), indicating that the 1,986 articles were published by 765 authors. Among these authors, there were collaborative groups that formed a link with each other and scattered individual authors. The top five authors were Michel Tousignant (12), Trevor Russell (13), Deborah Theodoros (14), Dahlia Kairy (14), and Anne J Hill (15) in **Figure 5**. Michel Tousignant and Dahlia Kairy collaborated on telerehabilitation related to stroke and COVID-19 (16–18), in which they constructed a research idea of telebased tai chi exercise to intervene in the stroke population. In addition, they verified effective improvements in pulmonary symptoms and quality of life in seven COVID-19 discharged patients who received an 8-week exercise prescription for remote pulmonary rehabilitation, including respiratory training, cardiovascular exercises such as walking training, stair training, and resistance training. There were some collaborations between Trevor Russell, Deborah Theodoros, and Anne J Hill, and their collaboration paid more attention to speech disorders. They organized groups of aphasia patients to share their personal life histories *via* online video conferencing from their homes,

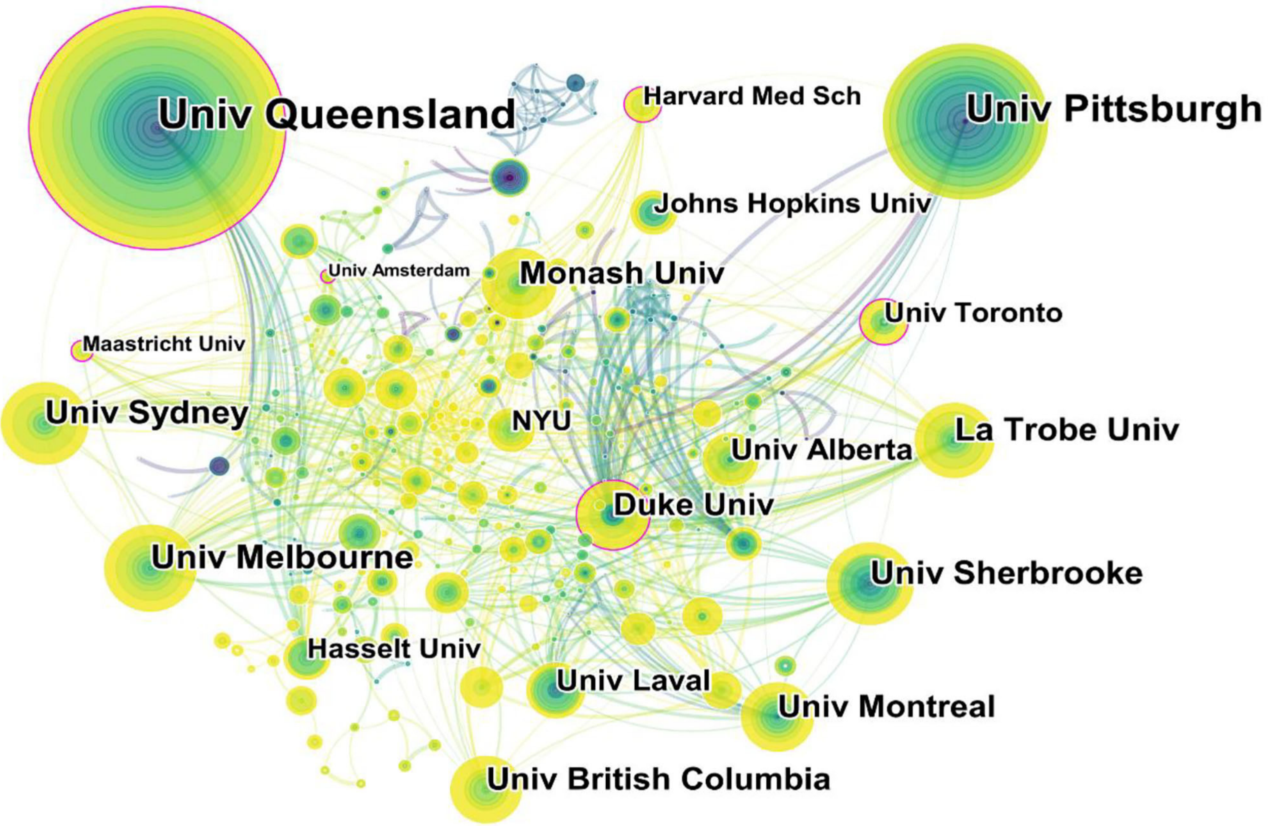


FIGURE 4 | Map of institutions researching telerehabilitation from 2000 to 2021.

which created opportunities for communicative success and built connections with others. Results showed that a multi-purpose group intervention for people with aphasia can result in improved communication, communicative participation, and quality of life (19). They also summarized the technical management review of communication and swallowing disorders in Parkinson's patients and found that the treatment of the speech disorder online was the most developed aspect of the technology-enabled management pathway (20).

The map of cited authors is displayed in **Figure 6**. Russell TG had the highest citation counts, followed by Kairy D, Tousignant M, Brennan DM, and Laver KE (**Table 5**). The top five authors in terms of centrality were Piron L, Tousignant M, Winters JM, Russell TG, and Hill AJ. In **Figure 6**, we can find that the node of "Piron L" had a distinct purple ring, indicating a high mediating effect, while the centrality of other nodes was not obvious. Piron L was based at the University of Padova (Italy) and had focused his vision on the combination of post-stroke rehabilitation with modern technology in the early 20th century. In 2001, he published a paper on the application of virtual reality as a tool to evaluate arm motor defects after brain lesions. The results showed a significant correlation with clinical scale scores (15). In 2009, PL combined telerehabilitation with virtual reality. A virtual reality system delivered over the internet that provides upper limb motor function training to stroke patients found that motor performance produced better results (14).

Combining author, cited author, and centrality, Michel Tousignant (Tousignant M) was a professor in the field and had an important influence on the development of telerehabilitation. He was from the University of Sherbrooke (Canada), and he was mainly devoted to investigating the telerehabilitation of musculoskeletal conditions, especially after knee arthroplasty. One of his opinions was that home telerehabilitation and routine rehabilitation were not significantly different in therapeutic efficacy or satisfaction, and a favorable cost difference was observed when patients were more than 30 km away from the provider (21–23).

Analysis of Cited References

Generating a cited reference co-citation map resulted in 1,141 nodes and 4,934 links (**Figure 7**). In terms of citation frequency, the first was the article published in 2017 by Cottrell MA (24). The article conducted the first systematic review to confirm the beneficial effect of real-time telerehabilitation for musculoskeletal conditions and suggested that rigorous clinical trials were warranted. Additionally, the randomized controlled trial published by Moffet H in 2015 (25), which was ranked the second list, demonstrated the non-inferiority of in-home

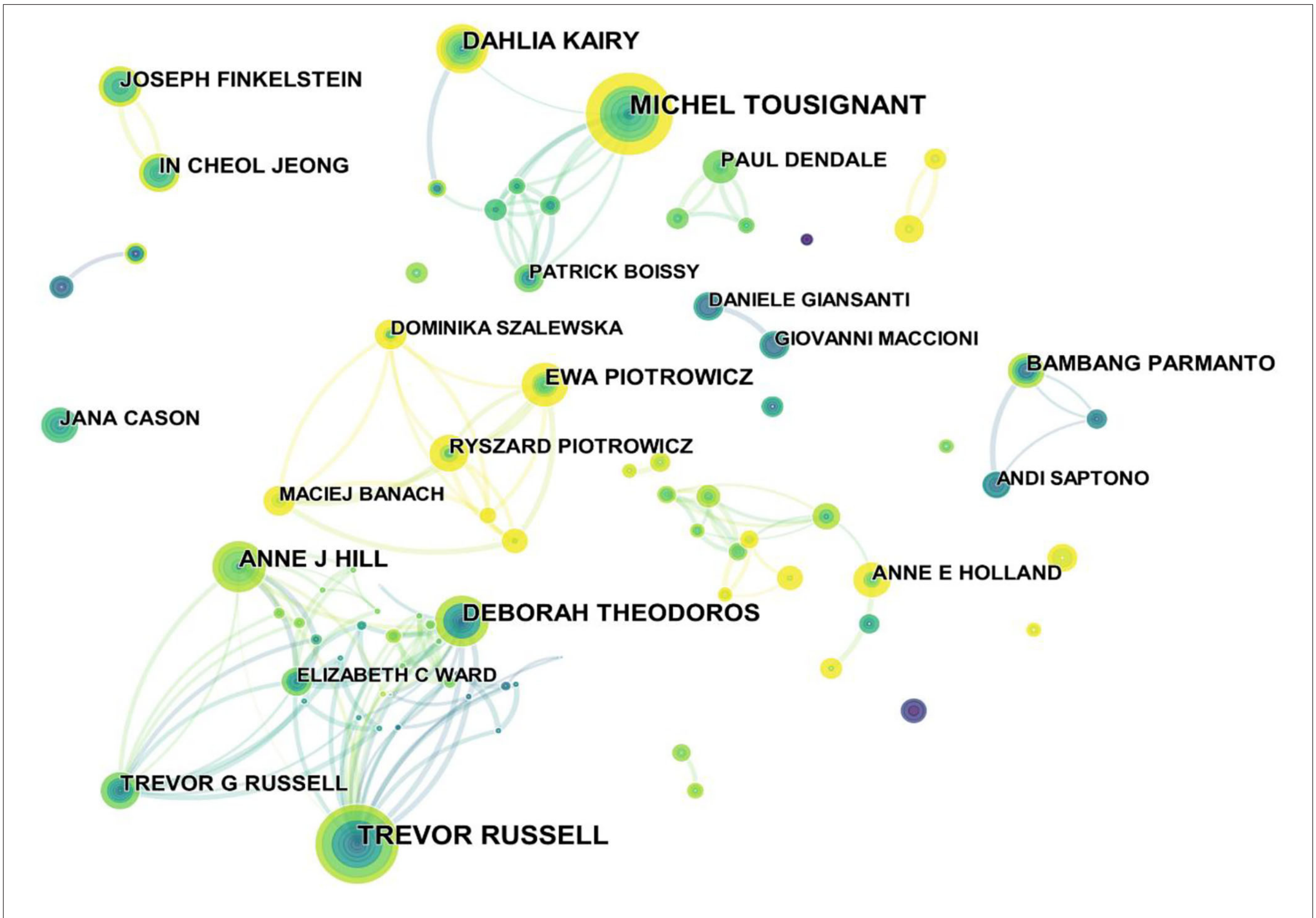


FIGURE 5 | Map of authors related to telerehabilitation from 2000 to 2021.

telerehabilitation after total knee arthroplasty and supported its use as an effective alternative to face-to-face service delivery. The review study published by Peretti et al. (26), which ranked the fourth reference, made a starting point that improving approaches and devices for telerehabilitation emphasized the need for proper training and education of people involved in this new area. The third and fifth places (Sarfo FS, Chen J) were all systematic reviews about the telerehabilitation of stroke published in J Stroke Cerebrovasc Dis (13, 27).

The centrality of cite references ranked the first conducted by Russell et al. (1), who carried out a single-blinded, prospective, randomized, controlled non-inferiority trial to compare the equivalence of the internet-based telerehabilitation program and conventional outpatient physical therapy in the treatment of total knee arthroplasty and the results revealed that the efficacy of the two treatments was similar, but telerehabilitation had better performance in the stiffness subscale of the WOMAC and patient satisfaction. Lum PS developed a device called Automated Constraint-Induced Therapy Extension ("AutoCITE") that automated the intensive training component of constraint-induced movement therapy to assess the effectiveness of "AutoCITE" training in a telerehabilitation setting when supervised remotely for participants with a chronic stroke (28). Brennan et al. (29), who was one of the members of the Telerehabilitation Special Interest Group, released the guideline about telerehabilitation in 2011 to inform and assist associated personnel in providing effective and safe services that were based on user needs, current empirical evidence, and valid technologies. The same centrality of Agostini M and Johansson T was published in J Telemed Telecare and IEE Trans Neural Syst Rehabil Eng, respectively (30, 31).

We performed cluster analysis on the cited references to clarify the topic and time distribution of these cited references (**Figure 8**). The Q value was 0.7984 and the S value was 0.9111 in this map, indicating that the clustering effect was good and the credibility was high. As can be seen from the colors in the figure, the most recent cited topics focus on stroke, knee, children, and cardiopulmonary rehabilitation. In addition to the above, another recent cluster is the outbreak of COVID-19 in recent years.

Analysis of Keywords

It was considered that the indicators for evaluating the most leading-edge topics or emerging trends were the increased frequency of keywords or the increased number of keyword

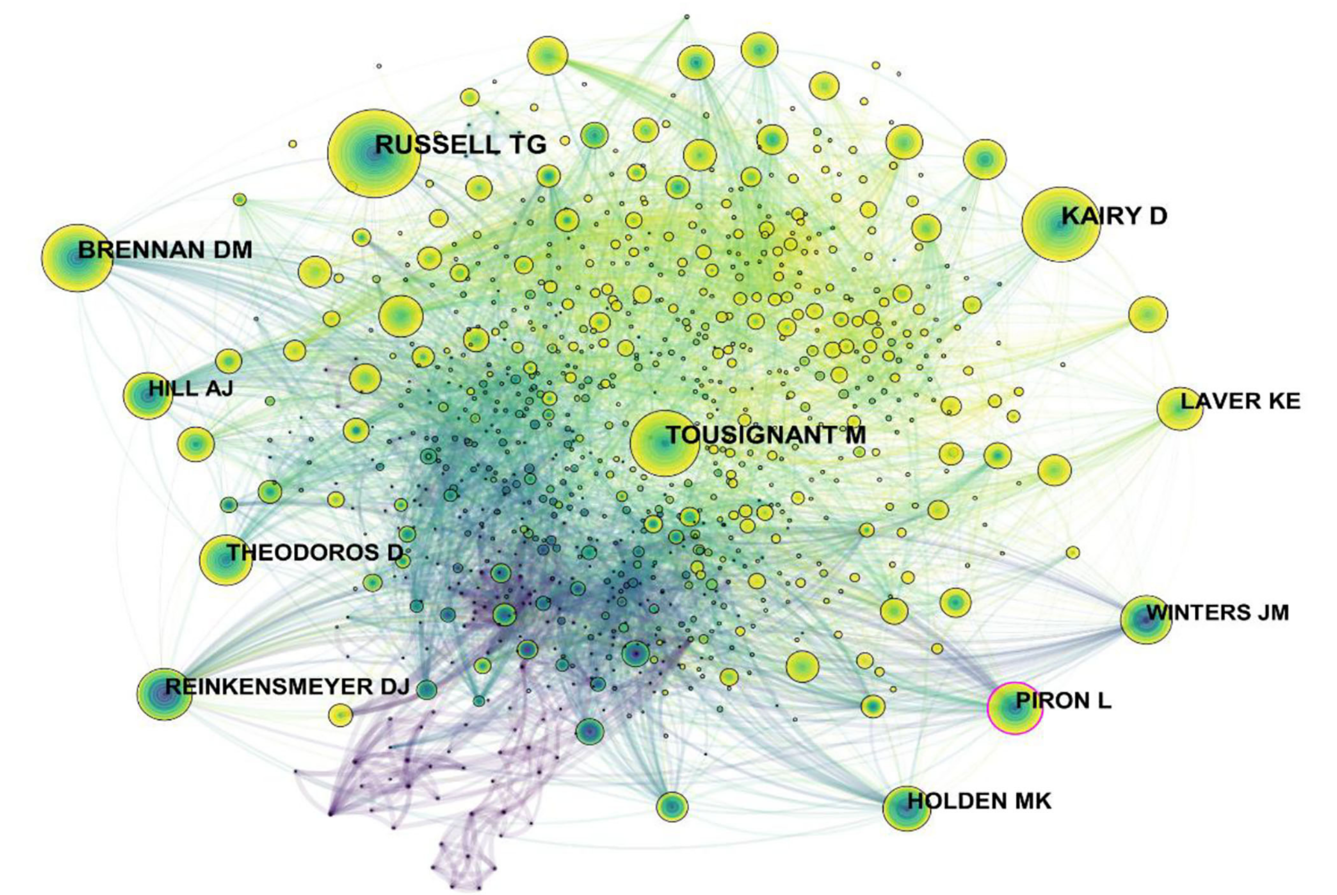


FIGURE 6 | Map of cited authors related to telerehabilitation from 2000 to 2021.

TABLE 5 | Top five Frequency and centrality of cited authors related to telerehabilitation.

Rank	Frequency	Author	Rank	Centrality	Author
1	274	Russell TG	1	0.14	Piron L
2	219	Kairy D	2	0.09	Tousignant M
3	205	Tousignant M	3	0.09	Winters JM
4	175	Brennan DM	4	0.07	Russell TG
5	133	Laver KE	5	0.07	Hill AJ

bursts in the citation within a certain period (32). The network map of keywords was generated and consisted of 541 nodes and 4,586 links (**Figure 9**). A total of 541 research keywords were identified in the field of telerehabilitation, which reveals the hottest topics. According to the frequency and centrality (**Table 6**), we can see the popular keywords were "care," "stroke," "telemedicine," "exercise," and "care," which had a high frequency and centrality. As a modern technology, telerehabilitation reduces the pressure on carers and provides help for caring work at the same time. At present, the most concerned patients of telerehabilitation are stroke patients, who have a long course of the disease and require a certain amount of time to recover. However, the current hospital stay period is short and the cost is high. Telerehabilitation solves the problems above. It can not only help and supervise the rehabilitation of patients after discharge but also save costs and ease the burden on medical workers. "Exercise" is also a popular word. The biggest difference between telerehabilitation and face-to-face rehabilitation lies in the therapist's "hands-on" and "hands-off." Therapists cannot touch patients with their hands, and the palpation and manipulation adjustments are limited in telerehabilitation. So, it is mostly about exercise instruction and training. Of course, exercise is also an important part of rehabilitation, which allows patients to participate actively, and remote management can better guide and supervise them. Furthermore, we can also find some words like "randomized controlled trial" and "quality of life" in the table. A randomized controlled trial is a gold standard for evaluating the efficacy of telerehabilitation, which provides high-quality evidence-based testimony. A single-blind method is used in most studies due to the particularity of intervention methods. The frequency of the keyword "quality of life" is increasing year by year, indicating that people pay much attention

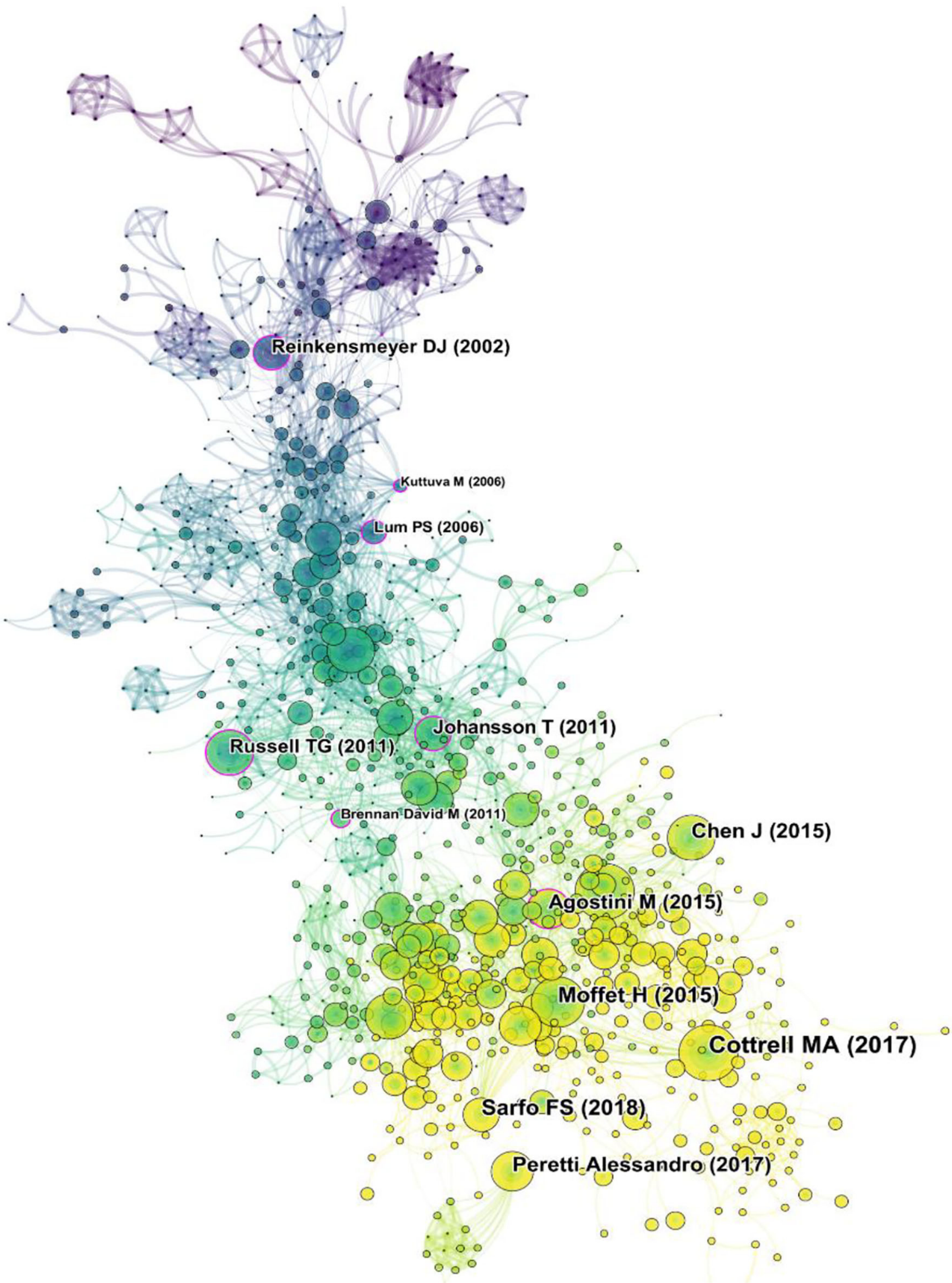


FIGURE 7 | Map of cited references to telerehabilitation from 2000 to 2021.

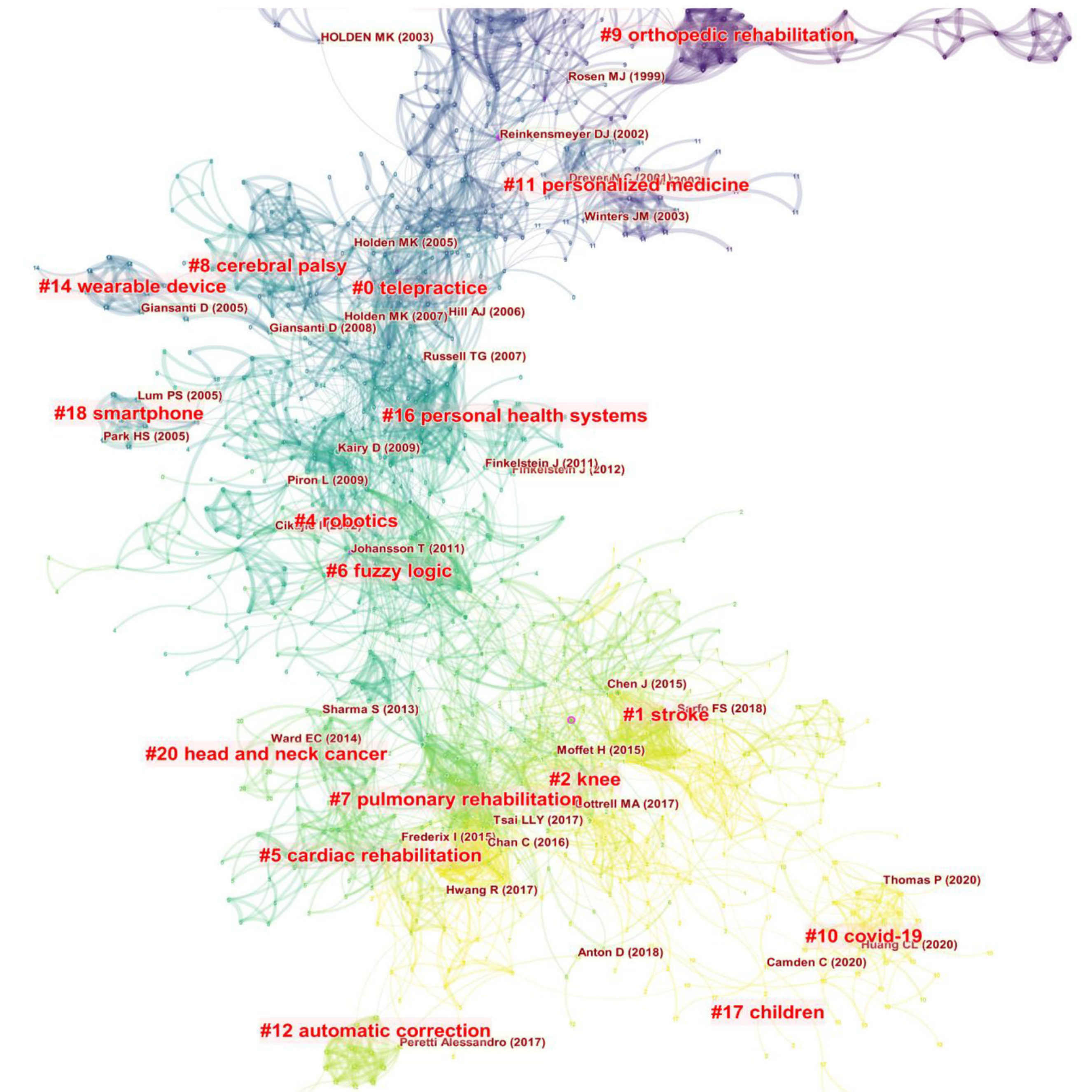


FIGURE 8 | The clustering map of cited references related to telerehabilitation.

to the quality of life for patients after telerehabilitation and care about the physical and mental changes of patients. The main measurements include HRQoL, EuroQoL-5, and Short form-36 questionnaire score (33–35).

The top 15 cited keywords with the strongest citation burst from 2000 to 2021 are shown in **Figure 10**. Among these keywords, "stroke," "upper extremity," "Parkinson's disease," "brain injury," "traumatic brain injury," and "arm" are the objects of intervention for telerehabilitation. The keyword "stroke" emerging from 2006 had shown the strongest citation burst of 10.7 (164). The keywords such as "Internet," "low bandwidth," "system," and "environment" were all about various technologies or application environments of telerehabilitation. Generally speaking, the technologies used for telerehabilitation can be divided into image-based telerehabilitation, sensor-based telerehabilitation, virtual environments, and virtual reality

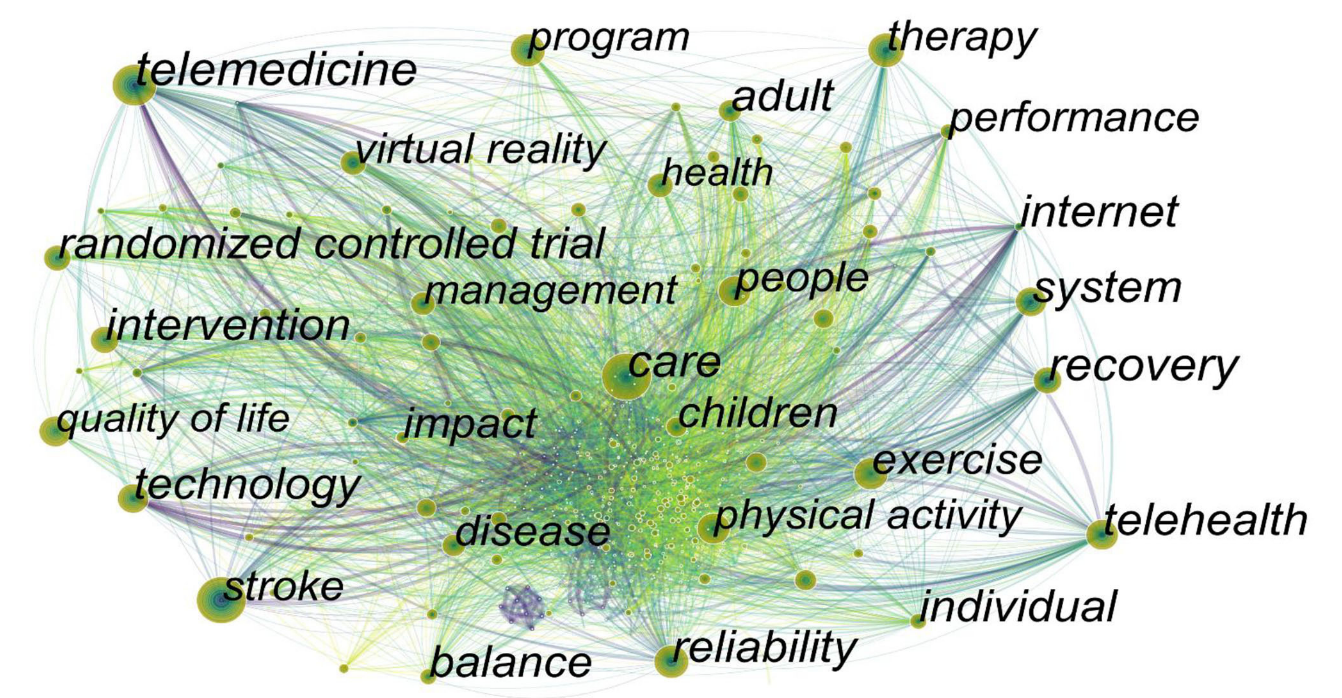


FIGURE 9 | Map of keywords to telerehabilitation from 2000 to 2021.

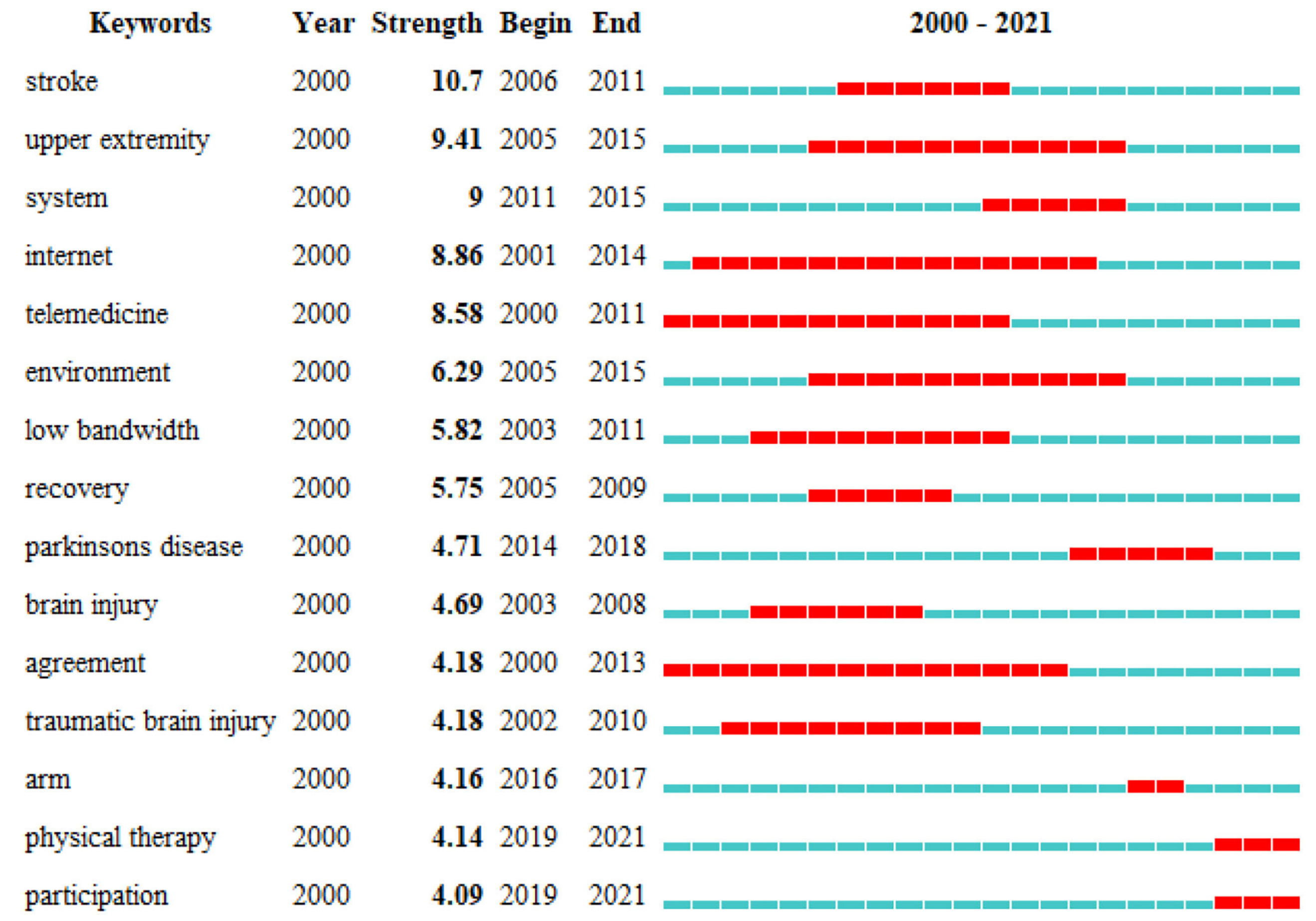
TABLE 6 | Top 10 frequency and centrality of keywords to telerehabilitation.

Rank	Keyword	Frequency	Rank	Keyword	Centrality
1	Care	214	1	Care	0.08
2	Stroke	164	2	Recovery	0.07
3	Telemedicine	150	3	System	0.06
4	Exercise	136	4	Reliability	0.06
5	Program	136	5	Randomized controlled trial	0.06
6	People	133	6	Individual	0.06
7	Telehealth	132	7	Internet	0.06
8	Quality of life	127	8	Telehealth	0.05
9	Intervention	125	9	Intervention	0.05
10	System	120	10	Adult	0.05

telerehabilitation (36). Videoconferencing is by far the most widely used, as per cost and technical difficulty. But back in the 1980s, telemedicine initially was limited to high-bandwidth applications. High cost, low access, and system complexity hindered the widespread adoption of broadband videoconferencing systems in medicine. Subsequently, successful research and application of low-bandwidth technologies enabled telemedicine to provide substantial help to underserved areas in a more affordable and accessible manner (37).

The most recent burst keywords were "physical therapy" and "participation." Physical therapy, as a large part of rehabilitation, plays with the ability to develop, maintain, and rebuild movement and functional capacity. Telerehabilitation in physical therapy has gained a lot of attention and its application is gradually expanding. Future clinical trials should strictly consider internal validity and optimal sample sizes, and non-inferiority studies should be recommended to prove that telerehabilitation is not inferior to standard rehabilitation. Moreover, the challenge is the feasibility of telerehabilitation in a variety of resource settings (38). The keyword "participation" included the views of the implementor, participants, and their relatives on telerehabilitation, and the development of an ICT-based rehabilitation to support a person-centered rehabilitation process for survivors and their significant others. It establishes a sense of connection between the medical staff and the patient and reduces the patient's feeling of abandonment when rehabilitation ends (39). A study from Denmark examined the perspectives of physiotherapists and occupational therapists on ICT. They proposed to develop a diverse personalized app just for post-stroke survivors (40).

We conducted cluster analysis on these keywords and summarized them, so as to have a more intuitive understanding of the current research topics related to telerehabilitation. After clustering, the Q value is 0.4591 and the S value is 0.8497, indicating that clustering is appropriate and meaningful. A total of 21 clusters were generated to reflect the hot trends, among which the top six clusters containing the most keywords are "cardiac rehabilitation," "stroke," "knee," "virtual reality," "telehealth," "children," and "caregivers" (**Figure 11**). From the timeline view (**Figure 12**), in terms of color warmth, "stroke" and "cardiac rehabilitation" are the latest studies, while "knee" and



Keywords	Year	Strength	Begin	End	2000 - 2021
stroke	2000	**10.7**	2006	2011	
upper extremity	2000	**9.41**	2005	2015	
system	2000	**9**	2011	2015	
internet	2000	**8.86**	2001	2014	
telemedicine	2000	**8.58**	2000	2011	
environment	2000	**6.29**	2005	2015	
low bandwidth	2000	**5.82**	2003	2011	
recovery	2000	**5.75**	2005	2009	
parkinsons disease	2000	**4.71**	2014	2018	
brain injury	2000	**4.69**	2003	2008	
agreement	2000	**4.18**	2000	2013	
traumatic brain injury	2000	**4.18**	2002	2010	
arm	2000	**4.16**	2016	2017	
physical therapy	2000	**4.14**	2019	2021	
participation	2000	**4.09**	2019	2021	

FIGURE 10 | Top 15 keywords with the strongest citation burst.

"children" appear earlier. In addition, virtual reality technology is often involved in the field of remote rehabilitation. Many studies have found that remote integration with virtual reality technology can improve the motor function of the upper limb (41, 42). Virtual reality technology can improve the interest and enthusiasm for patient training, and their combination can play a greater therapeutic effect.

DISCUSSION

Telerehabilitation, as an emerging and alternative therapy, has been widely valued and studied with the gradual development of technology, especially during the epidemic period, and has the advantages of being cost-effective and convenient. In this study, we searched the core data of WOS based on the search formula and obtained 1,986 literature data on telerehabilitation research from 2000 to 2021. Based on the bibliometrics analysis of CiteSpace, the spatial and temporal distribution and research hotspots of telerehabilitation were clarified. Over the previous 20 years, the related publications increased at a rapid rate. Notably, the largest increase occurred between 2019 and 2020, which may be linked to the demand for remote technology during the spread of COVID-19. In this study, the Journal of Telemedicine and Telecare published the most articles (101) and was the biggest cited (997). The average IF, Eigenfactor, CiteScore, SNIP, and SJR of cited journals were 4.666, 0.0381, 5.750, 1.280, and 1.710, respectively. The countries and institutions that had issued studies in telerehabilitation had relatively close cooperation. Generally, the United States, Australia, and some other European countries, with a high publication rate and centrality, all developed countries, proved to be the main leaders under technological advantages in this field. The most productive institution was the University of Queensland in Australia. But an important trend that deserved attention was that the research achievements of Asian countries increased very fast after 2019, China was the most prolific country in the Asian region. A total of 765 active authors from various countries had attempted to estimate and evaluate the effectiveness of telerehabilitation for diseases such as stroke, knee arthroplasty, speech disorders, heart failure, and so on. In recent years, they have focused on telerehabilitation of lung function in a post-COVID-19 world and the applicability of telerehabilitation to other diseases during the COVID-19 pandemic. These authors performed randomized trials or systematic reviews to compare

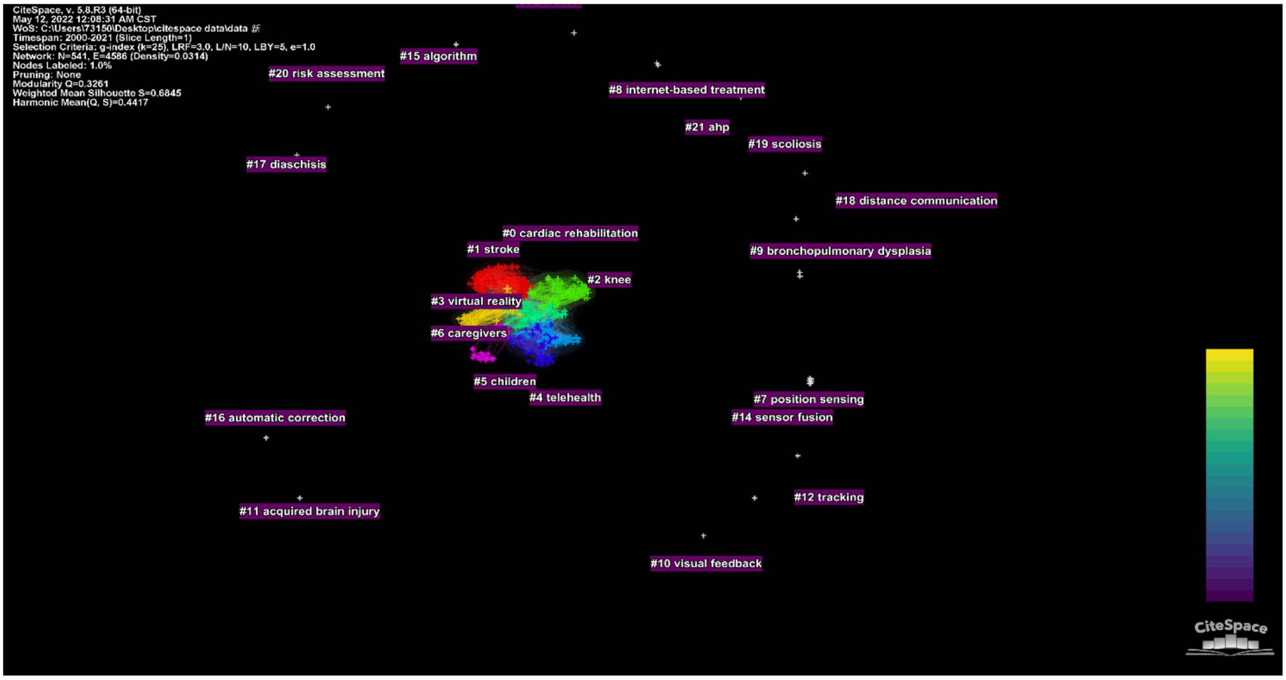


FIGURE 11 | The clustering map of keywords related to telerehabilitation.

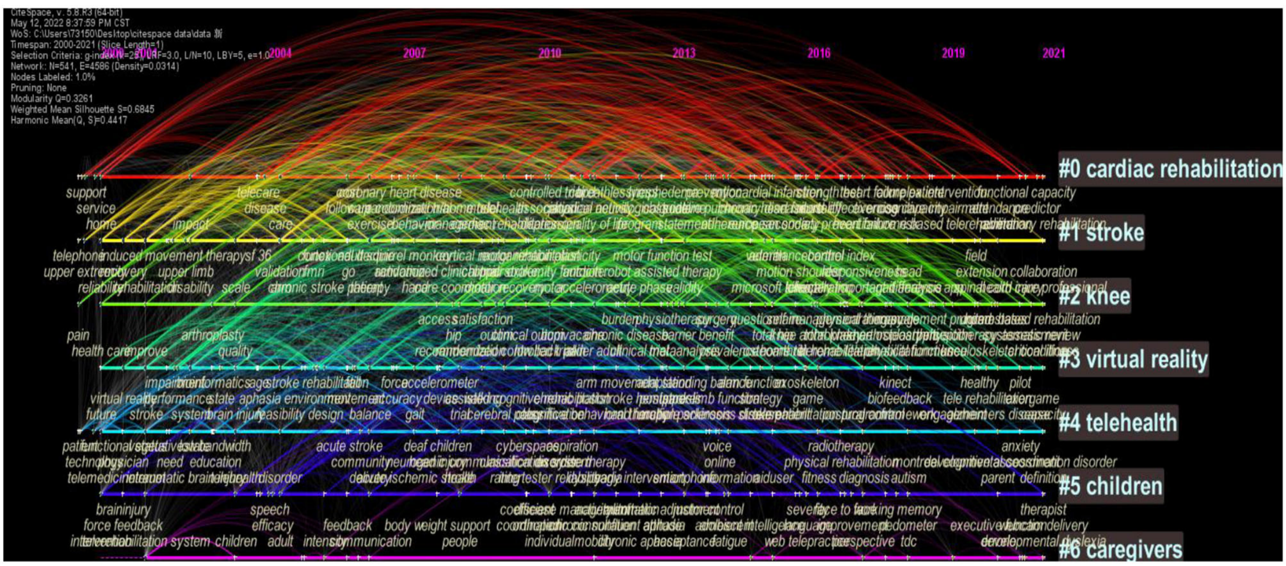


FIGURE 12 | The timeline view of keywords related to telerehabilitation.

telerehabilitation with usual face-to-face rehabilitation. The results showed that the effect of telerehabilitation was as good as that of usual rehabilitation in a therapeutic effect, and it obtained the satisfaction of patients and their families. People from remote regions got higher benefits, mainly reflected in saving transportation costs and time. Among these authors, Tousignant M was the most productive author and Russell TG ranked the first among the cited authors. The first cited reference was a review on telerehabilitation of musculoskeletal diseases published by Cottrell MA in 2017, and a cluster analysis of cited references showed that stroke, cardiopulmonary rehabilitation, knee, children, and COVID-19 were the latest hot topics cited.

From the keywords, we found that "stroke" has been a hot topic of attention and research. For stroke patients, full recovery is not guaranteed after restorative rehabilitation in the acute and subacute stages of stroke. To maximize recovery and maintenance of function, patients with chronic stroke must undergo ongoing rehabilitation or exercise interventions. Telerehabilitation helps stroke patients maintain vertical continuity of motor rehabilitation at home and helps reduce the workload of therapists. Therefore, stroke is in great demand for telerehabilitation and it has always been a research hotspot. In addition, cardiac rehabilitation, knee rehabilitation, and child rehabilitation are also the main application fields of telerehabilitation. Developments and innovations in telerehabilitation technology are being studied extensively. At present, video conferencing is the most widely used, and internet-based low-bandwidth communication provides a more cost-effective and easily accessible telemedicine solution. With the continuous development of modern technology, the combination of virtual reality technology and telerehabilitation brings new opportunities and development space. The frontier keywords were "physical therapy" and "participation". Since the COVID-19 outbreak, the World Confederation for Physical Therapy's task force has proposed a pragmatic approach to shifting service paradigms and scaling up telehealth physical therapy within a large medical center (43). In the future, higher quality clinical trials and systematic reviews are imperative in this important field of investigation. In addition, telerehabilitation aims to benefit people, so individualized intervention programs should be made based on the situation of different patients. Satisfaction surveys should not only be conducted for patients but also the opinions of family members and therapists should be included. Telerehabilitation development needs to support person-centered concepts in the future.

LIMITATION

Several limitations need to be noted regarding this study. First, we only analyzed the data from the Web of Science. Therefore, the results may not be comprehensive, and it is necessary to combine more database resources for analysis in the future. Second, although the search terms chosen were considered, we cannot guarantee that every piece of literature is completely related to the topic, and it is also uncertain whether all documents related to the topic have been retrieved. Third, if the search is carried out at a different period, the citation counts and centrality of the articles may be different. So, this study only represents the research in the past 20 years. It is necessary to update the study in the future. Even so, we believe that this study can still be used to describe the overall situation and developing trends in this field from 2000 to 2021 and provide suggestions for follow-up research.

CONCLUSION

In summary, this study uses visualization software CiteSpace to identify new perspectives concerning potential collaborators and cooperative institutions, hot topics, and research frontiers in the research field, providing a direction for exploring and developing telerehabilitation. Telerehabilitation research is mostly done in developed countries, and cooperative networks have been formed among the authors. Randomized controlled trials and reviews prove that telerehabilitation and traditional face-to-face rehabilitation are equal but more cost-effective. At present, the main area of concern for telerehabilitation is stroke, and future research may turn to the applicability of telerehabilitation in physical therapy in the pandemic era. At the same time, remote technology will be further developed in the future, allowing people in remote areas to access low-cost and stable internet configurations. In addition, the combination of telerehabilitation and virtual reality technology is also a highlight. In the future, the diagnosis and treatment of telerehabilitation will pay more attention to the people-centered concept and develop personalized diagnosis and treatment plans, which will not only satisfy patients but also be recognized by family members and therapists. With the continuous spread of the pandemic, telerehabilitation will be further studied and promoted.

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

MH contributed to conceive, design, and revise manuscript. JZ and LL contributed to data collection and analysis and manuscript writing. XW contributed to obtaining funding for the study and manuscript revision. All authors contributed to the article and approved the submitted version.

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Application of 5G network combined with AI robots in personalized nursing in China: A literature review

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The medical and healthcare industry is currently developing into digitization. Attributed to the rapid development of advanced technologies such as the 5G network, cloud computing, artificial intelligence (AI), and big data, and their wide applications in the medical industry, the medical model is shifting into an intelligent one. By combining the 5G network with cloud healthcare platforms and AI, nursing robots can effectively improve the overall medical efficacy. Meanwhile, patients can enjoy personalized medical services, the supply and the sharing of medical and healthcare services are promoted, and the digital transformation of the healthcare industry is accelerated. In this paper, the application and practice of 5G network technology in the medical industry are introduced, including telecare, 5G first-aid remote medical service, and remote robot applications. Also, by combining application characteristics of AI and development requirements of smart healthcare, the overall planning, intelligence, and personalization of the 5G network in the medical industry, as well as opportunities and challenges of its application in the field of nursing are discussed. This paper provides references to the development and application of 5G network technology in the field of medical service.

KEYWORDS

5G network, personalized nursing, AI, cloud platform, robotics

Introduction

With the continuous progress of information technology, the informatization degree of the medical field is continuously increasing, the business of information systems becomes increasingly complicated, and the size of daily data to be processed in hospitals is rapidly increasing. Meanwhile, the development of regional medical and healthcare demands network interconnection and real-time sharing of medical data. As a result, the communication network of the medical industry is facing huge challenges. In the post-epidemic era, a reform in the medical service mode to provide personalized service is of great significance.

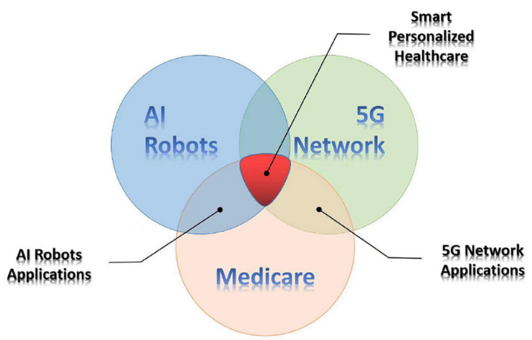

FIGURE 1
Logical relation diagram.

Intelligent medicine has been applied to all aspects of the medical system, such as health care, medical auxiliary diagnosis, and hospital management. A series of cutting-edge technologies, such as 5G medical treatment, cloud platforms and artificial intelligence will promote mankind to enter the era of intelligent medicine (Figure 1) (1).

With the improvement of the mobility and sensitivity of robots, medical robots and automation systems will become the right assistants for medical staff. Meanwhile, the functions of service automation, human-computer interaction and deep learning can effectively improve the work efficiency of medical staff, reduce medical costs and improve patient satisfaction. This makes future medical models possible, such as artificial intelligence, intelligent medicine, and human-computer collaboration (2, 3).

Because of its high data transmission rate, low energy consumption, and good reliability and security, 5G network technology has been widely applied in the field of medical service. This study analyzes the applications of 5G network technology in the field of medical service and summarizes the applications of evidence available types such as artificial intelligence (AI) in nursing and their performances. Combined with cloud healthcare platforms and AI, the 5G network can provide integrated medical and nursing services, including vital signs monitoring, disease diagnosis and treatment, rehabilitation nursing, and daily life nursing. Based on professional, comprehensive, efficient, and continuous nursing measures, academia and industry are striving to improve the service quality and meet the personalized needs of specific groups. 5G technology has been widely used in the world, laying a good foundation for the digital transformation of the whole industry (4).

The proposed solutions facilitate smart healthcare applications (including telemedicine, intelligent guidance, and mobile healthcare), thus improving the working efficiency and service level of medical staff. This review aims to evaluate and synthesize the literature for the development and application of 5G network technology in the field of medical services. The keywords used for searching the relevant literature included 5G network, personalized nursing, personalized care, artificial intelligence, robot, cloud platform, smart healthcare, and intelligent medicine. The search involved the databases Cumulative Index to Web of Science, PubMed, and MEDLINE. The articles on interventions and outcomes of intelligent individuality healthcare were selected, and animal studies, editorials, comments, and letters were excluded from the review. After duplicates were removed, 176 titles and abstracts were reviewed and screened for inclusion and exclusion criteria. A total of 143 articles were included in the final review. We evaluated the efficacy outcomes of applying the 5G network technology, the presence of intelligent medical care, and the type of AI robots involved in the services. The results of our research were synthesized and narratively discussed.

Advantages of medical networks using 5G network technology

With advantages such as high speed, short time, high density, and high spectrum efficiency, 5G network technology can rapidly connect people with things. Also, information transmission is free from limitations by time and space, and information utilization can be more convenient and rapid (5). First, high speed is the top advantage of 5G network technology, which allows data that occupy a large storage space (e.g., medical images) to be transmitted between hospitals in different regions or between different departments of one hospital in a short time. Based on this, the complete case data of patients can be easily accessed in regional medical treatment. Meanwhile, huge improvements in network capacity and transmission rate promote the application of technologies such as VR in the medical industry (6). Currently, the novel model of 5G-integrated cloud healthcare platform and AI robots has been gradually applied and populated in China. The model can provide standardized and personalized medical services (e.g., vital signs monitoring, drug delivery, health education, intelligent Q & A, remote visit, remote ward-round, intravenous infusion, mobile ward-round, logistics) to different patients based on the high bandwidth and low delay of 5G networks in hospitals, communities and families, fundamental functions of robots (e.g., autonomous walking, intelligent information recognition, transportation), and extraordinary computing power and professional database of cloud healthcare platforms (Figure 2).

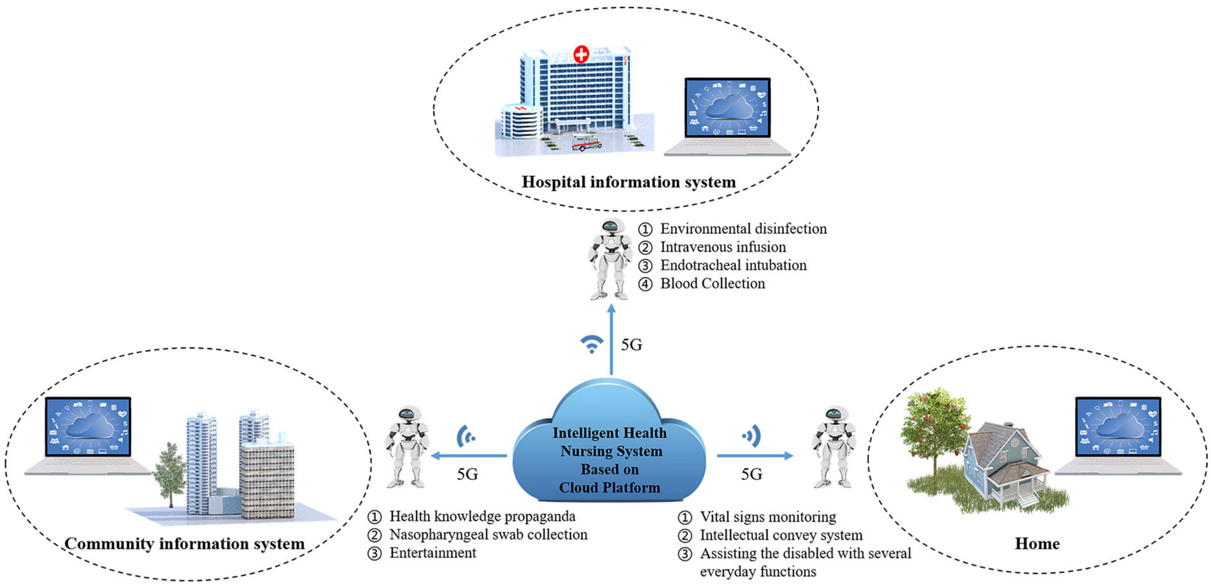

FIGURE 2
The logical architecture of 5G network combined with AI robots in personalized nursing.

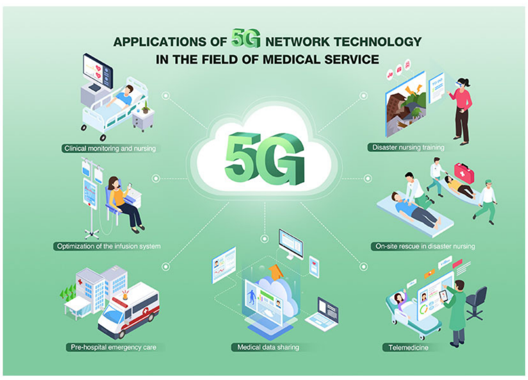

FIGURE 3
Application of 5G technologies in medical field.

Applications of 5G network technology in the field of medical service

With the continuous development of social informatization, medical services must seize the opportunity of 5G network technology to meet growing demands in modern medical service (7–10). The application of 5G network technology in the medical network will improve medical service quality and medical efficiency and enhance the patient experience, thus improving the service level of the entire medical industry (Figure 3) (10–15). In hospitals, 5G network technology can help to realize wireless monitoring, wireless infusion, mobile nursing, real-time patient position acquisition and monitoring, and real-time access to diagnostic images of patients (16–19). Such applications have high requirements for network isolation, security, and reliability because they are related to patient privacy. Meanwhile, image downloading and data acquisition have high requirements on bandwidth due to a large number of users and frequency utilization. With the help of THE 5G smart healthcare private network, mobile ward-round, wireless monitoring, medical image access, and mobile prescription can be achieved in hospitals. This will reduce the working intensity of medical staff, enhance service efficiency, and reduce inter-departmental coordination time, thus providing good services to patients and improving the satisfaction of medical service (20–22). Additionally, telemedicine consultation, remote examination, and video teaching can be achieved between different hospitals, attributing to significantly enhanced medical staff skills in primary medical units and medical services in remote areas. In this way, medical resources, hierarchical diagnosis and treatment, and mutual medical assistance can be integrated, and patients do not have to travel a long distance to major hospitals. For emergency rescue outside the hospital, early intervention (observation and treatment) of critical patients can be executed, and professional medical services can be provided to patients during golden rescue time to improve the cure rate.

Clinical monitoring and nursing

Mobile nursing and wireless ward-round have been partially applied in medical service. Owing to the wide applications of 5G network technology, mobile monitoring and nursing will be popularized and become more intelligent. For instance, wards such as ICU and NICU provide more comprehensive care for patients, while the main monitoring devices are generally connected to the 5G wireless network to ensure the life safety of patients at all times. A mobile nursing system (23). A smart nursing system can be established in the ward area based on 5G network wireless technology to measure and record patient indicators such as body temperature, heart rate, and blood pressure. Meanwhile, physical sign forms and nursing evaluation forms of different patients can be issued accordingly. Additionally, the application of 5G wireless network technology in clinical nursing can help to arrange nurse work, thus improving nursing efficacy.

The first 5G hospital mobile nursing PDA was launched to accelerate the establishment of new smart hospitals based on 5G network technology (24–27). Based on this, paramedics can obtain basic and nursing information about the patient by scanning his/her wristband bar code using a 5G nurse PDA handheld terminal. Meanwhile, each patient is evaluated individually, and personalized nursing plans and health education are provided to effectively relieve the work pressure on nurses. Besides, before infusion, the medical staff uses the PDA to scan the patient barcode and infusion bag barcode to guarantee infusion safety and eliminate infusion errors.

5G network and AI are two hot topics in the field of science and technology. As a novel communication infrastructure, 5G technology provides a basis for efficient and reliable transmission of a huge amount of data and information. AI achieves information learning and evolution with a cloud brain and a neural network. Their combination will promote the development of ward-round robots that can realize real-time remote ward-round to reduce the burden on nurses (28, 29). In terms of disease prevention, diagnosis, treatment, and nursing, 5G network technology supports real-time transmission of huge data on human health and helps medical institutions in continuous physical monitoring of wearers. In this way, continuous monitoring and sensory processing devices are developed, and real-time data of patients are continuously collected. Based on these data, AI can record and analyze individual patients comprehensively and continuously so that personalized healthcare schemes can be formulated. Meanwhile, doctors can make remote judgments and analyses according to relevant data such as medical records and images, and provide personalized treatment and nursing schemes in time (28, 30, 31). Additionally, the 5G+AI system enables multi-party simultaneous consultation and connection with other hospitals and peers in a 7×24 manner, and multidisciplinary consultation can be held anytime, thus enhancing diagnostic accuracy.

Kuroda et al. (32) proposed a clinical sensor network system to complete data input that is previously done by nurses, thus enhancing nursing efficiency and security. Meanwhile, intelligent management of special patients can be achieved using the Internet of Things (IoT) and 5G network technology. Through portable devices, each patient can be accurately positioned and tracked so that the nursing management is humanized. The Sichuan Cancer Hospital developed a 5G medical private network consisting of remote CT imaging, AI sketching, and remote radiotherapy, which is significant to tumor treatment. Also, 5G networks can determine the specific location of a patient, which makes a great contribution to healthcare. For instance, if a patient has an emergency outside the ward, the medical staff can quickly and accurately position him/her to avoid accidents.

Optimization of the infusion system

The application of 5G wireless network technology in hospitals can help to solve the important task of infusion system optimization (16, 33). Outpatient and emergency infusion rooms involve a series of steps, including dispensing and puncturing, and mistakes may occur in the infusion environment if there are a large number of patients. With the assistance of 5G wireless network technology, a mobile infusion information system can be developed, and paramedics can check the patient's identity and bar code of medicine to avoid mistakes. Additionally, the specific execution records of paramedics can be synchronized to the mobile infusion information system, providing immediate feedback on patient needs and enhancing nursing efficacy.

Pre-hospital emergency care

In cases of emergency such as chest pain, first aid is of great significance. 5G network and AI-assisted equipment allow communication between the ambulance and experts in the hospital and transfer vital signs, images, and other critical information in real-time (34, 35). In this way, guidance by experts can be delivered as early as possible, and emergency nurses can access the personal information, vital signs, and examination results of the patient at any time so that the best opportunity for treatment can be obtained (36). Additionally, sufficient preparations before admission can be made to make full use of time for treatment (37).

Disaster nursing training

Paramedics play an irreplaceable role in disaster relief. At present, only a few hospitals and medical colleges in China, offer teaching content related to disaster nursing. The incomplete knowledge system and absence of training for clinical nurses lead to an insufficient reserve of paramedics for disaster relief.

Due to the unique characteristics of disaster nursing, it is difficult for paramedics to practice in real situations. Current training methods mainly include scenario rehearsal combined with problem-based learning, hierarchical training method, action learning method, and multi-station simulated rehearsal method. The training specialized for disaster nursing needs to be optimized. The application of 5G network technology can change both training methods and concepts (25). 5G teaching enables trainers to constantly update their knowledge. Meanwhile, it makes the learning of trainees more autonomous and equips trainees with more learning choices, stronger practical capability, and more careful logical thinking. Especially, the combination of 5G network technology with virtual reality simulation and AI can simulate various disaster scenarios. It can convey information in multiple ways (e.g., text, image, sound, animation, and video) and attract the attention and embodiment of trainees (38). In this way, trainees can improve their emergency-dealing capability and operation capability by training in virtual scenarios created by real-time simulations, without limitations by time, space, and resources.

On-site rescue in disaster nursing

Nowadays, various disasters (e.g., tsunami in the Indian Ocean, Wenchuan Earthquake, and floods in South Africa) occur frequently, and medical rescue is facing a severe situation. Doctors and nurses are exposed to challenges that are more arduous than those in any other time of history. However, disaster nursing in China started late and has a huge gap with developed countries. Therefore, advanced technologies should be actively combined to improve the personalized nursing quality of paramedics in on-site rescue, thus enhancing rescue efficiency. With the assistance of 5G network technology, rational decision and allocation of first-aid resources for medical support in large-scale disasters and emergencies can be achieved using AI to enable effective and efficient handling of various disasters or emergencies by paramedics (25). The high-tech equipment based on 5G network technology (e.g., 5G ambulances, high-resolution remote video interactive systems, VR real-time panoramic experiencing systems, GPS positioning systems, UAV, and rescue robots) can provide real-time, accurate, and efficient recording of vital signs and pathophysiological information of patients (13, 39–41).

The development of the equipment also integrates cloud transmission and analysis technology, medical examination, and data transmission techniques. Additionally, remote consultation and operation can obtain comprehensive yet real-time information about patients, and even provide guidance and remote operations in specialized scenarios such as wound treatment and intravenous infusion nursing, thus improving nursing quality and efficiency.

Telemedicine

In the post-epidemic era, it is important to reduce the period and times of patients going to the hospital, simplify the diagnosis process, shorten the treatment period and facilitate patient treatment by using the Internet and 5G information technology (16, 42–44). Some hospitals in China have distributed electronic bracelets to patients to upload their temperature, heart rate, and blood pressure of the patients to the database as long as the electronic bracelets are with the patients every day. Then, the uploaded data are analyzed to provide guidance on diet, psychology, medicine, functional exercise, and intervention in dangerous situations. Meanwhile, the devices consist of reservation and registration, remote service, and emergency warning systems, which automatically make an appointment for the hospital process in cases of abnormal data uploading or vital signs to ensure a smooth medical process.

With the support of 5G network technology, information channels between hospitals, nursing institutions or communities have been developed, and services meeting diversified and personalized home care needs have been provided (13, 44, 45). Based on this, remote discussion on death and discharged medical records and remote teachings such as protection training and safe nursing training are conducted in an end-to-end mode and multi-party meeting. Meanwhile, intelligent data collection and process recording can be achieved by wireless communication and sensing technologies. The results are given after cloud processing and data analysis to make patient monitoring outside the hospital more convenient and efficient.

In the future, China will face severe population aging, and the incidence of senile diseases will increase correspondingly, resulting in increased demand for medical services. At present, China is exposed to an unbalanced distribution of medical resources and limited access to medical treatment in remote and under-developed areas. In this case, the growing demand for medical resources can only be satisfied by optimizing medical resource allocation and improving medical service efficiency. Patients in some areas can enjoy remote expert consultation and treatment in local hospitals or at home. Attributed to the wide application of 5G network and wearable devices and real-time transmission of vital signs and examination results, online diagnosis and treatment can be obtained regardless of regional restrictions, realizing rational allocation of medical resources (12, 46, 47). In this way, treatment efficacy is enhanced, and treatment time is reduced. Meanwhile, online teaching, nursing teaching, remote operation guidance, and case discussion can be made accessible to the medical staff at the grassroots level to improve the medical efficacy in remote areas.

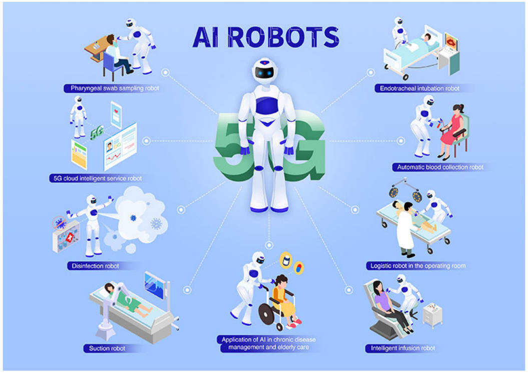

FIGURE 4
Application of AI robots in personalized nursing.

Medical data sharing

Currently, medical services in a hospital are relatively independent. Specifically, ultrasound and imaging examination, blood examination, treatment, and nursing are completed in different departments. Diagnosis and treatment require access to raw data information, including CT and MRI, which is impossible without information sharing between different departments. Currently, most hospital information systems support information sharing within the hospital. However, nurses have no immediate access to the historical data of patients kept by other medical institutions due to the limitation of network communication and transmission capacity. As a result, further development of regional medical treatment is limited. With advantages of large bandwidth, short delay, and network slicing, 5G networks can facilitate network interconnection, information sharing, and rational allocation of medical resources among different medical and health institutions in the region (15, 48–50).

AI robots

As an emerging discipline, AI is developed based on computer science, neuropsychology, philosophy, linguistics, control, and information theory (51). AI has been in the field of nursing for over four decades. Medline database was first mentioned in 1985 when expert systems were introduced to provide clinical decision support (52). Joseph Engelberger, the "Father of robots", invented the intelligent nursing robot "Helpmate". It is mainly used to provide smart care to the elderly living alone, and it can independently complete nursing work such as medicine delivery, meal delivery, nursing, and accompanying (53). The research on AI in medicine and health has grown rapidly in the last decade (Figure 4) (54).

Pharyngeal swab sampling robot

Under the background of the COVID-19 epidemic, rational use of pharyngeal swab robots can prevent the infection risk of medical staff exposed to nucleic acid testing, standardize nucleic acid sampling by pharyngeal swab, and improve the quality of oral nucleic acid sampling by pharyngeal swab. The robot system can realize the nucleic acid sampling and the examination of human oral respiratory tract pharyngeal swabs under visual guidance. It mainly performs initial positioning of the human intraoral cavity, taking throat swabs, oral throat swab nucleic acid sampling, and storing throat swabs. During the COVID-19 epidemic, the first pharyngeal swab sampling robot in China was proposed by a team led by Zhong Nanshan. The proposed robot can realize high-quality pharyngeal swab sampling and cause no adverse reactions to the subjects (55). It can be used for automated nucleic acid sampling of subjects by hospitals or communities. In the near future, personalized localization of individualized oral cavity, automatic extraction of the pharyngeal swab, automatic nucleic acid oral sampling, packaging and storage of pharyngeal swab after sampling, and recording of the information of the testing subject may be achieved. Combined with 5G networks, network data sharing with different regions will be enabled, which is of great significance to the prevention and control of the epidemic.

5G cloud intelligent service robot

5G cloud intelligent service robots can guide patients and broadcast epidemic prevention knowledge, thus greatly reducing staff workload while meeting the personalized needs of patients. Meanwhile, the risk of cross-infection is reduced.

The outpatient department of the first affiliated hospital of USTC (Anhui Provincial Hospital) imports AI technology to assist patients in APP registering, payment, triage, and report printing. It supports multiple interacting modes (e.g., sound and image) and can provide information broadcasting, communication, and other services in non-crowded waiting areas to provide healthcare education to physical examiners, thus improving medical experience and service quality. By combining 5G networks and online platforms, this robot employs online cloud processing instead of local deployment computing, making it intelligent and highly sensitive.

Disinfection robot

Because of their long history and mature technology, disinfection robots have distinct application advantages in the post-epidemic era (56). 5G cloud intelligent robots can realize medicine distribution in epidemic areas, preparation of disinfection solution, and floor cleaning and disinfection. For example, a robot with a disinfection water tank can complete infection following a specified route in an unmanned way. It saves human capital, improves cleaning efficiency, and greatly reduces the risk of cross-infection caused by long-term exposure to the inpatient area.

Suction robot

Remotely controlled or automated robots can replace paramedics to effectively reduce the close contact between paramedics and infected patients, as well as the exposure to high concentration droplets and aerosols in the air, thus reducing the infection risk and relieving the psychological burden and workload of paramedics. Meanwhile, the probability of iatrogenic cross-infection can be reduced. This is especially important during the COVID-19 epidemic. Tan et al. (57) developed an intelligent suction robot, which simulates practical sputum suction by imitating the rotation of the mechanical arm and hand. The proposed robot can effectively suck out sputum in the simulation model. Furthermore, the researchers improved the mechanical arm, i.e., the motion unit of the suction robot, so that the mechanical arm is stable during sputum suction, further increasing the success rate of tube delivery. Lokomat can assist patients with stroke, brain trauma, and spinal cord injury in gait training and improve functional recovery efficiency of lower limbs, while KNRC can complete feeding and care of patients with spinal cord injury (58, 59).

Endotracheal intubation robot

Wang et al. (60) proposed a minimized and portable remote robot-assisted intubation system (RRAIS). Animal tests revealed that the proposed robot system improved the at-first-attempt success rate and overall success rate compared with artificial laryngoscope intubation. Endotracheal intubation is performed by using the full magnetic navigation technology without opening the airway. Under guidance by an external magnet, the response magnet in the body moves to a preset target area. Meanwhile, a pilot strip is developed by placing a magnet at the tip of the endotracheal intubation guide. The tip can flexibly change orientation under a magnetic field. Additionally, the tip of the pilot strip can be shifted to the trachea by loading the external navigation magnet in the anterior cervical area. The feasibility and relatively high success rate of endotracheal intubation robot systems have been verified by human models and/or animal tests. However, these robots remain semi-automated and require assistance from paramedics (insert the machine and the endotracheal tube into the mouth). Thus, the unmanned, intelligent and personalized functions of these robots require further optimization.

Automatic blood collection robot

Venipuncture is the most common clinical surgery globally, with 1.4 billion performed each year in the USA alone. However, 27% of patients are exposed to unclear veins, 40% of patients are exposed to invisible veins, and 60% of patients are too thin for venipuncture. Leipheimer et al. proposed a blood collection robot (VeniBot), which is composed of an ultrasonic-image guided robot (drawing blood from veins) and integrated equipment consisting of a sample processing module and a centrifuge-based blood analyzer (61). Balter et al. (62) proposed a venipuncture robot that adopts near-infrared and ultrasonic imaging technology to select injection sites and insert the needle into the blood vessel center using a 9-DOF robot under image and force guidance. Also, a medical device is developed for end-to-end blood detection and providing diagnostic results at the nursing site fully automatically.

The Magic Nurse company developed a blood collection robot that can automatically achieve full-chain blood sample collection, including loading of blood collection vessel and needle, binding pulse-pressing belt, identifying venous vessels, spraying disinfection solution, accurate puncture, control of blood collection volume, and blood sample mixing. During the operation, the robot detects the vascular conditions of the patient to intelligently determine the personalized position, orientation, and angle of puncturing. The patient is only exposed to slight pain when puncturing and no pain after puncturing.

By combining machine vision technology and intelligent navigation control technology based on biometric technology and biometric-based intelligent navigation control technology, the blood collection robot can accurately identify the position, depth, and direction of blood vessels. Also, it can intelligently plan and navigate the puncturing path. In practical applications, the robot achieves a high success rate in blood collection and can realize intellectualization, informatization, and standardization of vein blood collection.

Logistic robot

The high-value consumables used in the operating rooms are characterized by a huge amount, various classifications, and high prices. Thus, researchers from the Bio-simulation Research Center in Nagoya, Japan developed the robot RI-MAN by combining organic materials with intelligent sensors. RI-MAN can safely transport patients and complete transfer operations, which is previously done by nurses (63).

The unique automatic delivery robot automatic transmission system takes the mobile robot as the carrier, and it is an autonomous driverless automatic handling system powered by batteries. With the popularization and promotion of various advanced sensor technologies and information technologies (e.g., positioning, obstacle avoidance, identity recognition, and automatic charging), the new intelligent logistics solutions can greatly improve the efficiency of logistics distribution in the operating room and save a lot of manpower (2, 3).

Shanghai Ruijin Hospital developed a logistic robot called NuoYa based on 5G, AI, and unmanned driving technologies. This robot can realize "dynamic object recognition", "intelligent scheduling", and "intelligent IoT" in the hospital and create a perfect full-scene, intelligent and real-time scheduling system for hospitals, achieving automatic distribution of materials within the hospital. 5G networks with ultra-large bandwidths are employed to transmit high-definition images around the robot to the server in real-time. Meanwhile, obstacles are identified and tracked through the deep learning algorithm. In this way, the robot can move freely, safely, and efficiently in the complex environment of the hospital. In Renji Hospital affiliated with Shanghai Jiaotong University, logistic robots have been used in operating rooms for the transportation of high-value consumables, instrument packs, and quilts. With these robots, utility nurses that walk frequently in and out of the operating room are not needed, and whole-process closed-loop management of materials can be achieved in the operating room. Additionally, human errors can be prevented, transportation efficiency can be improved, and human capital can be saved. For example, two robots can cover 20-25 operating rooms, and each robot can save about 30 min of round trips by nurses each time. The nurse may use this robot to carry medications, food, drinks, blankets, newspapers, and other important supplies to patients. The robot is equipped with infrared sensors for line-following and obstacle identification (31).

Intelligent infusion robot

Currently, nurse shortage, low puncturing efficiency, and the unbalanced distribution of medical resources are severe issues in the medical field. The intelligent infusion robot "FUXI" developed by the Fuxi Jiuzhen Intelligent Technology (Beijing) Co., Ltd combines AI, 5G networks, and big data, and it integrates infrared image recognition, ultrasound, and pressure sensing. Based on this, its puncture success rate reaches 96%, which drastically reduces expenditure on consumables, enhances utilization efficiency of resources, and relieves mismatch of nurse resources. In the future, intelligent infusion robots will be applied in various scenarios, including home nursing and emergency support. To date, the FUXI robot has been used in over 5,000 cases of animal tests, collecting 10,000 ultrasound images of human hand veins and over 100 cases of human-based experiments. A new generation of the robots with a puncture success rate of 100% is also being developed.

Application of AI in chronic disease management and elderly care

AI can simulate medical staff to provide individualized diagnosis, treatment, and nursing while meeting the needs of patients with chronic diseases for nursing services. Meanwhile, combined with digital therapeutics, AI can realize intelligent nursing management and clinical decision optimization. Berman et al. (64) proposed the digital therapeutics called Fare well, which consists of applications, remote sensors, and healthcare guidance provided by digital measures. After 12 weeks of diet and exercise intervention, 57% of patients exhibited decreased glycosylated hemoglobin and reduced use of medicine for diabetes. Attributed to the advances in AI, diabetes can be diagnosed, and diabetes-related complications can be predicted based on a computer-aided diagnosis (CADx) algorithm (65, 66). The CADx-based 5G intelligent diabetes monitoring systems can analyze the information of patients using big data and different machine learning measures, thus guiding personalized nursing of these patients (67).

Zeevi et al. (68) monitored the blood glucose of 800 patients for 1 week. Then, a machine learning algorithm integrating blood parameters, eating habits, anthropometric indicators, physical activity, and intestinal microbiota was proposed for personalized prediction of postprandial blood glucose. The experimental results demonstrated that AI-based personalized diet recommendations can effectively improve postprandial blood glucose and metabolism, thus providing objective references for long-term blood glucose control. Maeta et al. (69) analyzed the oral glucose tolerance test index of diabetic patients using the XGBoost machine learning algorithm. The method can effectively identify early symptoms and impaired glucose metabolism of Type-II diabetes (T2DM). Also, it helps to analyze disease progression and risk trends of patients, thus facilitating accurate treatment and nursing. These personalized AI-based interventions can effectively prevent and treat diabetes, improve the daily management of diabetes care, and reduce the risk of long-term complications (70).

In the medical field, the most mature application of AI is in intelligent elderly care (Table 1). By 2020, empty nesters in China would reach 118 million. Therefore, providing personalized nursing to the elderly, especially empty nesters, is of great significance. In the 1990s, developed countries such as USA and UK started the research on accompanying robots. Early robots were anthropomorphic ones with simple structures, stiff movement, and limited practicability.

By utilizing the AR technology, the operator can determine whether the remote robot follows the intended motion of the operator or fails due to overload or some problems. Meanwhile, the use of AR and VR technologies can facilitate remote control without depending on complicated platforms. The recent development of AR and VR technologies is creating

TABLE 1 Different types of home nursing robots.

AI robots in home nursing	Functions and applications
Accompanying robot	With the shape of a cute seal, the Paro (71) robot makes a vivid response (e.g., excited, sad) through the limbs to tactile stimulation of the machine (51). It can also adjust the patient's mood and monitor psychological changes.
	Elli.Q robot (72, 73) can collect information through communication with the elderly, comprehensively analyze his/her preferences and habits, recommend personalized activities, and monitor physical condition.
Intelligent diet robot	Handy 1 robot (72, 73) uses a five-DOF (degree of freedom) mechanical arm and three detachable trays to meet different needs. The laser scanning system takes food, while the mechanical arm puts the food into the patient's mouth.
	Winsford Self-Feeder robot (74) assists in eating using two mechanical arms. One mechanical arm is equipped with a spoon, while the other pushes the food on the plate into the spoon. When eating, the patient touches the jaw switch and the mechanical arm assists the patient to eat.
	My Spoon robot (75, 76) comprises one six-DOF mechanical arm fixed to the plate bottom and one fixed bowl. The user can operate by jaw movement, foot movement, or manual operation. It can assist patients paralyzed below the neck and elderly with stiff limbs to eat by themselves.
Logistic robot	Logistic robot NAO (77) can recognize images and sounds and perceive the surrounding environment through a CPU installed in the brain, a touch sensor, and a sonar system. It can complete the operation by sound and image recognition to realize a fully programmed process.
	Herb robot (78) can accurately identify the surrounding objects or environment by using sensors and non-visual signal devices to handle and transfer the elderly.
	Robear robot (79) can lift the elderly with a low walking ability off the bed and assist user to move. The machine is equipped with sensors, allowing a high-precision tactile perception of the robot. It can obtain the body mass index of the user to be moved upon touching him/her.
Nursing robot for disabled elderly	PerMMA robot (80): patients can operate the robot through a variety of interactive interfaces (e.g., microphone, joystick, or screen touch) according to their personal needs. The robot can handle daily affairs, including cooking, dressing, and shopping.
	Walking-assistant robot Welwalk WW-1000 (81) is specially designed for stroke patients and other patients with limited movement on one leg. A bracket with a motor is fixed between the knee and the lower leg to assist the user in flexion and extension. Also, it can help the user to keep still and maintain balance during movement.
	Life-assistant robot Human Support Robot (HSR) (82) can be operated remotely through voice and/or tablets to pick up objects on the floor or shelves far away.
	Nursing robot Robear (83) is equipped with an intelligent rubber, touch sensor, and torque sensor. The robot can sense the user and prevent him/her from injury. It can carry the elderly and provide support for his/her standing and walking.
	VGo robot (83) can realize telemedicine (disease monitoring and consultation communication) and promote personalized medical service between doctors and patients and health management. It can also monitor patient recovery and answer questions about health and medicine at home.
Chronic disease nursing robot	Kompa robot (84) can monitor the vital signs of the elderly in real-time and deliver the latest symptoms to the doctor via email. It can generate shopping lists and establish video conferences to facilitate doctor consultations.

new crossroads for which we are just beginning to understand (Table 2) (91).

Medical cloud VR/AR can render and model real-time computer images. Based on the large bandwidth and low delay of the 5G technology, the security and accuracy of telemedicine and nursing can be greatly improved, and AI can provide personalized medical and nursing solutions (4). Also, the VR technology coupled with the 5G network is featured with high resolution, high fluency and high authenticity, which makes VR scenes and sensory stimulation more realistic and refined, This will greatly improve the effectiveness of rehabilitation treatment and reduce the occurrence of VR stickness (1).

An Internet of an entirely new dimension will be created for machine-machine and human-machine interactions, which can provide a supper coverage network with low latency, high reliability, and high security. These are the changes for constructing real-time interactive systems (92). The combination of AI units, IoT devices and 5G communication services can transform the traditional healthcare scenario into a new scenario (Table 3) (94, 111–115). AI and 5G communication can assist clinicians and nurses by providing remote care settings directly to the patients (116). Meanwhile, the advanced analytics in AI machines can help decision-making and disease diagnosis, and the remote monitoring of patients helps to reduce hospital stays and prevents re-admissions (94, 95).

The interactions between patients and doctors have become easier and more efficient, which leads to higher service satisfaction. If any disorder or emergency occurs when monitoring patients through data analysis, an alarm will trigger the smart emergency services (e.g., ambulance) automatically

TABLE 2 Smart healthcare with 5G+VR/AR.

5G+VR/AR	Applications
Human system interface (intelligent robot)	It enables users to send and receive sensations in real and virtual environments (85).
VR-based Microsoft Kinect REMOVIEM system	It can be used for various home-based physical rehabilitation therapies especially for older adults (86).
Robot with VR telepresence	It can significantly reduce the operator's cognitive workload (87–89).
Remote-controlled robots with VR	It can complete common nursing duties inside hazardous clinical areas, thus helping to reduce the exposure of healthcare workers to contagions and other biohazards (89).
Robot-assisted optical camera communication (OCC) System	It can monitor the health conditions of people at home or in a hospital (90).

TABLE 3 Smart healthcare with 5G+artificial intelligence.

5G+artificial intelligence	Applications
Artificial humanoid robot	It can activate memories and emotions and can be accompanied by training programs that help people to accept nonhuman relationships (93).
The advanced analytics in AI robot	It can make decisions and disease diagnoses effectively (94, 95).
Remote monitoring robot	It helps to reduce the length of hospital stay and prevent re-admissions (94, 95).
Rehabilitation robot	It can sense the human kinematics and physiology data of patients through various sensors, and formulate a reasonable treatment plan (96).
Remote-controlled medical robot	It keeps a track of the health conditions of patients, makes necessary arrangements for regular check-ups, and even books appointments (97).
Telepresence robot	It helps caregivers in this task by providing audio and visual feedback to the caregiver (98).
Sam robot	It assists the medical staff in providing frequent check-ups and nursing patients personally at their residents (30).
Digi robot	It is used in reminding staff to provide treatment or medicine to patients and can help enforce social distancing and ensure the safety (28, 97).
Telecontrolled robot	It can efficiently address cognitive decline issues by reminding care-receivers when to eat, drink or take medication, and do exercise (97, 99).
Guide robot	It can detect the surrounding environment and process and feedback information to help users effectively avoid obstacles (100).
Self-governing robot	It helps the nurse to interact and take care of the patients and can also always perform accurate surgeries (97, 101).
Social robot	It can just interact with humans by abiding by a set of rules and social behaviors (97, 102, 103).
Endoscopy robot	It can be used to take biopsies from the tissue to test for diseases and conditions (including anemia, bleeding, inflammation, diarrhea, or cancers of the digestive system) (97, 104–106).
Sister robot	It can help frontline health professionals communicate with patients in the isolation room and deliver essential foods and medicines as well (107).
5G-enabled Telesurgery robot	It facilitates the outreach of the underserved population as well as the much-needed collaboration among the surgeons across various centers in real-time (25, 108–110).
Tele-nursing robot	It can gather vital signs, and perform a wide range of manipulation tasks in a quarantine area (89).

with the patient's details such as health reports, exact location, possible necessary medications, etc. Though the ambulance will send the patient to a hospital, the nearest health units will also be notified about the emergency case so that the patient can obtain timely care (117). It should be noted that self-determination medicine based on the algorithm and high-speed interactive information is different from personal or individualized medicine. Especially, the diagnosis and treatment plan will be timely, dynamic, and interactive, which enables individual status feedback about lifestyle elements, behavioral factors, and treatment effects and helps patients to obtain clinical services easily (118).

With cloud computing, sufficient resources are provided to robots to help them complete computation-intensive tasks, such as emotional recognition and feedback. This extensively improves robot intelligence and user experience (Table 4) (119). Dyumin et al. (120) proposed a structure for Cloud Robot, while in Ma et al. (121) developed a household healthcare robot. In a word, the robot integrated with 5G and cloud computing has gradually become a hotspot in this field.

TABLE 4 Smart healthcare with 5G+cloud intelligence.

5G+cloud intelligence	Applications
Cloud computing robot	Sufficient resources are provided to the robot for complete computation-intensive tasks (119).
Cloud-enabled Robot	It proposes a household healthcare robot integrated with a motion sensor and camera (120, 121).
Robot with 5G cognitive system	It is used for healthcare with a resource cognition engine and a data cognition engine. It can realize cognition of resources and realize cognition of healthcare business (10).
Cloud-assisted Robot	It can communicate with people and placate them in real-time as well as detect and transfer their emotions swiftly (122–124).
EPIC-Robot	The intelligent terminal receives the emotional results and guides the robot to achieve a real-time emotional interaction between the robot and the user (10, 122).
Cloud robot	It is connected to cloud computing infrastructure and shares training and labeling data for robot learning (125, 126).
Fog robot	It is addressing technology that is based on robot systems that use fog computing for processing data and services (127).
Cloud-enabled logistic robot	The distribution of high-value consumables in the hospital by the robot can effectively shorten the time of consumables application, and the distribution and the information are accurate with cloud computing (1, 128).

The "RIBA" nursing robot is specially designed for the elderly who are inconvenient to move. The robot can steadily and smoothly lift the patient off the bed and send him/her to the toilet, bathroom, or dining room (129). The LIECTROUX nursing robot (LIECTROUX ROBOTICS GmbH.) can independently perform health status testing, medicine taking, feeding, quilt folding, and transportation to the bathroom while recording the relevant information of the patient. Besides, this robot can protect the patient from injuries and work in a 7 × 24 way because it supports wireless charging once the battery is low.

A robot for patients with Alzheimer's disease is also reported. It enables patients to actively participate in the treatment by psychological induction, psychological conversation, and psychological hypnosis. Also, it plays the music that the patient is interested in to cheer him/her up. Besides, it helps patients to do moderate exercise as physical exercise can improve physiological health and the ataxia, which is related to the cerebellum. This robot can provide personalized care for patients at different stages according to specific conditions of the patient. In this way, the physiological and psychological pressures of patients with Alzheimer's disease can be greatly alleviated.

The "Zora" nursing robot can independently perform exercise facilitating, book reading, storytelling, and communicate with the elderly through voice recognition (130). Nursing robot Care-Obot 3 can do housework and communicate emotions by language. It has been used to take care of patients with walking difficulties and empty nesters (131). Indeed, it can help the elderly with disabilities to get rid of negative feelings, such as self-abasement and feeling lost (they regard themselves as a burden to the family and the society).

Challenges and prospects

Despite the wide application of hospital information systems, it is still challenging to integrate 5G networks with hospital information systems. First, cyber security should be further improved: applications of 5G network technology in smart healthcare involve multiple parties and aspects, which are exposed to a high security risk. Meanwhile, the application of 5G networks allows data sharing in the medical industry, but there are differences in the informatization degree of medical institutions in different regions, bringing risks to the quality and information security of medical data. Therefore, it is crucial to further strengthen the security of 5G networks. Besides, AI systems collect data such as vital signs, health conditions, eating habits, and medication details. Indeed, should actively participate in the design and optimization of AI systems. Also, AI experts should work with ethicists to develop corresponding systems and norms, establish an early warning system, clarify the responsible party for AI-induced risks, and standardize the authority of data collection and application.

Due to its late start, the smart healthcare industry in China suffers from a severe contradiction, and the supply-demand connection is ineffective, resulting in a dilemma where the platform is present, but the service is not. Meanwhile, smart healthcare is currently limited in the research in hospitals and colleges, and thorough market analysis is lacking. As a result, products/services provided cannot meet the diverse, multi-level, and personalized medical and nursing needs of the patients.

On the other hand, the effective need for smart healthcare is limited. Due to influences by traditional concepts, living habits, and education level, patients exhibit extremely limited cognition and acceptance of smart healthcare, and they have a low capacity for using smart products and insufficient financial capacity for smart healthcare services, resulting in a significant reduction of the effective need of smart healthcare by patients with chronic diseases. Besides, the application of AI in nursing leads to a novel nurse-patient relationship, as well as new challenges in nursing (132). Parviainen and Pirhonen (133) claimed that AI is an intermediate between nurses and patients and it allows reduced contact between patients and nurses at the cost of humanistic care. Sparrow and Sparrow (134) believed that AI cannot provide emotional communications, so patients tend to feel no respect.

Currently, AI nursing robots can perform reading and storytelling but cannot meet the emotional needs of patients. Meanwhile, this communication mode reduces communication efficiency and may intensify contradictions. AI nursing supports a wide range of functions, but it is limited by low applicability and feasibility. Due to the absence of paramedics in the early stage of design and development, most AI products cannot predict and solve practical problems. Besides, AI nursing leads to a situation where personalized nursing is not possible because patients and nurses can only passively accept and use existing functions. However, nurses are often not involved in the early analysis, development, and design phases of precision medicine and AI, and they only contribute their expertise in the late phases of testing (135). Moreover, nurses' involvement in AI research and co-design is also constrained by the lack of a common vocabulary and understanding between the experts in nursing and technological domains (136).

Social interaction is a huge challenge for robotics because of its significant perceptual demands. When a response to a social cue or body language is delayed, it may be interpreted as uncertainty or mistrust. Thus, it is necessary for robots in the workplace to better understand people and their intentions as well as predict their movement. Meanwhile, considering that safety is vital, robots must know what is in the environment and take action correspondingly. To achieve this, one approach is to study body language from body movements, postures, and facial expressions.

Another major limitation in applying these wireless technologies in health systems is inaccessibility to human emotions. The technology-based health interventions (including 5G) are not widely used in this field due to the lack of proximity of these modern modalities to the major stakeholder, i.e., the patients. Recently, researchers are trying to overcome this limitation by introducing the 5G-based cognitive system (5G-Csys) with speech emotion recognition (10).

Due to some problems in their development and application, most robots can hardly be practically applied. Thus, user-friendly robots with high security, low cost, and high flexibility are urgently needed to mitigate the present challenges and provide intelligent and user-friendly nursing services.

More attention should be paid to cyber security management because the medical industry has high requirements for security, reliability, and quality of data. To guarantee medical safety and protect patient privacy, we should propose a novel safety management mode, and intensify research and development in cyber security. Meanwhile, we need to improve safety management rules, operating procedures, and technical specifications to ensure good safety and reliability of the 5G smart medical network, data, and equipment. In 2017, AI experts in the USA jointly signed the Asilomar AI Principles (The 2017 Asilomar conference) and appealed to AI professionals globally to follow this principle to guarantee the future interest and safety of human beings. Besides, issues in security and privacy induced by data acquisition and application were emphasized.

The medical private networks and a balanced development should be promoted. At present, the levels of medical information networks used by medical institutions in different regions are drastically different from each other. However, an absence of network conditions may lead to the unavailability of some equipment or software systems, thus hindering the development of smart healthcare. Therefore, it is urgent to accelerate the construction of medical private networks, especially the fundamental networks in under-developed areas. In this way, access to the large 5G network can be provided, thus laying a solid foundation for the development of telemedicine.

Tactile Internet introduces a new dimension to human-computer interaction through building a real-time interactive system with low latency. 5G network plays an important role in the wireless field and shows its breakthrough potential (137), which greatly enhances the ability of touch and skill transmission (138), and realizes immersive remote operation and interaction with the physical world.

At present, only scholars adopt 5G technology and the latest development of AI and robotics to propose the new concept of 5G tactile Internet (139), but the combination of the three is less applied to the field of intelligent medicine. Remote diagnosis, remote surgery and remote care are components of many potential applications in the tactile Internet, and they can remotely provide real-time control and physical tactile experience (138). The popularity of the 5G network will provide an opportunity for remote implementation of personalized diagnosis and treatment and nursing.

The significance of setting a clear social and legal boundary for the relationship between robots and humans should be emphasized to guarantee the safety and privacy of the caregivers and patients. In future developments, more multipurpose robots should be developed to assist caregivers in various situations, and this can be realized through more cooperation between developers and caregivers (31).

In the future, computers will play a more complementary role in clinical applications by automating the routine matters that medical staff must conduct. In this approach, more space will be created for computers to participate in non-routine health decisions that humans can manage better. Meanwhile, doctors and nurses will likely promote the use of information technology because of its benefits. They can exploit their intuition and experience to oversee the working of algorithms and AI. Moreover, medical workers can manage personalized care better than a machine (116).

The original intention of AI nursing is to provide improved personalized nursing service and alleviate the shortage of paramedics. Hence, nurses shall actively participate in research and application of AI nursing so that AI nursing products with high professionalism, rational applicability, and excellent feasibility can be developed. Meanwhile, they should keep a detailed record of problems encountered during the use of these products to facilitate optimization. Based on 5G mobile communication technology and AI platforms, AI nursing meets personalized healthcare and nursing need, changes the current mode of medical service, and improves nursing quality. In the future, the construction of 5G intelligent hospitals will further combine the technical advancements in multiple disciplines such as biomedicine, robots, communications, and medical information to realize a real interconnection between healthcare and information technology, thus providing optimized conditions for diagnosis and treatment and nursing. The integration of computer and network communication technology into the field of medical service greatly enriches the connotation and capacity of medical information, and it allows full-path, accurate, and personalized services during the entire medical process. With the support of national policies and the premise of ensuring the security of medical information, 5G network technology will further facilitate medical transformation and improve the level of medical services so that patients can enjoy safe, convenient, and high-quality medical services.

AI robots that can provide senior care are crucial to China's aging society. To satisfy the needs of today's senior citizens, technology companies should solve this social issue by working with hospitals, medical staff and engineers, and people from different social, cultural, and humanitarian backgrounds (e.g., social scientists and public policy experts). It is important to engage more talents in the rising intelligent senior care industry to fill the technology gap and develop more user-friendly products and services for senior citizens. Besides, it should be noted that robots cannot replace humans for physical and emotional companionship.

It has been shown that personal assistant robots with support functions can assist older people to obtain better life quality through physical and mental exercises (140, 141). An advantage of telepresence robots is the timely treatment of patients with urgent needs, thus leading to shorter hospital stays (142). Meanwhile, these robots enable the user to communicate with friends and families, especially if the user is in social isolation. Besides, many of these robots are multi-functional, and they can check temperatures, analyze coughs, monitor emotions and conduct questionnaires through various sensors they are equipped with.

Machine learning is another field that should be concerned because robots need to make decisions, perform sensing, adapt to environments and learn from actions to achieve further improvements. In this approach, robots can perform more complicated tasks at a higher rate and use low-cost sensor alternatives in the future. For example, in a medical emergency, intelligent robotic systems can help an emergency medical technician (EMT) to insert breathing tubes or intravenous lines and transport the patient to the hospital. This greatly improves the ability of an EMT to provide urgent care. However, the main challenge for this is to adapt to new environments, so it is crucial to specify the task correctly for the robot.

As the number of remote-end applications increases, the fast-growing healthcare industry requires a powerful communication network to effectively connect patients, healthcare professionals, medical equipment, etc. to achieve information sharing. As the next evolution of wireless connectivity, 5G mobile networks will promote telemedicine and transform the future of healthcare delivery (143).

The promising features of 5G networks provide a basis for new exciting services, such as 5G eHealth. 5G networks can help to formulate novel eHealth solutions and deliver eHealth services globally, especially for remote caring, mobile health services, and smart pharmaceuticals (90).

As 5G and other emerging technologies confluence, such as the Internet of Things (IoT), big data, Artificial Intelligence (AI), and Machine Learning (ML), the application of these technologies to augment human capacity and improve the effectiveness of human potential will greatly change the healthcare industry. In the near future, 5G technology will facilitate novel healthcare applications and promote the development of healthcare services by integrating patients, medical practitioners, and social workers through its enhanced Mobile Broadband (eMBB), URLLC, and ubiquitous access services. Meanwhile, 5G will help to realize resource pooling of expert human resources through high-performance and reliable telemedicine (including enhanced telemedicine using the tactile Internet with haptic feedback). Besides, personalized healthcare can be achieved through the progress in big data, sensor technologies, and AI/ML. Additionally, routine activities of humans (e.g., diagnoses) will be supported by AI and ML algorithms. Based on this, the overall healthcare system will be enhanced and benefit the global economy. These are important trends in the field of healthcare driving the 5G era transition. Moreover, smart healthcare is growing quickly, and 5G will reconstruct the healthcare system by improving the quality of medical service intelligently, balancing the distribution of medical resources between urban and rural areas, and reducing healthcare costs. We are cautiously optimistic about these trends, although there is still a long way to go to achieve smart healthcare.

Author contributions

HL and CG contributed to data collection and analysis, manuscript design, and preparation. HL revised the manuscript. Both authors have agreed to be accountable for the content of the work.

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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Current status and trends in researches based on public intensive care databases: A scientometric investigation

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Objective: Public intensive care databases cover a wide range of data that are produced in intensive care units (ICUs). Public intensive care databases draw great attention from researchers since they were time-saving and money-saving in obtaining data. This study aimed to explore the current status and trends of publications based on public intensive care databases.

Methods: Articles and reviews based on public intensive care databases, published from 2001 to 2021, were retrieved from the Web of Science Core Collection (WoSCC) for investigation. Scientometric software (CiteSpace and VOSviewer) were used to generate network maps and reveal hot spots of studies based on public intensive care databases.

Results: A total of 456 studies were collected. Zhang Zhongheng from Zhejiang University (China) and Leo Anthony Celi from Massachusetts Institute of Technology (MIT, USA) occupied important positions in studies based on public intensive care databases. Closer cooperation was observed between institutions in the same country. Six Research Topics were concluded through keyword analysis. Result of citation burst indicated that this field was in the stage of rapid development, with more diseases and clinical problems being investigated. Machine learning is still the hot research method in this field.

Conclusions: This is the first time that scientometrics has been used in the investigation of studies based on public intensive databases. Although more and more studies based on public intensive care databases were published, public intensive care databases may not be fully explored. Moreover, it could also help researchers directly perceive the current status and trends in this field. Public intensive care databases could be fully explored with more researchers' knowledge of this field.

KEYWORDS

intensive care, scientometric investigation, research, public database, status

Introduction

Treatment of critically ill patients is one of the challenges of modern medical research. The illness severity of patients in ICUs varied from each other. Treatment decision-making of critically ill patients should be based on a large number of clinical data due to the heterogeneity of patients. However, medical workers in ICUs are too busy to collect complete data for investigations. Public databases can solve this dilemma by providing well-sorted data produced in the process of providing care for patients. Public intensive care databases are mainly multiparameter intelligent monitoring in intelligent care (MIMIC) and EICU collaborative research database (eICU-CRD) (1).

The MIMIC database is a free-access public single center database released by the Massachusetts Institute of Technology (MIT), Beth Israel Deaconess Medical Center, and Philips (2). It comprises deidentified health-related data (demography, basic signs records, medical intervention records, nursing records, imaging, and discharge records) from patients who were admitted to the ICUs of Beth Israel Deaconess Medical Center between 2001 and 2019 (3). eICU-CRD is a multi-center public intensive care database with over 200,000 admissions across the United States. Vital sign measurements, care plan documentation, diagnosis, and treatment information are collected in this database (4). Many investigations, such as evaluating the relative effectiveness of sepsis identification criteria (5) and an early prediction model of circulatory failure (6), have been conducted using public intensive care databases.

Scientometric analysis, a widely accepted research method based on statistical and visualization techniques, can depict hotspots and trends of a field. Unlike system review, scientometric investigation focuses on the metrological characteristics of literature and determines different characteristics, such as the journals, countries, institutions, authors, keywords, and references. Scientometric investigation usually includes three steps: (1) collecting data from databases; (2) analyzing data and drawing maps by software; and (3) reporting results. Several software, for example, VOSviewer and CiteSpace, have been developed for scientometric investigations. Lu et al. summarized the key topics through scientometric investigation of publications related to peptide receptor radionuclide therapy using VOSviewer and CiteSpace (7). The two user-friendly software allow beginners to know about the current status of a specific field and identify hotspots with ease.

Many studies based on public intensive care databases have been published. However, there is no in-depth analysis of the cooperation network, research hotspots, and trends of this field. This study presented a comprehensive view of the studies based on public intensive care databases, such as the number of publications per year, key journals, productive countries, institutions, and authors. We hope our study can promote the full utilization of public databases that are beneficial to researchers, clinicians, and patients.

Materials and methods

Data source and search strategy

Software could not analyze data from different databases at the same time. We retrieved English literatures from the Web of Science core Collection (WoSCC) in our study instead of searching other databases, such as Pubmed or Dimensions. Search strategies were ["eICU-CRD" (All Fields) OR "eICU Collaborative Research Database" (All Fields)] or ["Multiparameter Intelligent Monitoring in Intensive Care" (All Fields) OR "Medical Information Mart for Intensive Care" (All Fields)]. We selected "article" or "review" as the document types and excluded letters, news, conference summaries, and other documents. Retrieval time was limited from 2001 to 2021.

Statistical analysis

The quality of the journal (IF2021 and JCR) were obtained from 2021 Journal Citation Reports (JCR) (Clarivate Analytics, Philadelphia, USA). VOSviewer (1.6.18) was used to identify productive journals and co-cited journals, countries, institutions, and authors and visualize cooperation networks. In the VOSviewer network maps, nodes represent elements, such as countries, institutions, and authors. The size of the nodes represents the number of publications or occurrence frequency. The shorter distance between two nodes, the closer cooperation between two elements. The color of the nodes represents publishing time. The thickness of links represents cooperation intensity between two elements. The color of the links represents the first year of cooperation. Cold colors represent earlier years, while warm colors represent recent years. We used CiteSpace (5.8.R3) to conduct keyword clustering and detect the references with strong citation burstness to identify hot topics. Data were managed using Microsoft Office Excel 2019 (8).

Results

Annual growth trend of publications

In total, 606 publications were finally included for analysis. The number of publications published based on public intensive care databases from 2009 to 2021 was shown in Figure 1. Publications based on public intensive care databases were published every year since 2009. The number of annual publications represented a significant upward trend during the

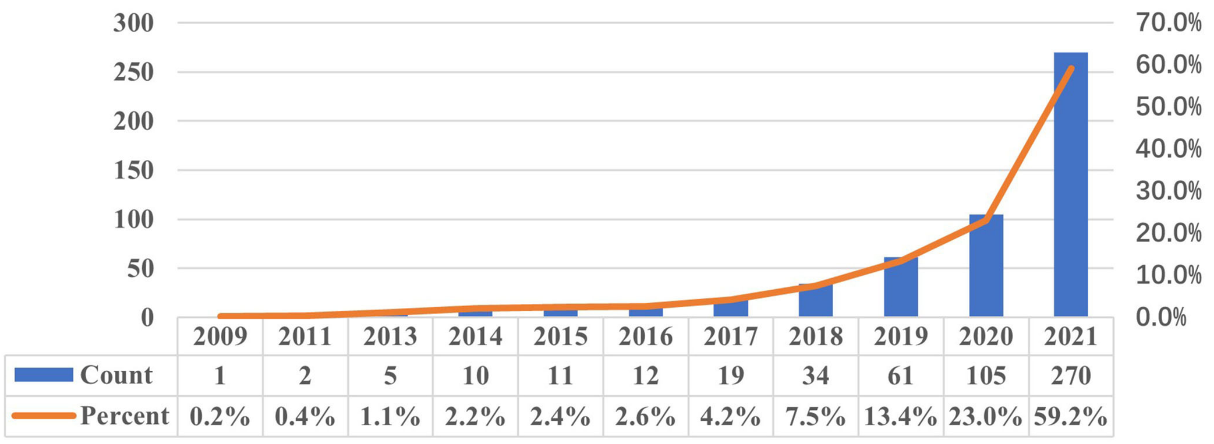

FIGURE 1
The number of publications per year (2009–2021).

investigation period. The annual publication number was 12 (2.6%) in 2016, 34 (7.5%) in 2018, and 270 (59.2%) in 2021.

Journals and co-cited academic journals

A total of 244 journals have published literatures based on public intensive care databases. The top 10 journals account for 30.7% (186/606) of the total publications included in this study (Table 1). There were eight journals with more than 10 publications, of which *Frontiers in Medicine* (IF2021 = 5.058, Q2) was the most productive journal with 30 publications, followed by the *International Journal of General Medicine* (IF2021 = 2.145, Q3), *Critical Care* (IF2021 = 19.346, Q1), and scientific reports (IF2020 = 4.996, Q2).

Two journals have a co-citation relationship when they are cited simultaneously in one or more publications. Among 14,054 co-cited academic journals, 10 journals had co-citations over 4,837 times. *Crit care med* had the most co-citations (IF2020 = 9.296, Q1), followed by *Intensive care medicine* (IF2021 = 19.346, Q1), and *JAMA-journal of the American medical association* (IF2020 = 157.335, Q1) (Table 1).

Country and institution analysis

A total of 48 countries have published literature based on public intensive care databases, mainly China (336), the United States (199), England (37), Canada (26), and Australia (19) (Table 2).

A total of 713 institutions have published literature based on public intensive care databases. MIT had the largest number of publications with 43, followed by Zhejiang University (40) and Sun Yat-sen University (36) (Table 2). Institutions with the more than eight publications were included to construct the co-institution map (Figure 2). MIT and Zhejiang University occupied important positions in the network of institute cooperation. According to the color of the links, institutions began to cooperate frequently since 2016. It may due to the release of MIMIC-III in 2016 which drew the attention of researchers around the world (3).

Author analysis

A total of 2,638 authors have published literature based on public intensive care databases. Top 10 authors have published 129 (21%) articles (Table 3). Leo Anthony Celi of MIT published the most articles (n = 25), followed by Zhongheng Zhang (n = 19) and Lee Joon (n = 14). Authors with the more than 6 publications were included to construct the co-author map. Leo Anthony Celi, who had participated in the release of MIMIC-III database, cooperated closely with researchers in this field. Zhang Zhongheng has closer cooperation with Chinese authors (according to the name of authors). However, the top two authors only jointly published one article based on the MIMIC database (9). Most of Chinese authors published literatures in recent years (Figure 3).

Keywords analysis

Co-occurring keywords reflect hotspots of studies based on public intensive care databases. Keywords with high frequency are listed in Table 4. Excluding keywords (intensive care unit, critically ill patient, management, and system) lacking guiding significance, "mortality," "machine learning," "sepsis," "acute kidney injury," "prognosis," "deep learning," "nomogram,"

TABLE 1 Top 10 journals in terms of publications and top 10 journals in terms of co-citations.

Rank	Journal	Count	IF2020	JCR	Co-cited journal	Count	IF2021	JCR
1	Front Med	30	5.058	Q2	Crit Care Med	1161	9.296	Q1
2	Int J Gen Med	29	2.145	Q3	Crit Care	641	19.346	Q1
3	Crit Care	18	19.346	Q1	Jama-J Am Med Assoc	592	157.335	Q1
4	Sci Rep	18	4.996	Q2	Intens Care Med	582	41.787	Q1
5	Bmj Open	17	3.017	Q2	Sci Data	485	8.501	Q1
6	JMIR Med Inf	17	3.231	Q3	New Engl J Med	349	176.079	Q1
7	J Am Med Inform Assn	16	7.942	Q1	PLoS ONE	276	3.752	Q2
8	Front Cardivovasc Med	15	5.846	Q2	Chest	269	10.262	Q1
9	Ann Transl Med	14	3.616	Q3	Circulation	242	39.918	Q1
10	PLoS ONE	12	3.752	Q2	J Am Med Inform Assn	240	7.942	Q1

TABLE 2 Top 10 countries and institutions in terms of the publication number.

Rank	Country	Count	Institution	Count
1	China	336	MIT (USA)	43
2	USA	199	Zhejiang Univ (China)	40
3	England	37	Sun Yat Sen Univ (China)	36
4	Canada	26	Beth Israel Deaconess Med Ctr (USA)	32
5	Australia	19	Wenzhou Med Univ (China)	28
6	India	13	Xi'an Jiao Tong Univ (China)	28
7	South korea	13	Ji Nan Univ (China)	18
8	Germany	12	Cent South Univ (China)	17
9	Italy	12	Chinese Peoples Liberat Army Gen Hosp (China)	14
10	Singapore	11	Beth Israel Deaconess Med Ctr (USA)	13

"prediction," "hospital mortality," and "mortality prediction" are the top 10 keywords with high frequency. A total of 15 keyword clusters were obtained by CiteSpace-6.1.2. Keyword clustering is the clustering of closely linked keywords from which you can see Research Topics form in a certain field (10). The top 9 clusters and keywords included in each cluster are listed in Table 5. "Acute respiratory distress syndrome," "Albumin ratio," "Arterial blood pressure," "External validation," "To-albumin ratio," "Retrospective study," "Bayesian filter," "Patient profiles," "Treatment-related complications," and "Prediction" are potential main topics in this field.

References with citation burst

"Citation burst" refers to a body of literature that is frequently cited over a period of time. References with a high citation burstness can, to a certain extent, reflect the emerging trends or topics within a field (10). The minimum duration of burst was set at 2 years. γ was set as 0.5. Table 6 lists top 17 references with the strongest citation bursts. The red line in the blue line represents the time interval of citation burst. The longest burst among the 17 references was "Multiparameter Intelligent Monitoring in Intensive Care II: A public-access intensive care unit database" (2). Nine references ended before 2018. Jia et al. explored risk factors for acute respiratory distress syndrome in patients mechanically ventilated, which brought a burst of study on risk factors (11). Abhyankar et al. developed a generalizable method for identifying patient cohorts from electronic health records by combining structured and unstructured data, which were of great benefit for identifying a large set of patients for investigations (12). Article entitled "Toward Ubiquitous Blood Pressure Monitoring *via* Pulse Transit Time: Theory and Practice" (13) and article entitled "Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease" (14) indicated that more methods and types of diseases are investigated. References related to machine learning and in-depth learning (5, 15) burst after 2019 and lasted until retrieval time, which manifested that machine learning was the frontier of studies based on public intensive care databases.

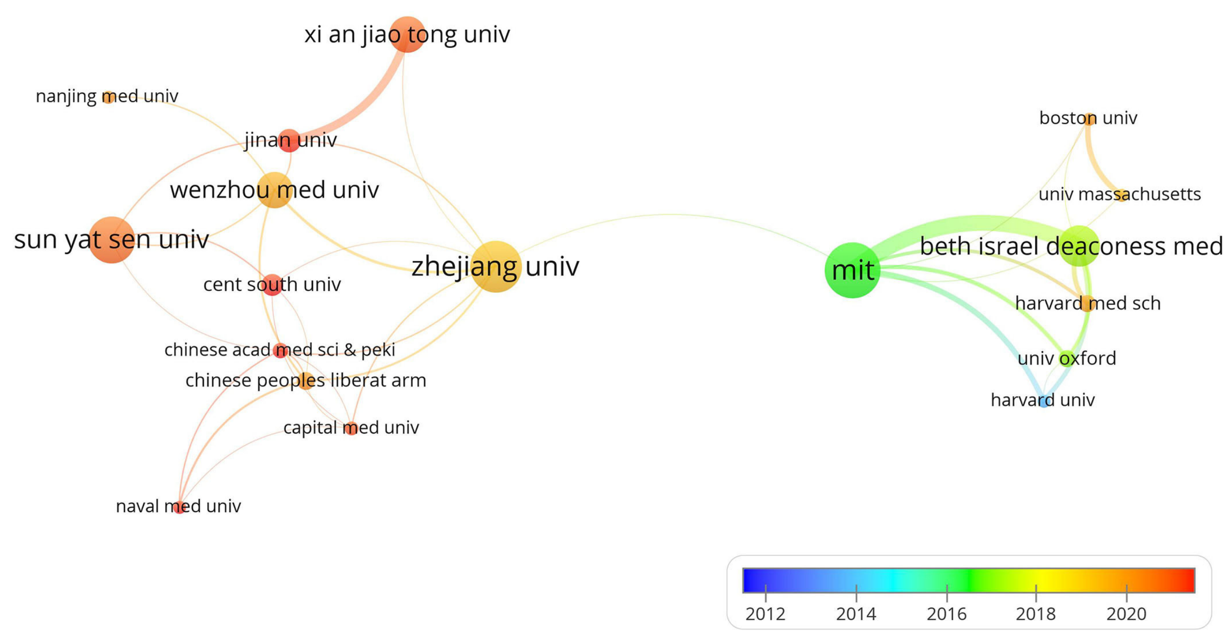

FIGURE 2
The network of co-institute.

Discussion

Basic information

A total of 606 articles in 244 journals with 14,054 co-cited references by 713 institutions from 48 countries were included in our study. Articles published in this field could be divided into two stages. Before the release of the MMIC-III database in 2016, only a few articles were published each year. After 2016, the number of articles published increased year by year. An upward trend suggested that studies based on public intensive care databases have received increasing attention in recent years. Moreover, according to the color of the links and nodes of author analysis, many Chinese articles were published in the last 2 years, indicating that public intensive care databases had attracted the attention of Chinese researchers. Critical Care Medicine and JAMA-Journal of the American Medical Association, which are journals with high academic influence, ranked the first and second in the co-cited journals. Meanwhile, the IF2021 of most productive journals is lower than 5, indicating the relatively low quality of publications in this field. Analysis results of institution, country, and author are consistent. For example, Zhang Zhongheng from Zhejiang University (China) and Leo Anthony Celi from MIT (USA) occupied important positions in the research based on public intensive care databases. It is worth noting that the cooperation between institutions in the same country is closer. Strengthening international cooperation may improve the quality of studies based on public intensive care databases.

TABLE 3 Top 10 authors in terms of the publication number.

Rank	Author	Publications
1	Celi, Leo Anthony	25
2	Zhang, Zhongheng	19
3	Lee, Joon	14
4	Lyu, Jun	14
5	Mark, Roger G.	11
6	Mcmanus, David D.	9
7	Xu, Fengshuo	9
8	Bashar, Syed Khairul	8
9	Han, Didi	8
10	Luo, Yuan	8

Research topics

Keyword clustering is the clustering of closely linked keywords from which you can see Research Topics forming in a certain field. According to the cluster name and included keyword, six areas are summarized by reading the full text of included literature in the cluster. According to the result of

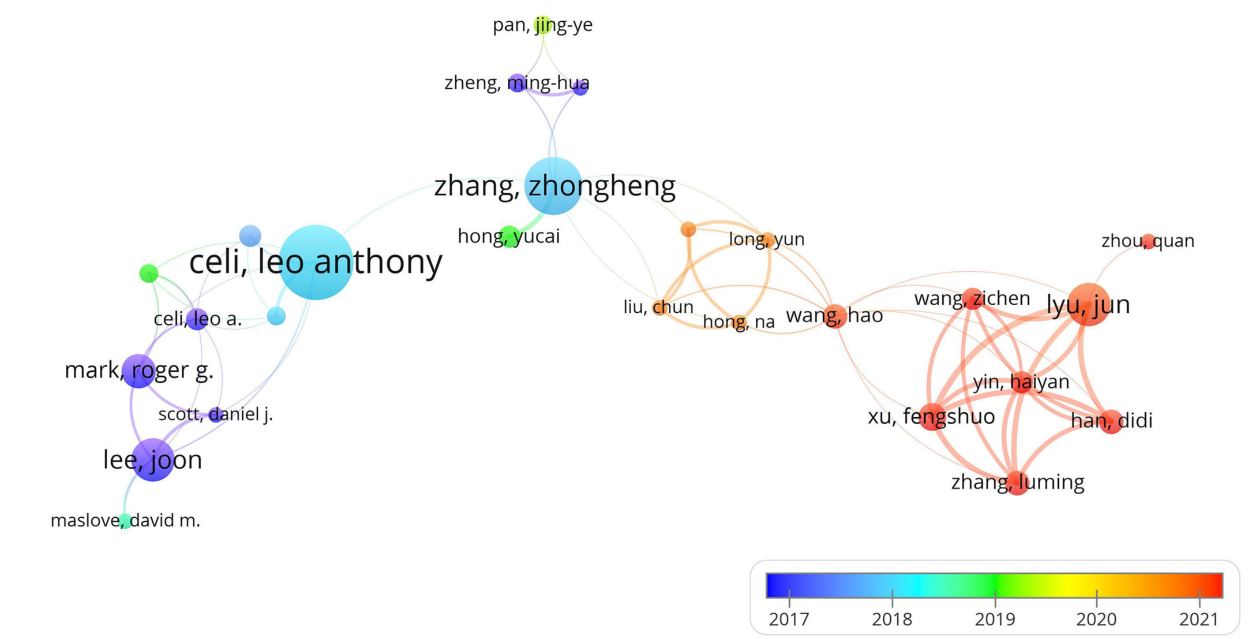

FIGURE 3
The network of co-authorship.

TABLE 4 Top 20 keywords with high frequency.

Keywords	Strength	Freq	Keywords	Strength	Freq
Mortality	104	112	Natural language processing	14	11
Machine learning	108	79	Atrial fibrillation	13	10
Sepsis	102	76	Lactate	18	10
Acute kidney injury	62	45	All-cause mortality	8	9
Prognosis	33	30	Data mining	8	9
Deep learning	35	27	Medical informatics	16	9
Nomogram	43	24	Mechanical ventilation	9	8
Prediction	32	19	Prediction model	19	8
Hospital mortality	20	16	Propensity score matching	16	8
Mortality prediction	15	14	Septic shock	8	8

keyword clustering, six hot topics could be roughly summarized after referring to included literature: (1) prediction of mortality, serious complications, and readmission of critically ill patients; (2) exploration of risk factors of mortality and prognosis of critically ill patients; (3) studies on vital signs of critically ill patients; (4) scoring system and external verification of standards or guidelines; (5) impact of treatments and drugs on outcomes of critically ill patients; and (6) introduction of databases and data processing methods.

Machine learning was used in the prediction of mortality, adverse prognosis, and morbidity of critically ill patients. The condition of patients in intensive care units changes rapidly. The prediction of serious complications or nosocomial diseases, such as acute kidney injury, pressure injury, and anemia, was conducive to taking preventive measures as soon as possible. Goodwin et al. developed a generalizable model capable of leveraging clinical notes to predict three nosocomial diseases 24–96 h in advance (19). Fialho et al. selected commonly texted variables, such as heart rate, temperature, platelets, non-invasive arterial blood pressure, spO_2, and lactic acid during the last 24 h before discharge (20). The collection of these variables selected is not complex in ICUs. Meanwhile, they were capable of predicting ICU readmissions and providing support for clinicians to make plans to reduce the risk of readmission.

One main subject of research based on public intensive care databases was to analyze whether some factors affected the

TABLE 5 Top 9 clustering and keywords included in each cluster.

ID	Cluster	Size	Keyword included
0	Acute respiratory distress syndrome	45	Prediction; hospital; mortality; APACHE; BMI
1	Albumin ratio	44	Septic shock; lactate; criteria; serum albumin
2	Arterial blood pressure	38	Model; algorithm; pharmacovigilance; morbidity
3	External validation	32	Sepsis; acute kidney injury; validity; patient readmission
4	To-albumin ratio	29	Score; heart failure; complication; data element
5	Retrospective study	27	Impact; risk factor; mechanical ventilation; neutrophil
6	Bayesian filter	24	Blood pressure; feature extraction; electrocardiogram; blood pressure estimation
7	Patient profiles	22	Admission; electronic health record; length of stay; arterial pressure
8	Treatment-relatedcomplications	16	Cost; anemia; prednisone; clostridium difficile infection
9	Prediction	3	Spinal anesthesia; heart rate variability; elective cesarean delivery

TABLE 6 Top 17 references with the strongest citation bursts.

References	Begin	End	2004–2021
Saeed (16), Comput Cardiol	2008	2010	
Saeed Mohammed (2006), AMIA Annu Symp Proc	2010	2011	
Li (2008), Physiol Meas	2008	2013	
Aboukhalil (2008), J Biomed Inform	2010	2016	
Jia (2008), Chest	2011	2016	
Scott (2013), BMC Med Inform Decis,	2014	2016	
Lehman Li-wei (17), AMIA Annu Symp Proc	2015	2016	
Lee (2011), IEEE Eng Med Bio	2015	2016	
Zhang (2014), J Thorac Dis	2015	2016	
Abhyankar (2014), J Am Med Inform Assn	2016	2017	
Abhyankar (2012), Crit Care	2016	2017	
Saeed (2), Crit Care Med	2012	2018	
Seymour (18), JAMA-J Am Med Assoc	2017	2018	
Mukkamala (2015), IEEE T Bio-Med Eng	2018	2019	
Eckardt (2012), Kidney Int Suppl	2019	2021	
Rajkomar (2018), NPJ Digit Med	2019	2021	
Desautels (2016), JMIR Med Inf	2019	2021	

prognosis or mortality of critically ill patients. Studies mainly focused on acute respiratory distress syndrome, sepsis shock, acute renal failure, intracerebral hemorrhage, and myocardial infarction (21–25). Factors analyzed in studies were lactic acid, body mass index (BMI), red blood cell distribution width (RDW), neutrophil to lymphocyte ratio, blood oxygen saturation, anion gap, and coagulation variables (26–31).

Studies on the vital signs of patients focused on estimating blood pressure, heart rate, and respiratory rate, reducing the probability of false alarms and detecting noise in electrocardiogram. For example, Chon et al. developed an automated method to detect noise from long-term electrocardiogram signals recordings in the MIMIC III database. This detection algorithm could accurately detect the presence of atrial fibrillation with only 5.7% false positives (32).

External verification of scoring systems, criteria, or guidelines is one of the applications of public intensive care databases. A number of cases were included in public databases that could be used to verify diagnostic criteria. Controversy existed in the diagnostic criteria of sepsis. Retrospective study conducted by Xueling Fang verified that sepsis-3 diagnostic criteria narrow the sepsis population at the expense of sensitivity, which may delay disease diagnosis (33). The modified Nutrition Risk in the Critically ill (mNUTRIC) score was introduced to evaluate the nutritional risk of patients in the ICU (34). Zheng et al. investigated the prediction value of mNUTRIC score of patient in cardiothoracic surgery recovery unit in the MIMIC database (35).

Exploring the effects of treatment is an emerging topic of studies based on public databases. Su et al. used the MIMIC database to select strategy for sedation depth in critically ill patients using a machine learning model (36). The efficacy and safety of loop diuretic use in critically ill patients on vasopressor support or in shock remain unclear. The relationship between loop diuretic use and hospital mortality in critically ill patients with vasopressor support was studied using data extracted from the MIMIC database. Results showed that loop diuretic use was associated with lower mortality without an obvious compromise in the mean arterial pressure (37).

Some of the included articles were about the introduction of databases, data processing, and data extraction methods. Public intensive care databases are highly susceptible to quality issues, such as missing information and erroneous data due to a large number of parameters. Venugopalan et al. used a MIMIC database as an example to demonstrate new imputation techniques for each type of missing data. The novel imputation techniques outperformed standard mean filling techniques in predicting ICU mortality (38). Rich information in clinical narratives can help to detect adverse drug events (ADEs) since details of the diseases (such as, signs and symptoms, disease status, and severity) are all typically recorded in clinical text. Deep learning methods were utilized to recognize drug names, attributes entities, and relations from clinical narratives in the MIMIC database. In comparison with traditional machine learning algorithms, it could simultaneously recognize entities of ADEs, the reason, and their relations with medications (39).

Strengths and limitations

Our study has several strengths. First, this is the first study to provide a comprehensive insight into the status, hotspots, and trends of research on public intensive care databases using the scientometric analysis. Second, CiteSpace and VOSviewer are widely used tools for scientometric analysis, which assures the reliability of results. Third, compared with system reviews, scientometric analysis is relatively more objective and comprehensive.

This is the first time that scientometrics has been used in the investigation of studies based on public intensive databases. This is different from other conventional scientometric investigations which reported the status of a certain field (a disease or a drug). Although more and more studies based on public intensive care databases were published, public intensive care databases may not be fully explored. Research using public data is mainly explored with a few countries, institutions, and researchers. As shown in the country analysis, studies based on public intensive care databases mainly in the United States and China (88% of included literature). According to the analysis of institutions and authors, Zhongheng Zhang from Zhejiang University and Celi Leo Anthony (14% of included literature) from MIT were key authors. Moreover, research topics were narrow, with only mainly six directions. Two of the six topics are related to the prediction of the outcome. Disease types explored are mainly limited to sepsis, acute respiratory distress syndrome, heart failure, and acute kidney injury. Judging from the published journals, quality of the studies based on intensive care databases is not high since most of the journals ranked as Q3 in JCR.

Our results can also help new researchers interested in this field quickly to get status, hotspots, and trends in this field. They can know which researchers or institutions to learn from and carry out studies quickly (top 2 authors). Database developers can know whether the databases are fully utilized as they imagine. If not, they can find out the reasons and make some improvements. For example, there is no index table for drug names, which makes studies evaluating the efficacy of drugs difficult to carry out. In addition, there are no images in the databases, which makes the machine learning studies based on original image impossible to carry out. Although public intensive care databases have been explored by more and more researchers (the number of publications in 2021 accounted for half of the total number of publications), the quality of journals is not high. This may be because studies based on intensive care databases can only do retrospective studies. Studies based on large amount of data in databases are valuable and should be recognized by editors. Studies based on data collected from on real clinical diagnosis and treatment without intervene are valuable for clinicians. Researchers should improve the quality of their literature by taking measures, such as working on more valuable questions and using scientific statistical methods.

Our study still has some limitations. First, our chosen software and data expertise did not allow us to combine data from different sources for the analysis shown here. This would have been valuable as it could have extended our analysis to a wider dataset. However, as argued in our search strategy section, for the statements that we make in our article on large scale trends, we feel that our sample size is large enough to make robust comments of the type given here. The main shortcoming of our approach is that geographic diversity may not be fully represented (due to the English-centric nature of WoS) (7, 8).

Conclusion

To our knowledge, this is the first scientometric investigation for studies based on public intensive care databases. Our study provided an overview of research hotspots, trends, key journals, authors, institutions, countries, and their co-operative relations. China contributed the most in the studies based on public intensive care databases. MIT and Zhejiang University, occupied important position in the network of institute cooperation. Leo Anthony Celi of MIT and Zhongheng Zhang of Zhejiang University had the highest number of articles and also cooperated most closely with other authors. The number of studies based on public intensive care databases increased quickly after 2018 with more and more disease, medicines, and research methods being explored by more researchers. Six main topics were summarized through keywords analysis. Until now, the research method of machine-learning is commonly used research method. This scientometric investigation could help researchers directly perceive the current status and trends in this field. As more and more researchers know about public databases, public intensive care databases will be fully-explored and promote the development of critical care medicine.

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/s.

Author contributions

ML and SD equally contributed to the conception and design of the research. ML contributed to the collection of literature, the acquisition, analysis, and interpretation of the data. Both authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, read, and approved the final manuscript.

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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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Online public attention toward allergic rhinitis in Wuhan, China: Infodemiology study using Baidu index and meteorological data

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Background: With the popularization of the Internet and medical knowledge, more and more people are learning about allergic rhinitis (AR) on the Internet.

Objective: This study aims to analyze the epidemiological characteristics and online public attention to AR in Wuhan, China, utilizing the most popular search engine in mainland China and meteorological data of Wuhan.

Methods: To study the Internet attention and epidemiological characteristics of AR in Wuhan, the search volume (SV) of "Allergic Rhinitis" in Mandarin and AR-related search terms from 1 January 2014 through 31 December 2021 were recorded. For user interest, the search and demand data were collected and analyzed.

Results: The yearly average Baidu SV of AR in both Wuhan and China increased year by year but began to decline gradually after the COVID-19 pandemic. Baidu SV of AR in Wuhan exhibited significant seasonal variation, with the first peak was from March to May and the second peak occurring between September and October. Correlation analysis revealed a moderate positive correlation between the monthly average SV of "Allergic Rhinitis" and "Mites" and "Mites + Pollen Allergy" in Wuhan, a weak positive correlation between the monthly average SV of "Allergic Rhinitis" and "Pollen Allergy," and a positive correlation between monthly SV of "Allergic Rhinitis" and the meteorological index of pollen allergy (MIPA).

Conclusion: The attention given to the topic on the internet, as measured by the search volume, was reflective of the situation in Wuhan, China. It has the potential to predict the epidemiological characteristics of AR and help medical professionals more effectively plan seasonal AR health education.

KEYWORDS

Baidu index, meteorological data, allergic rhinitis, pollen allergy, Mites, COVID-19

Introduction

Allergic rhinitis is one of the most common allergic diseases in China (1). AR is a non-infectious chronic inflammatory disease of the nasal mucosa caused by an immunoglobulin E (IgE) mediated inflammatory response to inhaled allergens, often presented with sneezing, itching, rhinorrhea and nasal congestion (2). It has been proven that AR also affects people's sleep quality, social activities, learning and work efficiency, leading to decreased productivity (3) and life quality (4). According to recent epidemiological studies, AR has affected nearly 200 million people in China (5). Moreover, the prevalence of AR has been still on the rise in recent decades, and AR has become a serious public health, medical and economic problem.

Avoiding exposure to inhaled allergens can relieve the symptoms and reduce the incidence. Wearing face masks is an effective way, which most people have been doing since the COVID-19 pandemic. Recent research has shown that COVID-19 lockdowns have been proposed as contributing to decreasing symptom severity in patients with AR (6). At present, the global pandemic of COVID-19 has infected more than 230 million people (7). To prevent infection, staying at home and wearing a face mask are the most direct and effective ways. During the pandemic, people were highly mobilized and followed the commands of the government (8–11). Most people avoided crowded places and wore face masks when outside homes. Especially in Wuhan, where the COVID-19 pandemic first broke out and China imposed its first lockdown, people kept staying at home until the lockdown was lifted. And until now, most people in Wuhan consciously wear face masks in public.

With the popularization of Internet devices and health education, mobile phones and computers have become a very convenient way to obtain medical information and consult on health problems (12). Many studies (13–15) have shown that the frequency of disease queries and related symptom keywords is strongly correlated with the severity of the symptoms and could reflect the true trend of searchers' needs. For example, big data based on the Google platform can reflect and predict the prevalence trend of AR in the United States (13). In China, 92.1% of the SV data is on Baidu's search platform, and the usage of Baidu's platform accounts for 93.1% of the search service usage (16). Baidu Index is a big data analysis platform provided by Baidu based on the data generated by a large number of users' search behaviors. It takes keywords as the statistical object and calculates the search volume of each keyword, which is finally shown to the users through a variety of intuitive and clear curve graphics. The Baidu Index has been proven to be feasible in monitoring and predicting the epidemiological characteristics of diseases (17), and can reflect the real needs of searchers to a certain extent (15, 17, 18). The Internet search data is able to provide guidance to medical and health professionals, contributing to making targeted disease prevention and control as well as health education (15).

Pollen and dust mites are the most common allergens associated with AR in Wuhan (19, 20). However, it is difficult to predict dust mite levels, and there is no pollen concentration prediction in Wuhan yet. Therefore, we replace pollen concentration with MIPA, which can reflect the real-time sensitization effect of pollen concentration on human citizens. In addition, for research purposes, we gathered search data on dust mite-related terms. According to the China Meteorological Administration, MIPA is defined as the level of meteorological conditions' influence on pollen allergy. Based on the observed pollen concentration in the Hubei area, we graded the pollen concentration grade as the basic levels of MIPA in Wuhan. Then, the levels of MIPA after modification of meteorological conditions are used as the final MIPA.

In this study, we collected "Allergic Rhinitis" and various allergen search data in Wuhan as online public attention toward allergic rhinitis. This study aimed to analyze the AR-related search trends and online public attention in the Wuhan area, as well as the people's demand. We also gained meteorological data in Wuhan to analyze the relationship between online attention toward AR and the MIPA, partly verifying the importance and feasibility of developing pollen concentration prediction. Given the inadequacy of traditional methods and the lack of data sources, Internet search data is able to provide new insights into the epidemiological characteristics of AR, improve the detection and prediction of AR, and track public interest in multiple health topics. Thus, medical practitioners can fully utilize Internet data to track AR prevalence and patients' needs to create related health care policies and health education.

Materials and methods

Keywords selection and data retrieval

This study mainly analyzed the temporal search trends of AR and AR-related terms in Wuhan. To reduce the results bias caused by different language habits, we selected the most frequently used keywords related to AR on the web, including "Allergic Rhinitis" and AR-related search terms, "Pollen Allergy," "Dust Mites," "Mites," "Dust Mites Allergy," "Mites Allergy," and "Mites Allergy + Pollen Allergy." And the daily search volume of the above terms was counted from 1 Jan 2014 to 31 Dec 2021 through the Baidu Index platform (15, 18, 21). Because the common allergens causing AR in China are dust mites and airborne pollen, we select the keywords "Mites allergy + Pollen Allergy" as the main allergens of concern to AR patients.

We obtained the monthly basic level of MIPA in Wuhan from the Meteorological Industry Standard of the People's Republic of China–QX/T324-2016 Meteorological Index of Pollen Allergy (22) issued by the China Meteorological Administration in 2016. The fixed-point meteorological data, such as daily temperature, relative humidity, wind speed and precipitation, was provided by the Wuhan Meteorological Bureau, which contributed to revising the basic levels of MIPA by adding or subtracting levels.

Besides, we also collected user demand graph data from the Baidu Index platform, which can partly and intuitively reflect what AR patients were usually concerned about.

Statistical analysis

The main variables examined were the search volume of AR, AR-related terms in Chinese and MIPA from 1 Jan 2014 to 31 Dec 2021.

Normality Test To verify the distributive normality of a data set, we used the Shapiro-Wilk test plus a graphical check of histograms and quantile-quantile diagrams.

Pearson and Spearman Cross-Correlations, when the data sets were normally distributed, the Pearson correlation R was used; otherwise, the Spearman correlation R was used. The correlation strength was assessed independently of the *P* values.

P values were used as a continuous measure of the strength of evidence against the null hypothesis. There were three independent hypotheses tested on a set of data in our study, namely the correlation between the monthly average SV of "Allergic Rhinitis" and "Mites," "Allergic Rhinitis" and "Pollen Allergy," "Allergic Rhinitis" and "Mites + Pollen Allergy" in Wuhan from 2014 to 2021, with *P* values corrected according to Bonferroni correction.

Software SPSS 26.0 (IBM Corporation, Armonk, NY, United States) was used for data analysis.

Results

Epidemiological characteristics of AR in Wuhan

From 2014 to 2017, the Internet attention to AR in China and Wuhan both continued to rise (Figure 1). The yearly average Baidu search volume of "Allergic Rhinitis" in China was 101,668, 124,868, 154,793, and 175,793, respectively and 7,091, 7,970, 8,983, 10,209, respectively in Wuhan. And it remained at a high level from 2018 to 2019. Since 2019, AR Internet attention in China and Wuhan has shown a declining trend. Meanwhile, the valley values and the peak values also gradually decreased after the COVID-19 pandemic (Figure 1). Compared with the same period from 2015 to 2019, the SV of "Allergic Rhinitis" in Wuhan decreased significantly in 2020 and 2021 (Figure 2).

With monthly SV as the ordinate and the month as the abscissa, the Baidu users' Internet attention to AR in Wuhan reached its obvious peaks from Sep to Oct every year and small peaks from Mar to May every year (Figure 2). Meanwhile, the periods when these two seasonal peaks appeared were the same

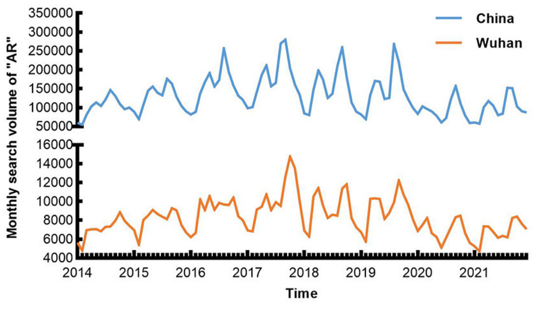

FIGURE 1
The yearly search volume of "AR" in China and Wuhan through Baidu search engine from 2014 to 2021.

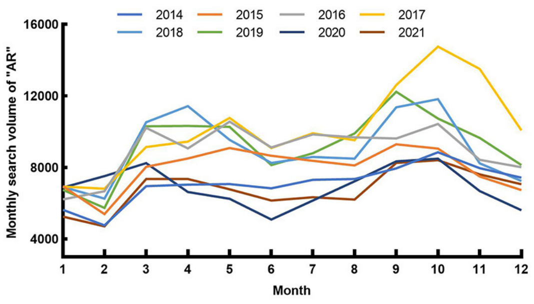

FIGURE 2
Epidemiological characteristics of "AR" in Wuhan from 2014 to 2021.

as in the whole country, and they also fell in line with airborne pollen in Wuhan (23).

Internet attention correlation analysis of "Allergic Rhinitis" and AR-related keywords in Wuhan

Considering people's awareness of dust mite allergens and different language habits, we collected the search volume of AR-related keywords that people might search for. It included SV of "Mites," "Mites Allergy," "Dust Mites," and "Dust Mites Allergy" from 1 Jan 2014 to 31 Dec 2021 in Wuhan and China. Among them, the SV of "Mites" was the highest in both national and Wuhan data, while the SV of other keywords was very low and had no obvious correlation with AR SV (Figures 3, 4). So, we collected the monthly average SV in Wuhan of "Allergic Rhinitis" and "Mites" from 1 Jan 2014 to 31 Dec 2021 for correlation analysis, and found a moderate positive correlation [$R = 0.578$, corrected $P < 0.001$, 95% CI: [0.419, 0.718], Figure 5] between the monthly average SV of "Allergic Rhinitis" and "Mites."

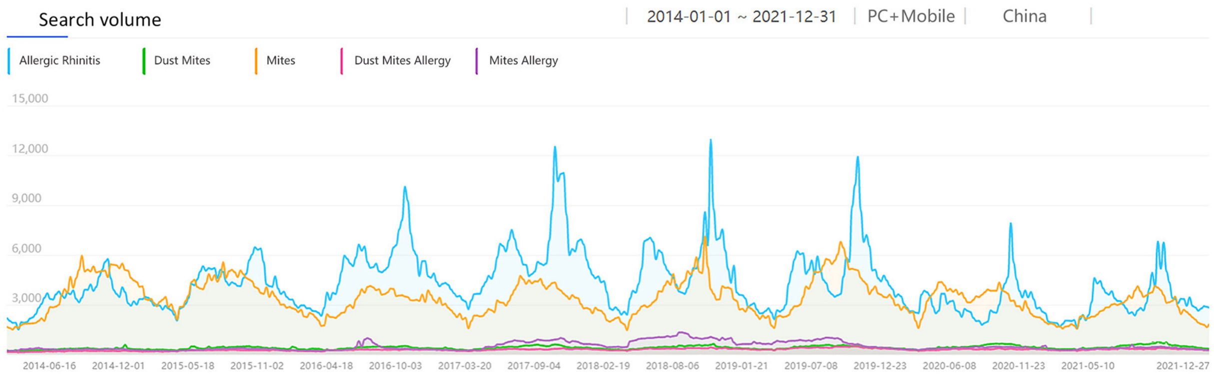

FIGURE 3
The search volume of "Mites" related keywords and "AR" in China from 2014 to 2021.

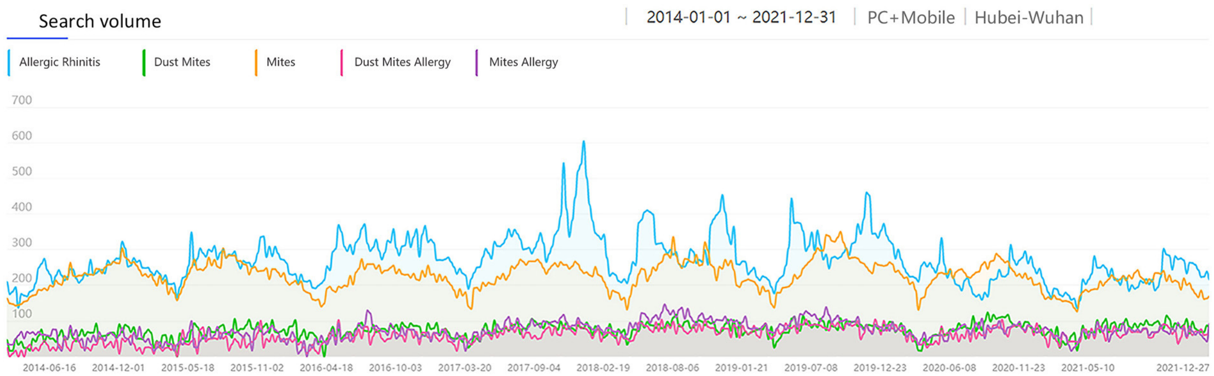

FIGURE 4
The search volume of "Mites" related keywords and "AR" in Wuhan from 2014 to 2021.

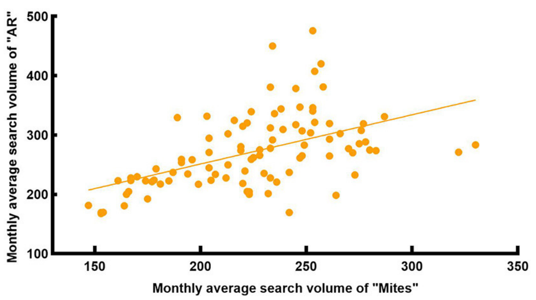

FIGURE 5
Correlation between the search volume of "AR" and "Mites" in Wuhan from 2014 to 2021.

Pollen is one of the most common allergens. Research shows (23) that airborne pollen in Wuhan had two peak periods throughout the year. The first peak was from Mar to Apr, and the second peak was from Aug to Oct. The airborne pollen in spring was mainly from Moraceae, Salix, Pendula, Cupressaceae, Pinus, while in autumn it was from Artemisia, Humulus and Ambrosia. We intercepted the monthly average search volume of the keywords "Allergic Rhinitis" and "Pollen Allergy" from 1 Jan 2014 to 31 Dec 2021 in Wuhan (Figure 6) for correlation analysis, which showed a weak positive correlation [$R = 0.378$, corrected $P < 0.001$, 95% CI: [0.187, 0.587], Figure 7]. There was a significant peak in the SV of "Pollen Allergy" in spring, while the SV in autumn was not high. Therefore, we analyzed the correlation between the SV of "Allergic Rhinitis" and "Pollen Allergy" in spring (Feb-Apr) and autumn (Aug-Oct), respectively. The results showed that the SV of the two keywords in Wuhan was strongly correlated in spring [$R = 0.806$, $P < 0.001$, 95% CI: [0.558, 0.911], Figure 8] and moderately correlated in autumn [$R = 0.541$, $P = 0.006$, 95% CI: [0.252, 0.750], Figure 9]. Otherwise, the SV trends of various airborne pollens in Wuhan (Figure 10) were almost consistent with the pollen season and showed that people knew little about certain airborne pollens (e.g., ambrosia, etc.).

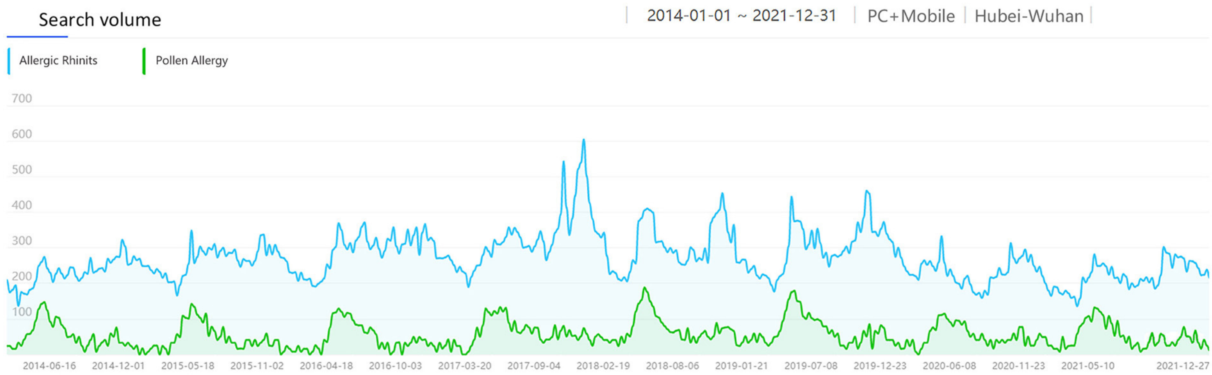

FIGURE 6
The search volume of "Pollen Allergy" in Wuhan from 2014 to 2021.

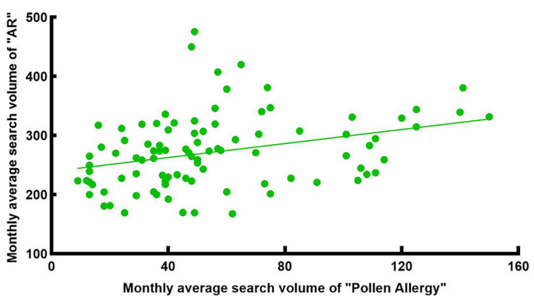

FIGURE 7
Correlation between the search volume of "AR" and "Pollen Allergy" in Wuhan from 2014 to 2021.

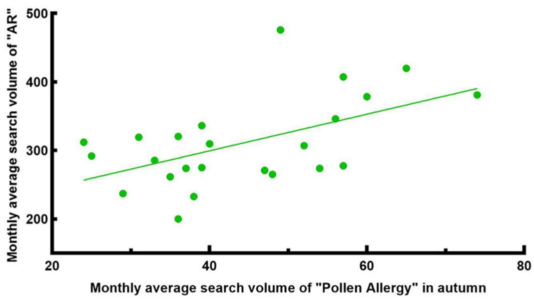

FIGURE 9
Correlation between the search volume of "AR" and "Pollen Allergy" in autumn from 2014 to 2021.

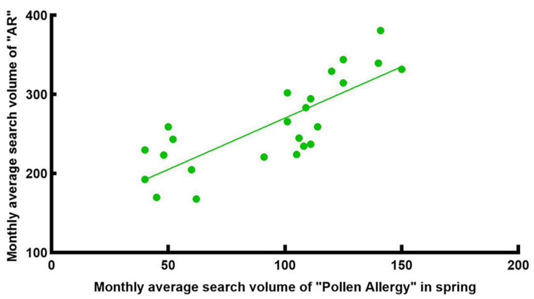

FIGURE 8
Correlation between the search volume of "AR" and "Pollen Allergy" in spring from 2014 to 2021.

As a city located in central China, the most common allergens causing AR in Wuhan include both pollen and dust mites. Therefore, we analyzed the correlation between the monthly average SV in Wuhan of "Allergic Rhinitis" and the SV of "Mites + Pollen Allergy" (Figure 11), representing the combined SV of the two keywords, and got a moderate positive correlation [R = 0.635, corrected $P < 0.001$, 95% CI: [0.501, 0.738], Figure 12].

Internet attention correlation analysis of "Allergic Rhinitis" and the meteorological index of pollen allergy in Wuhan

The correlation between monthly Internet attention to "Allergic Rhinitis" and the MIPA in Wuhan from 1 Jan 2014 to 31 Dec 2021 was shown in Table 1. Monthly SV showed a positive correlation with MIPA in 2014 [R = 0.370, $P = 0.236$, 95% CI: [−0.215, 0.900]], 2015 [R = 0.708, $P = 0.010$, 95% CI: [0.145, 0.950]], 2016 [R = 0.538, $P = 0.071$, 95% CI: [−0.126, 0.927]], 2017 [R = 0.378, $P = 0.226$, 95% CI: [−0.170, 0.884]], 2018 [R = 0.900, $P < 0.001$, 95% CI: [0.641, 0.975]], 2019 [0.911, $P < 0.001$, 95% CI: [0.684, 0.965]], 2020 (0.780, $P = 0.003$, 95% CI: [0.283, 0.962]], 2021 [0.731, $P = 0.007$, 95%

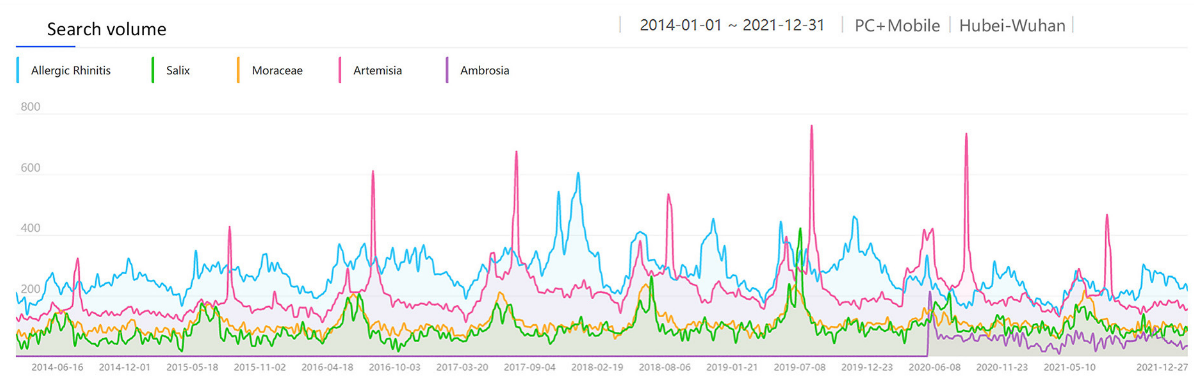

FIGURE 10
The search volume of various airborne pollens in Wuhan from 2014 to 2021.

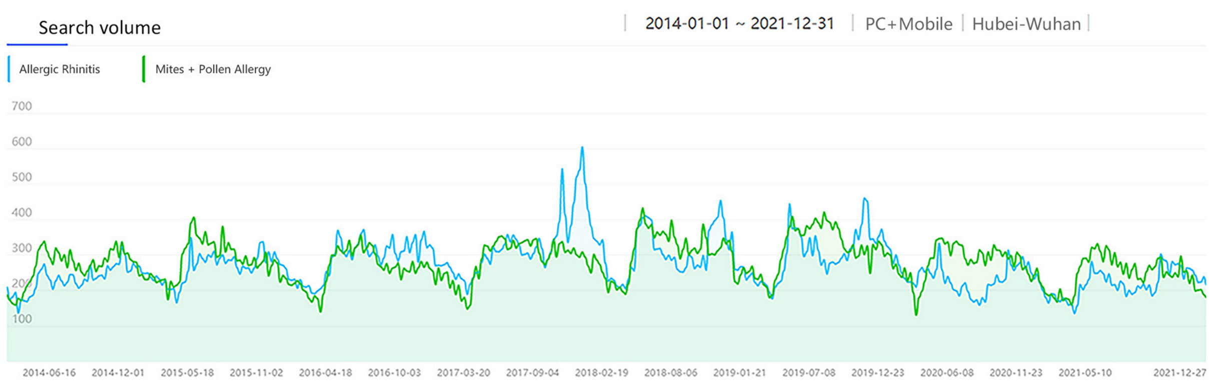

FIGURE 11
The search volume of "AR" and "Mites + Pollen Allergy" in Wuhan from 2014 to 2021.

CI: [0.296, 0.901]], and 2014–2021 [0.554, $P < 0.001$, 95%CI: [0.391, 0.686]].

Demand graph of AR

The demands for relevant search terms were reflected in the changes of users' search behavior. The comprehensive calculation of keywords and the correlation degree of related words, as well as the degree of the search demands of related words, were visualized on the Demand Graph (Figure 13). The Demand Graph showed that searchers were most concerned about "How to cure allergic rhinitis from the root," "Rhinitis," and "What are the symptoms of AR patients." And the search terms that were most relevant to "Allergic Rhinitis" included "What drugs should AR patients take," "What is the self-therapy for AR" and "Symptoms of allergic rhinitis." Besides, there were some moderately related words to "Allergic Rhinitis," including "Allergic conjunctivitis," "Seasonal allergic rhinitis," "Chronic rhinitis," "Allergic rhinitis" in children" and "What to do when allergic rhinitis patients have eye itching" and so on.

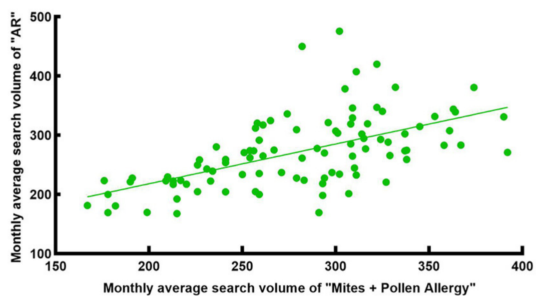

FIGURE 12
Search volume correlation analysis of "AR" and "Mites + Pollen Allergy" in Wuhan from 2014 to 2021.

TABLE 1 Correlation between the monthly search volume of "Allergic Rhinitis" and "the meteorological index of pollen allergy" in Wuhan from 2014 to 2021.

Year	Monthly search volume ($\bar{X}\pm$ s)	MIPA (M ± IQR)	R value	*P* value
2014	7,091.00 ± 1,065.34	1.50 ± 2.60	0.370	= 0.236
2015	7,970.42 ± 1,149.26	2.00 ± 2.00	0.708	= 0.010
2016	8,983.33 ± 1,413.96	2.00 ± 2.76	0.538	= 0.071
2017	10,208.5 ± 2,401.61	2.00 ± 2.75	0.378	= 0.226
2018	9,051.5 ± 1,872.10	2.00 ± 2.65	0.900	< 0.001
2019	9,240.67 ± 1,815.21	2.00 ± 2.75	0.911	< 0.001
2020	6,921.33 ± 1,084.13	2.00 ± 2.00	0.780	= 0.003
2021	6,787.00 ± 1,119.48	2.50 ± 2.75	0.731	= 0.007
2014–2021	8,281.72 ± 1,918.77	2.00 ± 2.00	0.554	< 0.001

Discussion

Principal results

With the rapid development of the Internet and modern information technologies, it is quite common to use Internet data to monitor people's anxiety, happiness, mood, and even the risk of suicide in a certain area (24–26). In the medical field, Google Trends, used for surveillance of disease outbreaks in 2009, has become a model of big data application (27), which uses aggregated Google search data to estimate the current global influenza epidemic in almost real time (28). As the Internet could supply the simplest and primary source of health care information, patients are more likely to have a preliminary consultation online before seeing a doctor (28). To date, Chinese research of search engine data is mainly based on the Baidu Index. There have been some Baidu Index-based relevant studies on the prediction of the brucella epidemic, kidney stones, AIDS, hand-foot-mouth disease, and other diseases (14, 15, 17, 29), which all showed quite good accuracy. Therefore, studying the infodemiology and infoveillance characteristics of AR might help to understand the actual epidemic trend and attention to patients to a certain extent (14).

At present, there has been a little AR-relevant research based on the Baidu Index in China, such as research on the temporal and spatial characteristics of AR epidemics (30), the correlations between search volume and the outpatient visit volume of AR in Beijing and Guangzhou (31), and the epidemiological relevance between adenoid hypertrophy and AR (32), and all the research partly verifies the feasibility of analyzing AR features from the Baidu Index. However, there is no web-based research on the epidemiological characteristics of AR in Wuhan or its association with the COVID-19 pandemic, nor on the people's awareness of allergic rhinitis or demand for AR through demand graph analysis. Meanwhile, as a city located in central China, Wuhan has seen rapid economic development in recent years, but there is a lack of current data on allergic diseases. During the COVID-19 pandemic, almost everyone in Wuhan was quarantined at home for at least 3 months, which made it very inconvenient to go to see a doctor and helped people develop the good habit of wearing face masks outdoors. In recent years, mobile phones and computers have become the preferred methods of obtaining medical information. Therefore, the Baidu Index platform may provide information about the incidence of AR in Wuhan and contribute to understanding the needs of patients.

In this study, we found that the Internet attention to AR in Wuhan and China gradually increased from 2014 to 2017 and remained at a high level from 2018 to 2019. After Wuhan was under lockdown on 23 Jan 2020 due to the COVID-19 pandemic, the Internet attention to AR in Wuhan gradually decreased. These trends are consistent with the reported development trends of AR incidence (4, 33), which indicates that the Internet attention to AR based on search data can reflect the prevalence trend of AR to some extent. Meanwhile, the data released by Nanshan Zhong, the leader of the National Health Commission Senior Expert Group in China, showed that the incidence of all 40 legal infectious diseases in China has decreased since the first half of 2020. Hence, it can be conclude that good hygiene habits, such as maintaining social distance and wearing face masks outdoors regularly, play an integral role in preventing COVID-19 pandemics and associated infectious diseases, as well as reducing the incidence and attacks of AR, which has been confirmed by studies (33–35). Thus, we suggest that AR patients should better maintain good personal hygiene habits and wear face masks outdoors, which can effectively protect them from AR attacks.

We also found that the Baidu search volume of AR in Wuhan showed significant seasonal variation. The first peak was from Mar to May and the second peak was from Sep to Oct, which was in line with the reported two peaks of airborne pollen in Wuhan (23). The two peaks are seasons for airborne pollen in Wuhan, when clinical symptoms are most pronounced and severe in AR patients, which suggests that pollen is an important allergen

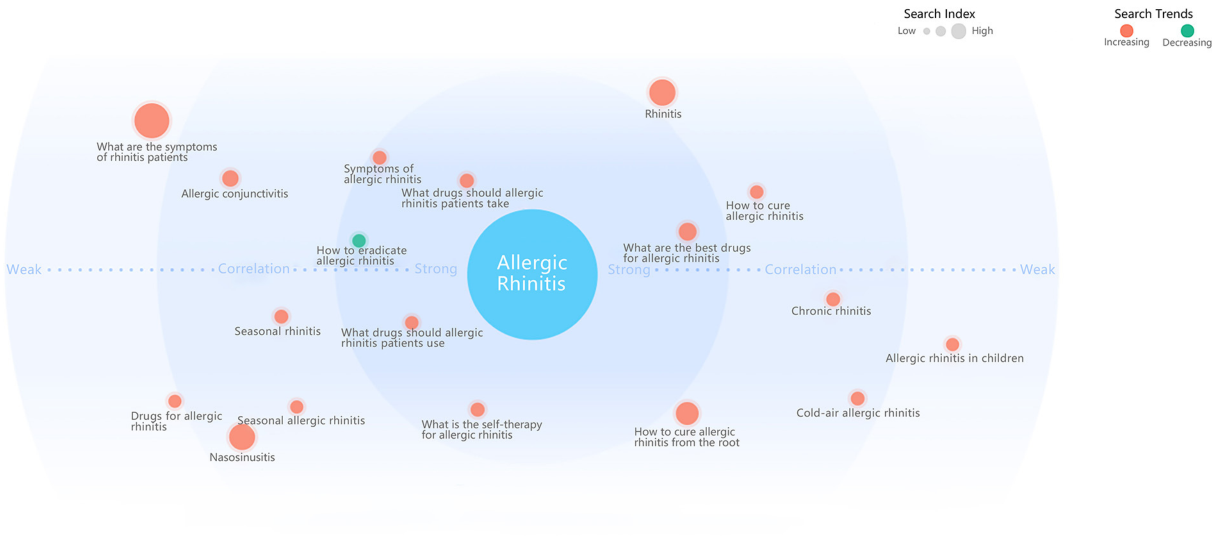

FIGURE 13
Demand graph of AR.

for people in Wuhan, though most studies based on allergen detection experiments report that mites are the most common allergen. Therefore, we can publish more targeted information about AR prevention and treatment on the Internet during the relevant time period. This, in turn, can enhance patient compliance with treatment and demonstrate the importance of health education in the AR prevention and treatment system.

In addition, there was a moderate positive correlation between the SV of "Allergic Rhinitis" and "Mites" in Wuhan, indicating that the AR patients in Wuhan are comparatively concerned about mites as a kind of allergen, and a considerable number of them searched for "Dust Mites" and "Allergic Rhinitis" at the same time to acquire knowledge of allergen prevention and control. Besides, the SV of "Allergic Rhinitis" and "Pollen Allergy" in Wuhan was strongly correlated in spring (Feb-Apr) and moderately correlated in autumn (Aug-Oct). The SV of the main spring airborne pollens in Wuhan, Moraceae and Salix, had obvious peaks in spring (Figure 10). Interestingly, the SV of the main autumn airborne pollen, Artemisia, had two peaks in spring too, which was due to the Chinese custom of using Artemisia during the Dragon Boat Festival in early June every year. As shown in Figure 10, people were also unaware of certain airborne pollens (e.g., ambrosia, etc.). Consequently, people in Wuhan need to raise their awareness of airborne pollen that can cause AR. A moderate positive correlation between the SV of "Allergic Rhinitis" and "Mites + Pollen Allergy" indicates that people in Wuhan are fully aware of AR and pay high attention to the related allergens.

To sum up, our study showed the trend characteristics of "Allergic Rhinitis" search volume are basically consistent with the results of previous epidemiological investigations (4, 5, 23, 33–35) and the correlations of "Allergic Rhinitis" and "Pollen Allergy," "Dust Mites Allergy," and "Mites" SV are the same as the assumption. It suggests that Baidu Index data has the potential to reflect and predict the prevalence of AR by analyzing users' search behavior and medical information needs, and partly guide AR health education in Wuhan, which is consistent with previous research that found Google trends can reflect the epidemiological characteristics of AR in the United States (13).

Pollen-induced AR has attracted more and more attention to people in China. This study found a positive correlation between the monthly SV in recent years and the MIPA. Pollen concentration plays a key role in the outbreak of AR and predicting pollen concentration in advance is very important to control AR. However, there are very few cities in China to carry out pollen concentration predictions (Beijing, Tianjin). Therefore, we select the MIPA instead of pollen concentration in Wuhan, which can reflect the real sensitization effect of pollen concentration on the human body. The positive correlation of AR Internet attention and the MIPA suggests that we can use the Baidu Index to develop a calculation model to predict the arrival and duration of pollen season, which is a real-time and simple method of self-health management for patients with AR. When the SV of "Allergic Rhinitis" begins to increase, which indicates the arrival of pollen season, and pollen-sensitized AR patients should be reminded to take active measures to prevent AR, such as wearing face masks or using medication. This will not only contribute to avoiding the onset of seasonal AR, reducing the pain of patients, but also help to save the expenditure of social medical resources. Of course, more studies are needed to confirm the relationship between SV of "Allergic Rhinitis," MIPA in different cities and actual pollen concentration.

Besides, we also collected user demand graph data, which can partly and intuitively reflect what AR patients were usually concerned about. As shown in the Demand Graph of allergic rhinitis, patients are most concerned about the therapy and symptoms of AR, and most AR patients search for "Nasosinusitis," "Chronic rhinitis," "Allergic conjunctivitis," and "Eye itching." Besides, the SV of related words, such as "Seasonal allergic rhinitis," "Allergic rhinitis in children," and "Can allergic rhinitis infect," is increasing. As can be seen from the Demand Graph, many AR patients are still not cured or relieved and are looking for a radical cure. In addition, a considerable number of AR patients are suffering from nasosinusitis and allergic conjunctivitis at the same time. In general, people would like to search for medical information about AR more and more.

Our results are based on Internet search data, which reflects the public awareness of AR in a comparatively objective way. However, research has shown that mass media have an impact on the search behavior of web users and play an important role in managing an infodemiology and conditioning the search behavior of web users (36, 37). Many users first acquire some knowledge of AR through media and form an initial understanding, such as learning the main symptoms of AR from videos and articles shared on social media platforms, common allergens causing AR in life and treatments for AR. Some people resonating with the knowledge of AR wonder whether they have AR or become interested in AR. These web users then search for AR-related terms through all kinds of search platforms to gain insight into the disease. Indeed, the words used in media coverage will affect the search terms chosen by web users (38), and people may search more due to more media coverage during the high season of AR. Besides, the majority of media popularization of science is conducted by medical professionals, providing specialized terminology and knowledge related to diseases, but there is still a small amount of misinformation without scientific basis, leading to bias in some search terms (39, 40). This bias has been taken into account and we have eliminated the effect of it on the results by searching multiple synonyms. In fact, due to the lack of public education about AR through the media in most cities in China, the impact of the mass media on the search behavior of web users is minimal. Nevertheless, these influences are mostly beneficial for the population, which inspires us to better guide our target audience with the help of web-based social media.

Limitations

The main limitations of this study should be addressed. First, Baidu Index only analyzes search data from Baidu, not social media platforms or other search engines, and provides limited data. Moreover, the impact of mass media coverage on web users' behavior is difficult to assess and eliminate. And these search behaviors may be also influenced by the diagnostic ability of the consulted doctors, such as the general practitioners' ability to distinguish between allergic rhinitis and non-allergic rhinitis. Second, the primary users of search engines are young and middle-aged people, which may lead to an age bias. The Internet and smartphone penetration rates in economically developed areas are higher than those in non-developed areas, resulting in a certain degree of regional bias. But with the development of the economy and the popularization of the Internet, the age-bias and regional bias will gradually decrease. Third, whether predicting the arrival of pollen season or the attacks of AR based on Internet search data, there must be a lag. We still need to study the approximate lag time further, and then bring the results forward when making predictions. Furthermore, information about AR patients could only be based on age, gender, and regions, but information such as the users' age and gender in a certain region, socioeconomic status, ethnicity, and educational background could not be obtained. More studies are needed in the future to adequately demonstrate the role of big data in understanding the population's needs and in the surveillance of diseases.

Comparison with prior work

To the best of our knowledge, this is the first study that analyzes the epidemiological characteristics of AR in Wuhan as well as the correlation between MIPA and the prevalence of AR based on the Baidu Index. This is also the first web-based research on the association of the Internet search trends with the COVID-19 pandemic. In recent years, the number of active users of Baidu has been growing, so Baidu's big data has great potential in medical treatment and disease epidemic surveillance and will play a more and more important role.

Conclusion

In summary, our study showed that Baidu Index data could reflect the real-world situation to some extent and has the potential to predict the epidemiological trends of AR. The Internet data can also be used by medical practitioners to monitor the prevalence of AR and the patients' needs, provide guidance to make disease-specific health care policies and health education, and optimize clinical consultations. Furthermore, developing a platform to predict pollen concentrations as well as the arrival and duration of the pollen season is an excellent method of prevention and management for AR patients. More importantly, keeping good personal hygiene habits and wearing face masks outdoors can help reduce the incidence and attacks of AR.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number (s) can be found in the article/supplementary material.

Author contributions

YW and ZG collected and analyzed the data, discussed the detail, and wrote this article together. HL performed the statistical analysis. YX supervised the study, modified this manuscript, and was major contributor in writing the manuscript. All authors read and approved the final manuscript.

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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's behavior of selection physician in online health communities: Based on an Elaboration likelihood model

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Background: With the rapid development of "Internet + medicine" and the impact of the COVID-19 epidemic, online health communities have become an important way for patients to seek medical treatment. However, the mistrust between physicians and patients in online health communities has long existed and continues to impact the decision-making behavior of patients. The purpose of this article is to explore the influencing factors of patient decision-making in online health communities by identifying the relationship between physicians' online information and patients' selection behavior.

Methods: In this study, we selected China's Good Doctor (www.haodf.com) as the source of data, scrapped 10,446 physician data from December 2020 to June 2021 to construct a logit model of online patients' selection behavior, and used regression analysis to test the hypotheses.

Results: The number of types of services, number of scientific articles, and avatar in physicians' personal information all has a positive effect on patients' selection behavior, while the title and personal introduction hurt patients' selection behavior. Online word-of-mouth positively affected patients' selection behavior and disease risk had a moderating effect.

Conclusion: Focusing on physician-presented information, this article organically combines the Elaboration likelihood model with trust source theory and online word-of-mouth from the perspective of the trusted party–physician, providing new ideas for the study of factors influencing patients' selection behavior in online health communities. The findings provide useful insights for patients, physicians, and community managers about the relationship between physician information and patients' selection behavior.

KEYWORDS

online health communities, Elaboration likelihood model, trust source theory, online word of mouth, patient selection behavior

Introduction

The development of Internet technologies has promoted the maturation of online community models. Online health communities (OHCs) are rapidly gaining popularity as a type of healthcare community (1), becoming a quintessential model of "Internet + healthcare," bringing together medical and health-related information (2). A variety of online healthcare services have emerged along with this, including an online search for health information, online consultation, appointment registration, and other services (3), as an important supplement to the offline medical system, online health communities provide a new channel for physician–patient communication and effectively alleviate the problem of difficult and expensive access to medical care (4). Online medical care breaks through the boundaries of geography and time, enabling patients to obtain health-related information at any time, make full use of medical and health resources, simplify the process of patient access, and improve the efficiency and quality of patient access. According to CNNIC, the size of online consultation users in China reached 298 million by December 2021 due to the COVID-19 epidemic (5). The rapid emergence of internationally renowned Internet healthcare platforms such as Teladoc, Good Doctor, Doctor on Demand, and PatientsLikeMe (6, 7) around the world has broken the limitations of space and time, saved costs, and treatment expenses, and protected the privacy of users. Therefore, more and more users are developing the habit of seeking health consultations online (8). During the COVID-19 epidemic, the number of consultations by the Good Doctor medical platform increased eight times, providing nearly 49 Million Online Consultations in 2021 (9), and online medical consultation will become the new trend in medical treatment.

Online health communities provide people with an important online place where they can search for health information, consult with doctors online, and exchange disease-related treatment experiences (10), mainly containing personal information of physicians and online word-of-mouth generated by patients (11). Online health community user behavior mainly includes knowledge sharing behavior, online health information searching behavior, selecting physician consultation and physician–patient interaction, online health management, etc. (12). Generally, after entering an online health community, patients need to select a suitable physician for consultation from among many physicians who provide online consultation services according to their conditions. However, the selection of different physicians and the online information of physicians can cause a certain information load (13), and the nature of healthcare services as a trusted commodity makes a serious information asymmetry between physicians and patients (14), which affects the selection of patients and increases the risk of their use (15). As service providers in the physician–patient relationship, physicians are an important guarantee of the online healthcare process and have a profound impact on the online physician–patient relationship, while medical health service is a high-trust demanding service, and patients may face the dilemma of selecting a quality physician from among many (16). How to make a good judgment and select a satisfactory physician based on the personal information and word-of-mouth information displayed by the physician has not only troubled patients but also aroused the interest of scholars.

A large number of previous studies have explored the factors influencing the selection of physicians. Early studies focused on offline physician–patient interactions, which occurred in brick-and-mortar hospitals and clinics (17), where physicians were always dominant in the traditional asymmetrical physician–patient relationship due to their medical expertise and the lack of freedom to select physicians as patients were required to obey hospital arrangements when seeking care (18). The influencing factors are mostly physician title, hospital rank, city, service attitude, and external word-of-mouth (10). The emergence of OHC has changed the way of physician–patient communication and service, and the existing studies on medical selection mainly focus on patient-generated word-of-mouth information (19), from the number of online reviews (20), positive and negative evaluations (21), online ratings (12), etc., and mostly use cross-sectional data such as questionnaires or experiments (11). As the provider of online physician–patient trust, physicians are the leaders of online medical services, and physicians' personal information is a direct indication of their trustworthiness. Based on this, this article constructs a multiple linear regression model from the information of physicians' OHC, with the Elaboration Likelihood Model theory as the structure, where the central route combines trust source theory and the peripheral route combines online word-of-mouth theory, to explore the influencing factors of patients' selection behavior and the moderating effect of disease risk on online word-of-mouth.

Literature review

OHC and patients' selection behavior

Online health communities are Internet platforms that provide health-related activities such as information search, disease consultation, experience sharing, and providing mutual encouragement for groups of people with the same disease or the same characteristic attributes (22). OHC can be divided into three categories according to the main participants in the online health community: ① Online patient communities: These communities are primarily composed of patient participation and exist in the form of forums and postings where patients can communicate and share their conditions, and provide a variety of information and emotional support (23). ② Online physicians community: The main participants are physicians, health industry personnel, and researchers in related fields. Physicians can conduct various exchange activities on the platform to learn from others' treatment experiences, expand their treatment horizons and improve their medical skills, as represented by the Lilac garden medical website (24). ③ Online physician–patient community: A media platform used for communication by physicians and patients, and based on which various professional medical services such as disease consultation and online consultation are provided. Representative websites include Good Doctor, 39Health.com, MedHelp, etc. (8, 25).

This article focuses on patient selection behavior in physician–patient communities. Physician behaviors in OHC mainly include: regularly updating personal information and consultation information, publishing articles, and responding to patient inquiries (8). Patient behaviors mainly include browsing and searching for information, selecting physicians, consulting physicians, and online evaluation (16). Current research on patient behavior in OHC focuses on online health information-seeking behavior (26), knowledge sharing behavior (27), online health information-seeking behavior (28), physician–patient interaction, healthcare service research (29), online health management (30), and other aspects. Much of the research on patient selection behavior has been done from a trusted perspective. Trust is one of the important components of the physician–patient relationship (31). While healthcare is a high-trust service, patients may face difficulties in judging the quality of services and making selections about the treatment options available to them (32). Quan et al. (10) confirmed that factors such as physicians' offline reputation and physicians' titles have an impact on patients' medical selection industry based on consumer trust theory. Gong et al. (11) explored, based on the trust theory, that the personal qualities of physicians and online reputation have an impact on patients' selection of physicians. In addition, physician reputation is often used by scholars to explore the impact on patient selection. Han et al. (33) explored the impact of online reviews (positive and negative reviews) on consumers' selection of physicians through a scenario-based experiment. Yuqi et al. (34) used data from third-party platforms for medical services to confirm the impact of online reputation on patients' selection of medical care. Shan et al. (31) used online trust theory to conduct an eye-tracking experiment and found that patient-produced word-of-mouth information influenced patients' selection of physicians through cognitive perception trust and affective trust. However, most of these studies related to trust in online health have been conducted from the trusting party–patient perspective, directly exploring the subjectively perceived trust of the giver. For patients, the information presented by physicians is a signal that their attributes can characterize their trustworthiness to a certain extent, while the online word-of-mouth of physicians is also a signaling mechanism that indirectly conveys trustworthiness. Therefore, it is necessary to explore how the personal information and online word-of-mouth of the trusted party–physician influence the decision-making of the trusting party–patient through the signaling mechanism of trust.

Elaboration likelihood model

The elaboration likelihood model (ELM) is a classical theory of information influence route in the field of psychology proposed by Cacioppo and Petty (35). It states that the persuasion process consists of two routes that lead to attitude change, the central route, and the peripheral route with the difference lying in the level of the individual's likelihood of elaboration processing of the exposed information. The central route is related to the content of the information, and individuals who process information through the central route tend to think deeply about the relevant arguments in the information and make analyses and judgments (36). Individuals who process information through the peripheral route pay less attention to the quality of the information itself and rely heavily on the credibility of the source and the environmental characteristics of the information to judge the credibility of the target (36, 37). The impact of routes can vary as each user has a different level of knowledge base, ability, and motivation to engage in information processing (38). The main variables of the central route include information quality or content quality and the main variables of the peripheral route include source credibility and electronic word-of-mouth (39).

Elaboration likelihood model has been widely used in social media and e-commerce to verify users' attitudes or trustworthiness judgments on online reviews (40), social media messages (41), and second-hand information posting contents (42). Some existing studies explore applications in online communities, e.g., Shi et al. (43) explore factors influencing users' information dissemination behavior on online social networking sites based on the elaborate likelihood model. Bao and Wang (44) extend the understanding of the consumer information adoption process in brand microblogs from central and peripheral routes based on ELM. Wang et al. (45) analyzed the factors influencing the probability of increasing the likelihood of an idea being pre-selected or reviewed based on an ELM survey of Xiaomi MIUI community data. However, the ELM has rarely been applied in research on the patient selection of medical treatment in OHC. Only Xianye et al. (46) explored the effect of physician response information and online word-of-mouth on patients' intention to seek care through ELM in OHC. In the online healthcare field, misidentification of physician information and access choices can pose significant access risks; therefore, it is necessary to further explore the impact of different physician information on patients' medical selection through ELM models.

Trust source theory

Mayer et al. (47) define trust as the willingness of the trusting party to demonstrate its vulnerability to the trusted party, regardless of its control and regulatory capacity, based on the expectation that the trusted party will behave beneficially. Sako and Helper (48) have argued that an explicit strategy for nurturing and sustaining trust can only be feasible if the determinants of trust are identified. The issue of determinants or drivers of trust is also known as the "trust source." Mayer et al. (47) constructed a trust model from a dynamic perspective, identifying the components of trustworthiness of trust sources as benevolent, ability, and integrity trust. With the emergence of the Internet in recent years, the trust source theory has attracted more and more attention. An example is Wu et al. (49) who studied the impact of online responses from landlords on listing sales based on the trust source theory. Bansal et al. (50) argue that trust can be considered as a multidimensional construct of specific beliefs, and he finds that consumers' shopping intentions on Amazon.com are influenced by the reliability of the website's capabilities. Lu and Wu (16) found that trust in the ability of Taobao merchants positively stimulated consumers' purchase intentions in terms of benevolence, ability, and integrity.

In the online healthcare field, one of the important factors for the success of online health services is physician–patient trust. Existing scholars have conducted studies on physician–patient trust, such as (51), who found that the trustworthiness of websites, hospitals, and physicians, as well as perceived benefits and perceived risks, have significant effects on online patient trust. Yi et al. (52) found that argument quality, source expertise, perceived information quality, and perceived risk significantly affect users' trust in online health information. Shan et al. (31) found that the frequency of physician responses and the number of services willing to be opened positively influenced patients' selection behavior based on a trust source credibility model. As a provider of services in an online health community, the physician's personal information is an important trust source. Healthcare is a high-trust demanding service and patients may face difficulties in not being able to determine the quality of the service and make selections about the treatment options available to them (16). Trust as one of the important guarantees of relational exchange has a profound impact on the online physician–patient relationship; therefore, it is necessary to study the patient's selection behavior in online health communities from the perspective of patient trust. This article classifies patient trust in terms of information presentation. Benevolent, ability, and integrity trust in the information sources were used to represent patients' trust in different dimensions of physician information.

Online word-of-mouth

Word-of-mouth is a verbal exchange of information about products, brands, services, vendors, etc. between consumers without the purpose of commercial promotion (53). It plays an important role in influencing consumer selection and brand formation (54). Gelb and Johnson (55) were the first to introduce the concept of "online word-of-mouth (OWOM)," which they considered a form of word-of-mouth communication that also includes the communication and exchange of information through the Internet. Consumers share their shopping experiences and reviews online, especially in common areas of interest such as movies, books, and restaurants (25). Compared with traditional word-of-mouth, OWOM has the characteristics of two-way interaction and low cost, which can break through the original spatial and temporal boundaries of communication (56). In recent years, several Internet healthcare third-party platforms have also introduced online reviews of physicians, creating an OWOM in healthcare (19).

A growing body of literature in recent years has begun to focus on the impact of OWOM on patients' selection of medical treatment. The impact of OWOM on patients' probability of booking a physician appointment is mainly discussed (12, 21), with less attention paid to the impact of OWOM on the selection of online healthcare services. For example, Bensnes and Huitfeldt (20) studied the effect of online ratings of Norwegian primary care physicians on the volume of their appointment (offline) services and found that physicians with high ratings served a significantly higher number of patients than those with low ratings. Xu et al. (12) constructed a BLP-type model to portray the heterogeneity of patients' selection of physicians in a US online physician appointment platform by extracting information from the reviews and found that higher ratings significantly increased the probability of a physician being appointed. Shukla et al. (19), using data from an Indian online physician appointment platform, found that the introduction of OWOM had a "cannibalization" effect, whereby the demand for physicians with high ratings increased significantly, cannibalizing the services of physicians without ratings. This article enriches the evidence related to Internet healthcare services by using data from a large Chinese online healthcare platform. In particular, this platform integrates online physician reviews and Internet medical services on a single website. This allows this article to simultaneously examine the impact of online physician information and OWOM on patient selection behavior.

Research hypotheses and research model

Physician information and central route

Information content and information quality are the main variables of the central route (39), involving the persuasive strength of the evidence embedded in the information (57). Studies have shown that in the online healthcare field, physician information is one of the most important considerations for patients when selecting healthcare services (31), with the content of information influencing the recipient's perceived usefulness of the information, which in turn influences behavior (57, 58). This article classifies physician–patient trust into benevolent trust, ability trust, and integrity trust based on Mayer et al. (47) three-factor division of trustworthiness of trust sources.

Benevolent trust is the willingness of the trusted party to do something beneficial to the trusting party out of altruistic motives. When the trusted party is perceived to be benevolent, the trusting party increases trust (11). Singh and Sirdeshmukh (59) point out that the more services an agent provide to a principal and the harder they serve, the stronger their benevolent trust is represented. In OHC, physicians, who may not be able to respond to patients' inquiries on the platform promptly due to busy schedules such as offline diagnosis or surgery may have a certain negative impression from the patients due to concerns about their unavailability, which may affect selection. From the patient's perspective, the more frequently the physician logs in and uses the online platform, the more viscous the physician is to the platform and the more importance they attach to patient matters, which enables the patient to perceive stronger trust in the physician's benevolence. In addition, a physician's benevolence is reflected in the degree to which they are accountable to patients, and a physician doing their job is an important indicator of good faith trust. Professionally responsible physicians create more opportunities to communicate and engage with patients by opening more types of health services and increasing the number of hours they are online. For physicians who open more types of services, the patient's selection of consultation services will not be limited to the physician's online consultation only, which can meet the patient's treatment needs. Therefore, we propose the following hypothesis.

H1a: *The more recent the physician was last online the more patients selected that physician.*
H1b: *The number of services opened by the physician positively influences the patient's selection behavior.*

Ability trust refers to the skills or talents that enable the trusted party to influence a particular area. A trusted party is only worthy of being trusted if they are highly competent in some specific area (11). Patients use medical skill level and professional competence to make selection decisions (51). The medical title level of physicians is generally formed by the comprehensive certification of physicians' academic level, working years, and professional qualification level (60). Physicians often also undertake scientific research tasks in universities, and their academic titles are the titles granted by their universities to show their scientific and academic abilities in their professional fields. Therefore, the physician title in this article is composed of both medical and academic titles. In addition, the number of physician's articles, both original and shared, which are published on the platform by the physician to help patients and make them aware of disease help patients judge the professional level of physicians. Therefore, we propose the following hypothesis.

H2a: *Physician's title positively influences patients' selection behavior.*
H2b: *The number of physician articles positively influences patients' selection behavior.*

Integrity trust refers to the willingness of the trusted party to reveal their true information without concealment and proactively promote trust by reducing information asymmetry and information risk present in online interactions (11). In OHC, where users perceive a great deal of information risk due to the virtual nature of the web, disclosing true information is one of the ways to enhance trust. While online consultation is about patients' personal life and health, patients are more inclined to trust physicians who can honestly present more personal information. Physicians can select whether to use their real avatars and fill in their biographies and professional fields with the level of detail of their biographies and professional fields when registering on the platform varies from person to person. In this article, the above three indicators are used as a measure of the degree of physician disclosure, i.e., an indication of integrity and trust in physicians. Therefore, we propose the following hypothesis.

H3a: *Physicians use of avatars positively influences patients' selection behavior.*
H3b: *Physician's introduction positively influences patients' selection behavior.*
H3c: *Physician's professional field positively influences patients' selection behavior.*

In the field of information systems, trust is often classified into two different types, initial trust and continuous trust depending on the stage of formation (61). As the frequency of physician–patient interactions increases and relationship development progresses, the intensity of trust changes. Manski (62) argues that users in social networks are a group in nature and individual behavior is not only influenced by their own psychological and physical characteristics but also by the behavior of other users. In OHC, it is influenced by similar groups of users, who use a decision-making behavior based on information about similar patients who have previously selected that physician. The number of patient consultations after offline diagnosis measures the patient's continued trust in the physician. A higher number of patient consultations after offline diagnosis represents more patients who approve of the physician's services, which will increase the level of trust in the physician by other potential patients. Therefore, we propose the following hypothesis.

H4: *The number of patients' consultations after a physician's offline diagnosis positively influence patients' selection behavior.*

OWOM and peripheral route

Peripheral routes involve meta-information about the information (e.g., the source of the information) that is not contained in the information and is preferred by information receivers to aid in decision-making when they lack the ability and motivation to process the information (36). OWOM information is usually used as a peripheral route in ELM models (57, 63). In the e-commerce environment, OWOM is an effective signal of product quality and to some extent affects product sales (64). He et al. (65) found that OWOM influences final purchase behavior by enhancing consumers' trust in merchants. See-To and Ho (66) found that OWOM increases consumers' trust in merchants by trusting subjects' perception of trust in third-party evaluations influencing purchase intentions. Gottschalk and Mafae (67) argued that OWOM has a significant impact on users' decisions. In OHC, OWOM for physicians is divided into patient-generated and platform-generated (19), such as the number of patients' votes, thank-you letters, virtual gifts generated by patients, and the comprehensive recommendation hotness generated by the platform. The number of patients' votes, thank-you letters, and virtual gifts is the quantity of physicians' OWOM, which characterizes physicians' ability and service from the quantitative perspective, while the comprehensive recommendation hotness is the quality of physicians' OWOM, which characterizes the recognition and affirmation of physicians from the qualitative perspective. Comprehensive recommendation hotness is a platform that indicates to some extent a physician's contribution to the community based on their past performance, such as the length of online service and satisfaction with efficacy. Patients can perceive trust through OWOM, which can facilitate decision-making. Therefore, we propose the following hypothesis.

H5a: *The number of patient's votes for physicians positively influences patients' selection behavior.*
H5b: *The number of thank-you letters from physicians positively influences patients' selection behavior.*
H5c: *The number of virtual gifts of physicians positively influences patients' selection behavior.*
H5d: *The comprehensive recommendation hotness of physicians positively influences patients' selection behavior.*

Moderating effect of disease risk

In the online shopping environment, consumer purchase decision behavior is differentially influenced by the moderating effects of product type and consumer characteristics (68). In the online health field, the factors influencing patients' healthcare selection behavior can also be influenced by the type of disease and the psychological characteristics of the patient. For patients suffering from different diseases, their perceived needs and involvement vary (69). Disease risk measures the severity of the consequences of a particular type of disease (70). The risk of disease is related to physical factors (i.e., health status) and physiological factors (i.e., distress, anxiety) (71). The more severe the physical and physiological consequences, the higher the risk of disease. Patients with high-risk disorders may have poorer health status than those at lower risk of developing the disease. Patients at high risk will be more worried and will have a greater desire to find higher quality physicians (16). In addition, patients with high-risk diseases require higher quality services than patients with low-risk diseases (60). Because of its association with mortality, patients with high-risk diseases may be more motivated to make more cognitive efforts to obtain a better physician. Compared to patients with low disease risk, patients with high-risk diseases have a greater cognitive demand for fact-based information presented by physicians, and cognitive demand affects the degree to which users process information (72). Patients with high cognitive demand may be more motivated to exert more cognitive effort to process fact-based information related to the physician themselves, i.e., have a high level of involvement (73). Patients with different diseases attach different importance to the physician's online reputation. When the patient's disease is serious, the patient will consider the physician's serviceability more comprehensively, and negative reviews will have more influence than positive reviews at this time with the patient shunning a physician with negative reviews. When the disease is mild, the patient believes that it will be cured soon and only wants to receive treatment as soon as possible. Therefore, we propose the following hypothesis.

H6a: *Disease risk significantly moderates the relationship between the number of patients' votes and patients' selection behavior.*
H6b: *Disease risk significantly moderates the relationship between the number of thank-you letters and patients' selection behavior.*
H6c: *Disease risk significantly moderates the relationship between the number of virtual gifts and patients' selection behavior.*

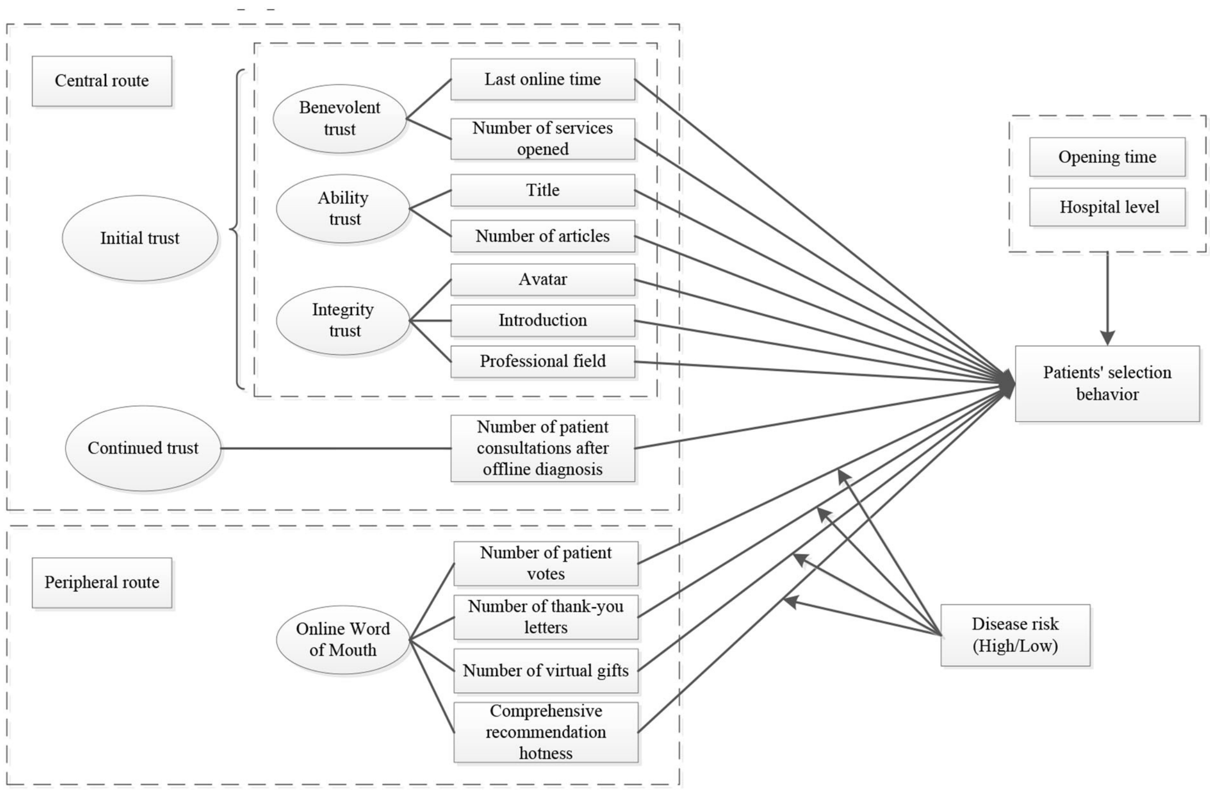

FIGURE 1
Conceptual model of patients' selection behavior in OHC.

H6d: *Disease risk significantly moderates the relationship between comprehensive recommendation hotness and patients' selection behavior.*

Based on the above assumptions, the theoretical framework model shown in Figure 1 is constructed in this article.

Research method

Sample selection and data collection

Data were collected from the Good Doctor website (www.haodf.com) in China. Founded in 2006, Good Doctor is currently a fully functional and well-established physician–patient-based OHC. Good Doctor includes 890,000 doctors' information on the platform, and physicians have opened various online health services to meet the needs of different patients, whose main services include online consultation, team consultation, appointment booking, and private physician. The Good Doctor platform has been established for a long time, and has many physicians with high stickiness and a large patient user base. In addition, the personal information and OWOM information of physicians are open and transparent on their personal homepages, which makes it easy to obtain data and is suitable for the research object of this study.

The physician's personal homepage shows the following information in detail: the physician's avatar, title, hospital, professional field, introduction, service type, total consultations, total articles, patient votes, number of thank you letters, number of virtual gifts, and comprehensive recommendation hotness. A sample of Good Doctor's personal homepage is shown in Figure 2.

Disease risk refers to the mortality rate of a diagnosed disease, reflecting the severity of the disease. Based on the experience of previous studies (70, 73), we selected lung cancer as a high-risk disease and pneumonia as a low-risk disease. According to the Chinese Health and Health Statistics Yearbook 2021, lung cancer ranked first among malignant tumor deaths. In addition, common pneumonia, the most common respiratory disease, is an infectious disease with high curability and low mortality and is comparable with lung cancer as a respiratory disease. In particular, it is noted that pneumonia in this article is a common type of pneumonia that is different from COVID-19.

We used the Python crawler program to obtain the real physician data on the Good Doctor website, and crawled pneumonia and lung cancer treatment physicians according to

FIGURE 2
Good Doctor website physician information page.

the disease classification, crawling time for 1 December 2020, 1 January 2021–1 June 2021, the time interval of 1 month, a total of 13,955 physician data. After the data were coded for cleaning, removing invalid null data, completing missing data, and other cleaning data methods finally obtained 10,446 physician sample data, with an efficiency rate of 74.9%.

Measure of variables

The specific variable descriptions are shown in Table 1. Physician titles are qualitative variables, which need to be quantified: chief physician = 4, associate chief physician = 3, attending physician = 2, resident physician = 1, and other = 0. The academic titles of physicians range from high to low: professor (researcher) = 4, associate professor (associate researcher) = 3, lecturer = 2, assistant professor = 1, and other = 0. And the two different levels of the system were normalized. As shown in equation (1).

$$TotalTitle = \frac{[DIG\left(MedTitle\right) + DIG\left(AcaTitle\right)]}{2} \qquad (1)$$

TotalTitle represents the title after normalization, and *DIG(MedTitle)* and *DIG(AcaTitle)* represent the quantification of medical and academic titles.

On the Good Doctor platform, physician avatars, professional fields, and introductions are uploaded or filled in at the discretion of the physician. For the processing of these online disclosures, the presence or absence of a physician's personal avatar is quantified numerically, with an avatar = 1 and no avatar = 0. The professional field is divided into profile ratings based on word count in a fixed order, with quartiles as the threshold, and 4–1 points, respectively, by word count, and personal introductions are quantified in the same way.

The control variables used in this study were the opening time of the physician's webpage and the hospital rank, where the hospital rank is based on the Chinese Hospital Rank Management Standard, which ranks hospitals into three levels: level 1 is the basic hospital, which usually provides medical services to the community, level 2 is the secondary hospital, and level 3 is the tertiary hospital. Level 3 hospitals employ more staff, have more beds, and are usually considered to

TABLE 1 Description of variables.

Variable type	Variable name	Description
Dependent variable	Selection	Number of patient inquiries
	Last_online	Physician's last website login time
	ServiceNum	The number of online health services opened by physicians, including online consultation, appointment booking, private physician, team consultation, 1 for opening a certain item, 0 for not opening, and the total sum is the number of opened services
	AcaTitle	Professor (Researcher) = 4, Associate Professor (Associate Researcher) = 3, Lecturer = 2, Assistant Professor = 1, Other = 0
	MedTitle	Chief Physician = 4, Associate Chief Physician = 3, Attending Physician = 2, Resident Physician = 1, others are 0
Independent variable	ArticleNum	Number of scientific articles by physicians
	Avatar	Whether there is an avatar, with avatar for 1, no avatar for 0
	Professional	professional field in distribution according to word count, 1 for the first 25%, 2 for 25–50%, 3 for 50–75%, and 4 for 75–100%
	Introduction	Introduction according to the word count distribution, the first 25% is 1, 25–50% is 2, 50–75% is 3, 75–100% is 4
	Reported patient	Number of patients reported after consultation with physicians
	Vote	Number of patient votes received by this physician
	Letter	Number of thank you letters received by this physician
	Gift	Number of virtual gifts received by physicians from patients
	Heat	Comprehensive recommended hotness
Adjustment variables	Risk	1 for high-risk lung cancer and 0 for low-risk pneumonia
Control variables	Open_time	Number of months between collection time and opening time
	Rank	Hospital level is divided into Grade A and other, Grade A is 1, other is 0

provide a higher quality of service than the other two levels, so quantifying the hospital-level numbers, level 3 hospitals = 1 and the rest of the hospitals = 0. In our study model, these variables are used to control for the effect on patient selection.

The results of the descriptive statistics of the variables are shown in Table 2. The dependent and independent variables may not be normally distributed, so the dependent variable and the continuous-type independent variables that are positively skewed are transformed by taking the logarithm (ln(x+1)). The skewness of the variables was all controlled below 3 and could be placed in the regression model for subsequent analysis and testing.

The correlation analysis of variables is shown in Table 3, and all independent variables were significantly correlated with the dependent variable, except for the control variable hospital grade, which was within the normal range of correlation.

Model construction

To test hypotheses H1a–H6d, we construct the following model. The mathematical model of the empirical study is presented in equation (2).

$$\begin{aligned}\ln\left(Selection_{it}+1\right) = {} & \beta_0+\beta_1 OpenTime_{it}+\beta_2 HospitalRank_i \\ & +\beta_3 ServiceNum_{it}+\beta_4 LastOnline_{it} \\ & +\beta_5 TotalTitle_{it}+\beta_6\ln\left(ArticleNum_{it}+1\right) \\ & +\beta_7 Avatar_{it}+\beta_8 Professional_{it} \\ & +\beta_9 Introduction_{it}+\beta_{10}\ln(ReportedPatient_{it}+1) \\ & +\beta_{11}\ln\left(VoteNum_{it}+1\right)+\beta_{12}\ln(LetterNum_{it}+1) \\ & +\beta_{13}\ln\left(GiftNum_{it}+1\right)+\beta_{14}Heat_{it}+\beta_{15}Rsik_i \\ & +\beta_{16}Risk_i\times\ln\left(VoteNum_{it}+1\right)+\beta_{17}Risk_i\times \\ & \ln(LetterNum_{it}+1)+\beta_{18}Risk_i\times\ln\left(GiftNum_{it}+1\right) \\ & +\beta_{19}Risk_i\times Heat_{it}+\varepsilon_{it} \end{aligned} \tag{2}$$

In the model, *Selection* represents the number of consultations by the physician, *OpenTime* represents the opening time of the physician's personal website, *HospitalRank* represents the hospital rank of the physician, *ServiceNum* represents the number of services opened by the physician, *LastOnline* represents the last time the physician was online, *TotalTitle* represents the physician's title, *ArticleNum* represents the number of articles published by the physician, *Avatar* represents whether the physician has a personal avatar, *Professional* represents the physician's professional field, *Introduction* represents the physician's introduction,

TABLE 2 Descriptive statistics of variables.

Variables	N	Minimum	Maximum	Mean value	Standard deviation	Skewness
selection	10,446	0	36,900	1363.41	2666.342	5.166
open_time	10,446	0	158	90.47	42.875	−0.167
hospital	10,446	0	1	0.98	0.149	−6.412
last_online	10,446	0	4	2.57	1.841	−0.607
service	10,446	0	4	1.42	1.109	0.339
title	10,446	0.5	4.0	2.983	1.0867	−0.592
article	10,446	0	5,003	29.08	174.434	18.332
avatar	10,446	0	1	0.69	0.464	−0.801
professional	10,446	1	4	2.49	1.123	0.010
introduction	10,446	1	4	2.50	1.120	0.003
report	10,446	0	22,911	488.15	1228.069	8.369
vote	10,446	0	2,020	123.74	207.883	4.104
letter	10,446	0	1,109	59.70	108.419	4.355
gift	10,446	0	3,208	119.04	298.196	5.674
heat	10,446	2.9	5.0	3.817	0.4178	1.245

ReportedPatient represents the number of patients reported by the physician after the initial consultation, *VoteNum* represents the number of patient votes the physician received, *LetterNum* represents the number of patients' thank you letters received by the physician, *GiftNum* represents the number of virtual gifts received by the physician, *Heat* represents the platform recommendation heat of the physician, *Riski* represents the risk size of the physician's specialization in the disease, β_0-β_{16} represents the regression coefficient, ε represents the time perturbed error term, and *Risk* × *ln (VoteNum+1)*, *Risk* × *ln (LetterNum+1)*, *Risk* × *ln (GiftNum+1)*, and *Risk* × *Heat* test for the moderating effect of disease risk.

Analysis of results

In this study, Stata 16.0 software was used to conduct multiple regression analysis on panel data to estimate the influencing factors of each variable in a hierarchical regression, as shown in Table 4. Model 1 contains only control variables, model 2 adds independent variables such as $ServiceNum_{it}$ based on model 1, and model 3 adds four interaction terms on the basis of model 2, by the adjusted F-value is significant and R^2 is significantly increased, indicating that the introduced explanatory variables have a strong explanatory effect on the explained variables and the model fit is better.

From the regression results of model 2, it can be seen that there is no significant relationship between patients' selection behavior and physicians' last online time (β = 0.0013, sig = 0.311>0.1), and hypothesis H1a is not supported, indicating that patients do not value physicians' last online time in selecting physicians on medical platforms. The number of physicians opening services representing benevolent trust significantly and positively influenced patients' selection behavior (β = 0.0295, sig = 0.000<0.01), and hypothesis H1b was supported. It indicates that in the face of patients with different needs, physicians with a high number of open services can meet different needs, and patients are more inclined to select physicians with a rich number of services. The physician's title, which represents trust in competence, negatively influenced patients' selection behavior (β = −0.0253, sig = 0.009<0.01), and hypothesis H2a was not supported. Higher medical and academic titles of physicians instead lead to fewer patients consulting with that physician, possibly because physicians with higher titles have busier offline work, such as managing a hospital or teaching at a university. The number of articles representing ability trust significantly and positively influenced patients' selection behavior (β = 0.0842, sig = 0.000<0.01), and hypothesis H2b was supported. That is, the higher the number of articles published by physicians on the platform, the stronger the ability to trust that patients can perceive. The physician avatar representing integrity trust significantly and positively influenced patients' selection behavior (β = 0.0860, sig = 0.000<0.01), and hypothesis H3a was supported. Patients feel more authentic when physicians put their personal avatars on their personal homepages, and the sense of unknown and fear during a consultation is diminished. The personal introduction written by the physician has a significant negative effect on patients' selection behavior (β = −0.0096, sig = 0.007<0.01), and hypothesis H3b is not supported. When the content of a physician's personal introduction is excessive and complicated, patients may feel that the physician's expression is tedious and makes it impossible to find the core content, instead, a short and concise introduction is more likely to attract patients' attention.

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TABLE 3 Correlation analysis.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
selection	1.000															
open_time	0.190***	1.000														
hospital	−0.008	0.001	1.000													
last_online	0.605***	−0.174***	0.004	1.000												
service	0.653***	−0.056***	−0.011	0.689***	1.000											
title	−0.084***	0.413***	−0.001	−0.343***	−0.238***	1.000										
article	0.631***	0.214***	−0.029***	0.406***	0.476***	−0.041***	1.000									
avatar	0.415***	−0.076***	−0.026***	0.435***	0.455***	−0.182***	0.360***	1.000								
professional	0.258***	0.037***	−0.061***	0.185***	0.281***	0.012	0.283***	0.153***	1.000							
introduction	0.059***	0.331***	0.027***	−0.145***	−0.030***	0.423***	0.134***	−0.035***	0.172***	1.000						
report	0.819***	−0.024**	0.000	0.633***	0.652***	−0.254***	0.519***	0.397***	0.249***	−0.063***	1.000					
vote	0.818***	0.161***	0.022**	0.537***	0.545***	−0.123***	0.512***	0.335***	0.252***	0.060***	0.833***	1.000				
gift	0.908***	0.135***	0.003	0.598***	0.615***	−0.160***	0.612***	0.400***	0.232***	0.021**	0.842***	0.876***	1.000			
heat	0.584***	0.008	0.026***	0.500***	0.465***	−0.082***	0.389***	0.268***	0.219***	0.037***	0.678***	0.733***	0.637***	1.000		
letter	0.825***	0.109***	0.026***	0.573***	0.581***	−0.173***	0.527***	0.354***	0.250***	0.028***	0.844***	0.978***	0.885***	0.729***	1.000	
risk	0.058***	0.064***	0.059***	0.104***	0.078***	0.062***	0.042***	0.068***	0.000	0.002	0.105***	0.193***	0.131***	0.236***	0.183***	1.000

***$p < 0.01$, **$p < 0.05$.

TABLE 4 Regression results.

Variables	Model 1	Model 2	Model 3
open_time	0.0112***	0.00232***	0.00236***
	(4.06)	(4.88)	(4.81)
hospital	0.0294**	0.0117	0.0125
	(2.15)	(0.27)	(0.29)
last_online	—	0.00135	0.00119
		(1.01)	(0.90)
service	—	0.0295***	0.0279***
		(5.86)	(5.59)
title	—	−0.0253***	−0.0225**
		(−2.62)	(−2.35)
ln (article+1)	—	0.0842***	0.0863***
		(8.64)	(8.90)
avatar	—	0.0860***	0.0844***
		(6.68)	(6.62)
introduction	—	−0.00956***	−0.00819**
		(−2.68)	(−2.31)
professional	—	0.00443	0.00529
		(0.54)	(0.65)
ln (report+1)	—	0.178***	0.172***
		(24.95)	(24.22)
ln (vote+1)	—	0.288***	0.137***
		(13.75)	(4.47)
ln (letter+1)	—	0.304***	0.0260
		(11.72)	(0.53)
ln (gift+1)	—	0.249***	0.159***
		(24.49)	(10.81)
heat	—	0.0977***	0.125***
		(7.76)	(7.67)
risk × ln (vote+1)	—	—	0.235***
			(5.86)
risk × ln (letter+1)	—	—	0.376***
			(6.31)
risk × ln (gift+1)	—	—	0.155***
			(7.78)
risk × heat	—	—	0.0764***
			(2.93)
Constant	4.638***	3.251***	3.208***
	(17.78)	(41.48)	(39.00)
N	10,446	10,446	10,446
R^2	0.030	0.384	0.395
F	17.80***	388.31***	316.10***

t-values in parentheses; ***p < 0.01, **p < 0.05.

There was no significant effect of the physician's description of professional expertise on patients' selection behavior (β = 0.0045, sig = 0.591>0.1), and hypothesis H3c was not supported. When a physician's professional field is described too broadly, patients may feel that the physician is studying too many directions and is unable to focus on a particular medical technique, being general rather than specialized. The number of patient consultations after office diagnosis significantly and positively influenced patients' selection behavior (β = 0.178, sig = 0.000<0.01), and hypothesis H4 was supported. Patients' recognition that many patients similar to themselves have consulted the physician strengthens the intensity of their internal trust in the physician and increases the likelihood of consulting services.

In response to the effect of OWOM on patient selection behavior, the number of patient votes for physicians significantly and positively influenced patient selection behavior (β = 0.288, sig = 0.000<0.01), and hypothesis H5a was supported. A higher number of votes from physicians evidenced more patient recommendations, thus promoting patient selection. The number of thank-you letters from physicians significantly and positively influenced patient selection behavior (β = 0.304, sig = 0.000<0.01), and hypothesis H5b was supported. The number of heartfelt gifts from physicians significantly and positively influenced patient selection behavior (β = 0.249, sig = 0.000<0.01), and hypothesis H5c was supported. Heartfelt gifts are required to be purchased on the Good Doctor platform. Compared with the number of patient votes and thank-you letters, the number of gifts highlights the level of physician service at the level of price and reflects patients' emotional inclination toward physicians. The platform's comprehensive recommendation hotness also significantly positively affected patients' selection behavior (β = 0.0977, sig = 0.000<0.01), and hypothesis H5d was supported. The comprehensive recommendation hotness is the rating of physicians by the Good Doctor platform based on their past performance, which reflects the superiority of physicians from the validity level and has a certain "celebrity doctor effect" to attract more patients to select. From the regression coefficients, we can see that the number of physicians' OWOM is more influential than the platform's comprehensive recommendation hotness, probably because the number of physicians' OWOM is generated from patients who have previously consulted with them, which is more convincing to potential patients.

The regression results from model 3 showed that for the influences on the peripheral route, disease risk significantly and positively moderated the number of patient votes (β = 0.235, sig = 0.000<0.01) and virtual gifts (β = 0.155, sig = 0.000<0.01) as well as the comprehension recommendation hotness (β = 0.0764, sig = 0.003<0.01) on patient selection behavior, hypotheses H6a, H6c, and H6d were supported. When patients have high-risk diseases, due to the complexity of the disease, most patients are unable to judge through their existing knowledge and experience, and therefore may rely more on OWOM information from third parties. OWOM information to a certain extent also reflects the physician's professional and technical ability and service communication ability. Therefore, for high-risk diseases, patients will consider their physicians' personal information more thoroughly, and the moderating effect of OWOM cannot be ignored. The moderating effect of disease risk on the number of thank-you letters and patients' selection behavior was not significant (β = 0.026, sig>0.1), and hypothesis H6b was not supported. The possible reason is that patients suffering from low-risk diseases do not have a certain level of appreciation for physician treatment, reducing the effect on patients' selection behavior.

The moderating effect of disease risk on OWOM information of physicians in the peripheral route was further explored by subgroup regression. The results of the subgroup regressions are shown in Table 5. As shown by the comparison of the subgroup regression results, for high-risk diseases, physician title and professional field had no significant effect on patient selection behavior, while for low-risk diseases, both physician title (β = −0.0376, sig = 0.009<0.01) and professional field (β = −0.0418, sig = 0.01<0.05) had a significant negative effect on patients' selection behavior. The possible reason is that patients with low-risk diseases have some knowledge about the disease and do not pay much attention to the physician's title and professional field, but focus on quick and easy access to medical services. There was no significant effect of physician avatar on patients' selection behavior in high-risk diseases, while there was a significant positive effect on patients' selection behavior in low-risk diseases (β = 0.0687, sig = 0.002<0.01). This suggests that patients with low-risk diseases care more about the physician who displays their avatar, which makes them perceive closeness and increases the likelihood of selecting a physician. In terms of influencing factors on the peripheral route, for high-risk diseases, the number of thank-you letters significantly and positively influenced patients' selection behavior (β = 0.437, sig = 0.000<0.01); for low-risk diseases, the number of thank-you letters did not have a significant effect on patients' selection behavior. Compared to patients with low-risk diseases, patients with high-risk diseases had a sense of "life after surviving a disaster" after treatment and were more likely to express their gratitude to physicians in the form of thank-you letters than patients with low-risk diseases. Also, the results of the group regression are consistent with the results of the previous model, indicating that the model is robust.

TABLE 5 Regression results of subgroups.

Variables	High-risk (lung cancer)	Low-risk (pneumonia)
open_time	0.00389***	0.00114
	(7.37)	(1.36)
Hospital	0.0121	0.0110
	(0.22)	(0.18)
last_online	0.00134	0.000171
	(0.89)	(0.08)
service	0.0207***	0.0245**
	(4.16)	(2.70)
title	0.00674	−0.0376***
	(0.58)	(−2.60)
ln(article+1)	0.0423***	0.136***
	(4.13)	(8.14)
avatar	0.00513	0.0687***
	(0.38)	(3.11)
introduction	−0.00979***	−0.00651
	(−2.77)	(−1.01)
professional	0.00853	−0.0418**
	(1.08)	(−2.57)
ln (report+1)	0.118***	0.148***
	(18.55)	(8.29)
ln (vote+1)	0.381***	0.159***
	(17.50)	(4.20)
ln (letter+1)	0.437***	−0.0494
	(16.91)	(−0.86)
ln (gift+1)	0.350***	0.170***
	(31.95)	(9.54)
heat	0.0766***	0.132***
	(4.88)	(6.70)
Constant	3.314***	3.487***
	(34.29)	(26.51)
N	5,616	4,598
R^2	0.579	0.238
F	460.07***	85.60***

t-values in parentheses; ***p < 0.01, **p < 0.05.

Discussion and implications

Conclusion

Due to information asymmetry between the two parties, the current state of physician–patient distrust exists in online healthcare services (31, 74). This article uses ELM as the structure, the central route is based on trust source theory and the peripheral route is based on OWOM theory. Data collected from Good Doctor with quantitative analysis methods are used to formulate the appropriate research models using variables for the context. We construct a multiple linear regression model and empirically test the proposed research hypotheses. The results are shown in Table 6, and most of the hypotheses are supported.

The main findings of the study: first, the number of opened services, articles, and avatars in the central route all had a significant positive effect on patients' selection behavior. The title and personal introduction had a significant negative effect on patients' selection behavior. According to the personal information of physicians, the more types of services opened by physicians, the more articles published, and the use of personal avatars promoted patients' initial trust in physicians and thus

TABLE 6 Summary of results.

Hypothesis description	Result
H1a: The more recent the physician was last online, the more patients selected that physician	Not Supported
H1b: The number of services opened by the physician positively influences the patient's selection behavior.	Supported
H2a: Physician's title positively influences patients' selection behavior.	Not Supported
H2b: The number of physician articles positively influences patients' selection behavior.	Supported
H3a: Physicians use of avatars positively influences patients' selection behavior.	Supported
H3b: Physician's introduction positively influences patients' selection behavior.	Not Supported
H3c: Physician's professional field positively influences patients' selection behavior.	Not Supported
H4: The number of patients consultations after physician's offline diagnosis positively influences patients' selection behavior.	Supported
H5a: The number of patients' votes for physicians positively influences patients' selection behavior.	Supported
H5b: The number of thank-you letters of physicians positively influences patients' selection behavior.	Supported
H5c: The number of virtual gifts of physicians positively influences patients' selection behavior.	Supported
H5d: The comprehensive recommendation hotness of physicians positively influences patients' selection behavior.	Supported
H6a: Disease risk significantly moderates the relationship between the number of patients votes and patients' selection behavior.	Supported
H6b: Disease risk significantly moderates the relationship between the number of thank-you letters and patients' selection behavior.	Not Supported
H6c: Disease risk significantly moderates the relationship between the number of virtual gifts and patients' selection behavior.	Supported
H6d: Disease risk significantly moderates the relationship between comprehensive recommendation hotness and patients' selection behavior.	Supported

their selection of them for medical consultation services. Higher titles and more complex personal introductions, on the contrary, reduce potential patients' initial trust in the physician and constrain patients' selection. The number of patients reported after the consultation represents patients who continue to trust the physician. The higher the number of patients reported after the consultation, the more patients approve of the medical services provided by the physician, increasing the occurrence of potential patients' selection behavior. Second, both patient-generated OWOM information and platform scoring significantly contribute to patient selection behavior, and patient-generated OWOM information has a greater impact on patient decision-making. Finally, disease risk significantly moderates the relationship between OWOM information and patients' selection behavior. Patients with high-risk diseases have less knowledge about the disease and pay more attention to the experience sharing given by others to assess the physician's medical skill, while patients with low-risk diseases have more knowledge about the disease and pay more attention to the physician's personal information when selecting a physician.

Theoretical contribution

This article makes several theoretical contributions to the literature.

First, we propose a relatively comprehensive model of the factors influencing patient selection behavior based on ELM. Previous studies on the patient selection are mostly based on trust theory and social exchange theory to explore the influence of peripheral routes such as OWOM on patient selection (11, 19, 51). This article considers the trusted source of physicians' personal information as a central route factor, as well as OWOM marginal routes. It enriches the theoretical research in the field of patients' selection behavior.

Second, previous studies on physician–patient trust have focused on patient-generated information (30, 75) with the few studies on physician information only discussing the relationship between the three elements of trust and physician–patient interactions (11). This article divides physician–patient trust into initial and continued trust according to the development stage of the physician–patient relationship (61). Additionally, it explores the influence of the three elements of initial trust source and the number of patients' consultations after diagnosis on the physician–patient relationship in continued trust. The study enriches the research in the field of physician–patient trust.

Third, this article considers disease risk as a moderating variable between OWOM information of physicians and patients' selection behavior. Previous research on the impact of OWOM on patient selection behavior has focused on the moderating effect of demographic information such as gender, age, and education level (11, 21). This study explores the moderating role of disease risk by examining the difference in patients' selection of physicians under two different disease risks. It expands the application of OWOM in OHC.

Managerial implications

The findings of this study provide several managerial insights.

First, it can provide patients with a basis for selecting quality physicians and improve their trust in physicians when making decisions. Patients should focus on the personal information data of the physician such as avatar, the number of services opened, the number of articles, and the number of patients reported after the consultation. These can be used to identify quality physicians with proper medical skills and ethics. At the same time, we should pay attention to the physician's online reputation and the evaluation of similar patients is an important basis to help patients make decisions.

Second, for physician services, it encourages physicians to improve the quality of online services through increased participation in the platform, requiring them to improve their homepages as well as maintain a good relationship with patients. Physicians should pay attention to the improvement and management of personal information, choose an affable avatar display, and a more concise resume; within the scope of their ability, they should carry out diversified types of services, while improving their level of professional competence and focusing on personal OWOM management.

Third, for the platform construction, it helps to design and improve the platform mechanism to provide more sound services for physician–patient communication. Enhancing the disclosure of physicians' personal information, increasing the display of objective data of physicians' online services, and improving the evaluation indexes of the platform will help patients enhance their trust in physicians and help them make decisions.

Limitations and future research

Due to the limitations of the research method and subjects, there are areas for improvement in this study. First, the study data were only from two diseases on the Good Doctor platform, which is somewhat one-sided, and the study results lacked wide generalizability. In future, we may consider selecting physician data from multiple platforms for integrated analysis or selecting multiple high and low-risk disease groups for exploration. Second, the study only considered the objective data of physicians, and since online medical services need to be purchased to obtain, there is a lack of reference to the content of physician–patient interaction, and the interactive content can be incorporated into the model for impact factor analysis in future.

Data availability statement

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

Author contributions

Study conception and design: MQ. Data collection: WZ, CY, SL, and SQ. Data analysis and drafting of the article: CY and WZ. Critical revision of the article and accepts all responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish: WZ. All authors read and approved the final manuscript.

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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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Internet search data with spatiotemporal analysis in infectious disease surveillance: Challenges and perspectives

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With the rapid development of the internet, the application of internet search data has been seen as a novel data source to offer timely infectious disease surveillance intelligence. Moreover, the advancements in internet search data, which include rich information at both space and time scales, enable investigators to sufficiently consider the spatiotemporal uncertainty, which can benefit researchers to better monitor infectious diseases and epidemics. In the present study, we present the necessary groundwork and critical appraisal of the use of internet search data and spatiotemporal analysis approaches in infectious disease surveillance by updating the current stage of knowledge on them. The study also provides future directions for researchers to investigate the combination of internet search data with the spatiotemporal analysis in infectious disease surveillance. Internet search data demonstrate a promising potential to offer timely epidemic intelligence, which can be seen as the prerequisite for improving infectious disease surveillance.

KEYWORDS
internet search data, spatiotemporal analysis, infectious disease, surveillance, prediction

Introduction

In recent years, it has been realized that internet search data have great potential in infectious disease surveillance, which can be proved by increasing the use of such data to conduct rapid epidemics tracking and surveillance (1). As those data can offer timely surveillance intelligence with a high spatial resolution (2), they could be seen as a novel data source to monitor diseases and epidemics at both space and time scales.

The query "internet search data" in disease surveillance refers to social media data, internet search data, medicine sales data, and online news data (3). Infectious diseases continue to pose public health threats with a large social burden (4), and sometimes, they can cause significant pandemics, such as the coronavirus pandemic. To decrease the effects of infectious diseases on our society, it is critical to improve infectious disease surveillance (5).

The main aim of developing a disease surveillance system was to successfully predict possible diseases and epidemics or even outbreaks *via* their ability of early warning based on the data sources (6). Traditional infectious disease surveillance is based on the passive report system, which collects disease notifications from healthcare organizations. This kind of system is typically accurate but can delay up to 2 weeks from patients' diagnosis to the notifications being compiled into the surveillance system (7). As a result, this lag in the reporting process can post an adverse impact on the capability of the infectious disease surveillance system. Such a system may not offer real-time epidemiological intelligence, which leads to the reduction of the efficiency of infectious disease's quick response (8).

Public health experts consider spatiotemporal uncertainty in several manners. The geocoding process, e.g., using disease surveillance data with unreliable coordinates, could lead to spatial uncertainty. In addition, temporal uncertainty in disease surveillance typically causes a time lag between the occurrence of symptoms and case reporting *via* case identification after medical diagnosis (9). In the disease surveillance field, spatiotemporal uncertainty can present at the stages of data collection and statistical analysis. As a result, considering the spatiotemporal uncertainty can indeed contribute to the improvement of surveillance and even decision-making. The lack of spatiotemporal information in data collection and statistical analysis processes may lead to potential errors (e.g., false alarms) in disease surveillance and weaken the benefits of health actions, which is aimed to reduce the impact of diseases (10, 11).

However, few studies argued the use of internet search data with spatiotemporal analysis approaches in infectious disease surveillance. In this review, we present the challenges and possible future directions for researchers to investigate the combination of internet search data with spatiotemporal analysis in infectious disease surveillance.

The application of internet search data

The development of internet-based surveillance

Earlier, internet-based surveillance relied on online news as the main kind of data source, which results from the passive reading of online information for internet users at Web 1.0 (12). However, current studies of internet-based infectious disease surveillance use various internet data sources, including search query data from online search engines and social media such as Twitter (13). This mainly results from the information revolution and the rise of Web 2.0, which triggered the use of the internet as a new tool to actively and frequently seek health-related information (14). Thus, disease activity can be estimated by collecting and tracking changes in frequencies of related internet searches for key terms (15).

Several famous internet-based infectious disease surveillance systems have been successfully built using non-structured, event-trigged, internet search data. The Public Health Agency of Canada developed The Global Public Health Intelligence Network (GPHIN) to assist public health agencies, as well as the World Health Organization (WHO) Global Outbreak Alert and Response Network to detect infectious disease outbreaks using retrieved online information, such as online news. The network has first displayed its great ability during the severe acute respiratory syndrome (SARS) outbreak in 2003, with 2-months earlier reports for SARS than the official one by WHO (16).

Moreover, in the age of "Web 2.0," the technologies of the proliferation of Really Simple Syndication (RSS) and Asynchronous JavaScript and XML enable researchers to develop more interactive infectious disease surveillance, such as HealthMap (17). This powerful internet search data-based surveillance used a wide range of internet external feeds, such as online news to collect valuable disease-related information, and then visualized the critical information, such as disease type, date, and location to the public as an early warning.

The internet search data type

A variety of internet search data can be applied for infectious disease surveillance. Generally, the applied categories include internet search metrics (The volume of internet search activity) and mined social media data (The volume of social media posts). Additionally, the combination of the above internet data source with other data sources also has a great potential for surveillance, such as self-diagnosis questionnaires online, medication sales data, and school absenteeism data.

As a new tool, internet search data relies on the basis that the population group who have a great possibility of infections will actively search related information online about their health conditions. Thus, disease epidemic patterns can be tracked by watching the dynamic of search volume in related internet search activities for certain internet search queries. Internet search data enables investigators to discover disease patterns from timely intelligence at a larger spatial scale (18). As internet use worldwide is currently dominated by various search engines by country, reviewed studies used the dominating internet search engine data by study settings. In our review, several studies using Google (19, 20), Baidu (21–23), and other search term data (24–27) have been performed worldwide to successfully detect infectious disease events.

Social media communication is an increasingly utilized platform to monitor personal health information and contents, which is the main advancement of it compared to other internet data sources (28). Moreover, the interest in using social media data to track infectious diseases is increasing because of the timely data generated by internet users on the platform (29). Thus, social media data are a perfect source for detecting disease in the early stage because of their timeliness characteristic. This characteristic also enables health authorities to contact the public in the early phase of disease outbreak detection (30). We identified several original, exploratory studies on infectious diseases targeting social media users between 1 January 2000 and 30 June 2017. Both Twitter and other blogs claimed to be seen as valuable social media data sources in infectious disease surveillance (31–34).

The data processing of internet search data

Through the common data collecting and processing steps of our reviewed studies (Figure 1), first, all data related to infectious diseases were collected from the internet. The studies that used "internet search data" as a variable collected the search volume from search engine websites and that used "social media data" as a data source that collected diseases-related contents through their application programming interface (API). In this stage, most of the included articles in this systematic review collected their data using key terms within specific time periods and locations. However, for social media data, not all data collected are associated with the specified diseases (35). Textual analysis of data was needed to identify disease-related and non-disease-related data to detect and track disease events. Thus, the second stage involves efficient social media data filtering and classification. Machine learning approaches are commonly performed in reviewed studies to classify whether the collected social media data are relevant to disease events (36). The final stage is to evaluate the predictive accuracy and time efficiency of internet-based surveillance compared to conventional surveillance.

The spatiotemporal internet search data with analysis approaches

Traditional data analysis approaches often generate correlations with biases under the assumption that the independent variables have no autocorrelation at both spatial and temporal scales (37). However, such autocorrelation is very common in the real world.

The main advancement of internet search data is including rich spatiotemporal information, with uncertainty contents at both space and time scales. Internet search data generated from users' Internet Protocol Address can accurately reveal the users' locations. For example, internet search volume data (e.g., Google Trends) aggregated the internet search activities in a certain area with search terms. The geographically tagged tweets indicated the specific locations where the health issues occurred. This can avoid the spatial uncertainty between the real locations of the users and the geocoded address using coordinates, which has been widely used in traditional disease surveillance (38). Moreover, internet search data are produced in real time, including personal health issues, symptoms, and so on. Thus, using internet search data in disease surveillance can limit the time lag in the disease reporting process (39).

Spatiotemporal analysis in the domain of disease surveillance refers to analyzing the surveillance data with geospatial attributes in a time series (40). Elliott et al. identified several spatiotemporal analysis approaches in epidemiology, including disease mapping, disease cluster identification, and correlation analysis (41). Disease mapping is used to show the geographic location of events or attributes, which is useful for communicating trends or averages in an area. Moreover, disease cluster identification can ensure an unusually large aggregation of a relatively uncommon medical condition or event within a particular geographical location or period, which can be seen as an essential prerequisite for identifying an outbreak. Furthermore, the term "correlation analysis in disease surveillance" refers to measuring the strength of the association using statistical methods between event occurrence and potential risk factors, such as environmental factors and sociodemographic factors.

The advances in spatiotemporal analysis approaches can compensate for the residual variability as the spatial variation in data analysis processing, which may lead to a decrease in the effects of potential errors (42). It is critical to simultaneously include the spatiotemporal components and spatiotemporal uncertainty variables in the surveillance (43). Spatiotemporal analysis approaches have additional advances compared to the analysis methods that purely applied spatial or temporal analysis approaches, which is due to the dynamics in spatial patterns over time and temporal patterns at different spatial units. Overall, the spatiotemporal analysis approaches enable simultaneous data analysis at both space and time, as well as the investigation of any unusual spatiotemporal patterns (44).

The spatiotemporal visualization in surveillance

As both internet search data and infectious disease surveillance data have rich information in space and time, an increasing number of studies used spatiotemporal visualization tools to map such variables. These tools enable researchers to show the spatiotemporal distribution of the route of disease transmission combined with the related internet search data. For instance, the HealthMap allows the demonstration of the map of currently active infectious diseases. Furthermore, the

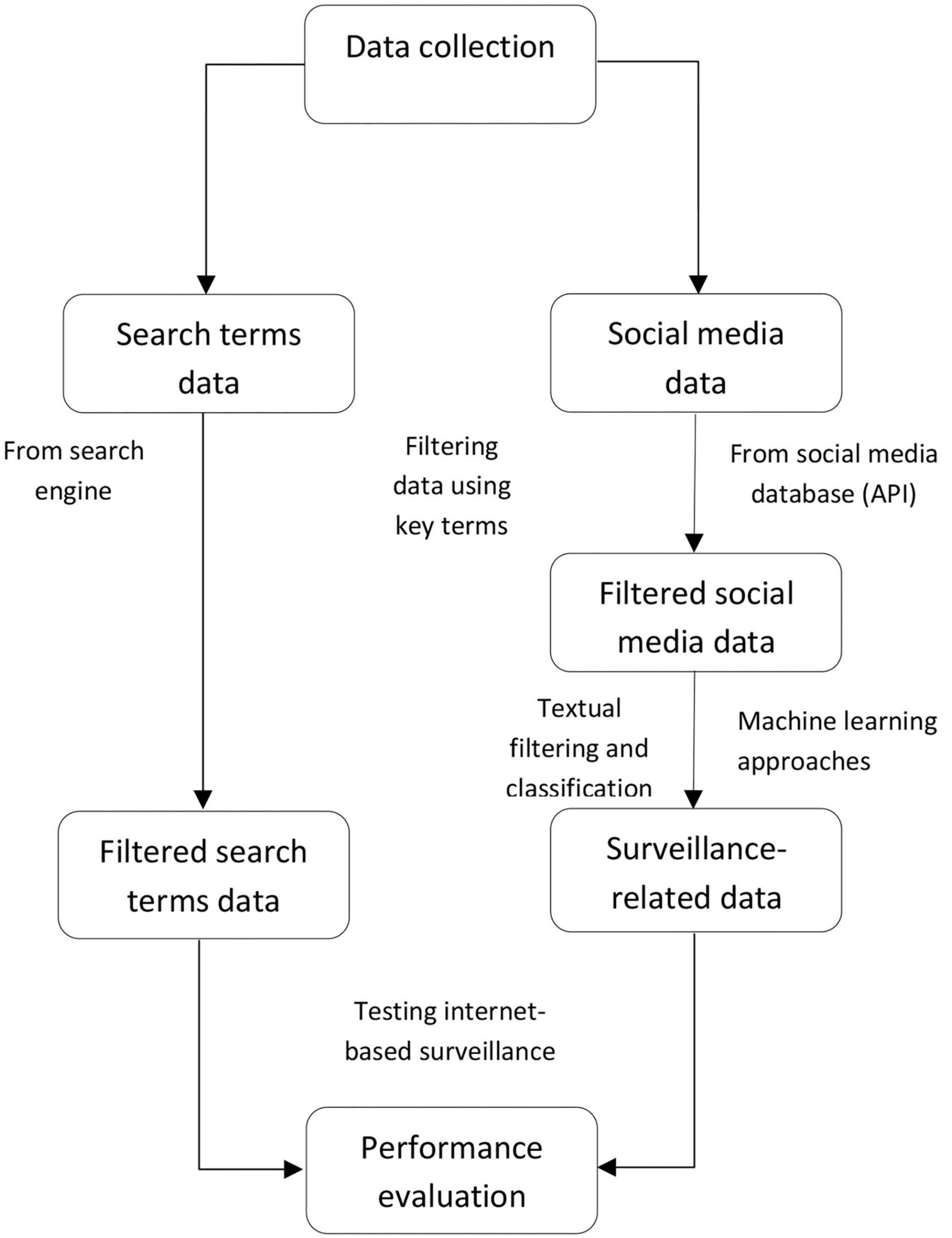

FIGURE 1
The flowchart of data collecting and processing for internet search data.

map contains the links for further latest information about the diseases, which were retrieved from the internet (45).

The spatiotemporal clustering in surveillance

The detection of disease clusters plays a critical role in surveillance, which can help health organizations to identify relatively high-risk areas. Mackey and colleagues investigated the clusters of Tweets with COVID-19-related symptoms or experiences from March 3, 2020 to March 20, 2020. The results indicated that the regions with a larger number of population-normalized COVID-19 confirmed case exhibited more tweets with COVID-19 associated symptoms or experiences (46). Chowell et al. applied online news data and health bulletins to discover the clustering of Ebola virus disease (EVD) cases from January 2014 to January 2016. In the study, there was a high correlation coefficient (Spearman rho = 0.86; $P < 0.001$) between the monthly clusters number retrieved from online news and the officially reported number of EVD cases using traditional surveillance (47).

The application of spatiotemporal models in surveillance

The high resolution of internet search data at both space and time has great promise to enhance disease surveillance by developing adaptive spatiotemporal models at different levels (national, state, and local government) of public health authorities (48).

Generous et al. applied internet search data on Wikipedia to forecast location of the disease in 14 countries with spatiotemporal linear models. Overall, the models successfully estimated the disease activities at a variety of time scales (49). Ma and Yang attempted to use Google Trends data to predict COVID-19 patterns in the United States at both national and state levels *via* regularized linear model, which incorporated a cross-state, cross-region spatiotemporal framework. The proposed model performed well in the predictions up to 4 weeks ahead (50). Zhang et al. developed seasonal auto-regressive integrated moving average (SARIMA) models in different local regions to discover the relationships between seasonal influenza epidemics and Google Trends data with identified key terms. The spatiotemporal contents were considered through the different parameters in the models by region, which can better fit the spatial heterogeneity (51). Li et al. developed generalized additive models (GAM) to predict dengue fever using Baidu Index data at the city level. The results indicated that internet search data (Baidu Index) promoted the forecasting performance at different time scales, compared to the model not using Baidu Index data (23).

The feature of internet search data provides a great opportunity to develop spatiotemporal models in surveillance at a finer spatial scale and time series. This enables public health authorities to better understand disease risks, especially in areas where traditional disease surveillance is poor (52). Furthermore, the flexible spatiotemporal modeling enables internet search data to generate dynamic surveillance in near real time (e.g., disease mapping and risk mapping) (53–56).

The challenges in internet search data and spatiotemporal analysis

The access to internet

As the internet search data is mainly based on the search activity online, it is crucial to consider the ability of internet access. A previous study reported that the majority of internet users were located in developing areas, such as Asia (53.7%), South America (10.2%), and Africa (10.1%) (57). As a result, these regions can be seen as the ideal places to collect internet search data. These regions may have great opportunities to develop infectious disease surveillance using internet search data.

The internet search behavior

The overall performance of the models that purely used internet search data in infectious disease surveillance is widely noticed in previous research. However, such models may be subject to bias and come with potential errors. For instance, internet search data was applied to forecast the number of influenza peaking cases, but the number was two-fold higher than the number reported by the CDC (58). The accuracy of using internet search data in surveillance can be varied by internet search behaviors and media-driven bias. The widespread media reports may lead to many internet search activities by internet users who were not ill (59). Google Flu Trends (GFT) pioneered the internet search data-based flu surveillance in the world. GFT kept watching any changes in internet search behaviors to update its predictive models annually, which contribute to the goodness-of-fit to the reference flu surveillance data (60).

The development of finer spatiotemporal analysis resolution

The main aim of developing infectious disease surveillance was to timely collect disease-related intelligence, which can contribute to decrease the impact of epidemics on the vulnerable population (32). Internet search data source is in an ideal location to conduct quick surveillance and monitoring as it can timely reflect epidemic patterns at the defined spatial units, where internet access is available (35). Internet search data usually included geographic information. Search engines usually provide search volume data at the state or even lower level, and social media data usually include users' geographic locations. This nature can identify high-risk areas of infectious diseases by determining the areas with high volumes of internet data generation.

Google Flu Trends have made some great progress in the finer spatiotemporal resolution analysis, which offers city-level or finer spatial resolution internet search data in influenza surveillance (61). Although a finer spatiotemporal resolution in internet search data is limited by the capacity of data aggregation and internet search volume, the rapidly increasing use of internet search as a health knowledge tool could lead to the development of a better spatiotemporal analysis using a finer resolution internet search data in space and time (62).

Developing integrated surveillance using internet search data with spatiotemporal analysis

The surveillance system purely based on internet search data may generate noise value and failed predictive results. First, the accuracy of internet-based surveillance may be impacted by the levels of internet access (63). Second, it is acknowledged that there are different internet-seeking behaviors, self-reporting, and media-driven bias between different sectors of the community (64). Previous studies reported that media bias can adversely impact internet-based surveillance systems (65). Third, the absence of involving other risk factors for infectious diseases, such as climatic and socio-economic factors, may contribute to the noise or failed prediction of infectious disease events. Finally, exploring spatiotemporal clustering plays a crucial role in surveillance. This enables health authorities to trigger disease intervention in high-risk windows to reduce the burden and impact of infectious diseases.

The successful surveillance systems for infectious diseases are affected by the complex conditions and the transmission patterns of the disease, and social-environmental variables (66). Previous studies indicated that infectious diseases have strong climatic and social-environmental patterns (67, 68). The involvement of climatic and social-environmental factors could improve the predictive performance of epidemiological models (69–71). The prediction results can contribute to the decision-making of certain control measures and surveillance, such as the allocation of healthcare resources, social distance control, vaccination plan, and health education.

Thus, a dynamic, integrated surveillance system using big data has the potential for timely and specifically detecting infectious disease events and reducing the potential errors introduced by factors such as fear-based searching. We designed a flowchart of a dynamic spatiotemporal model for infectious

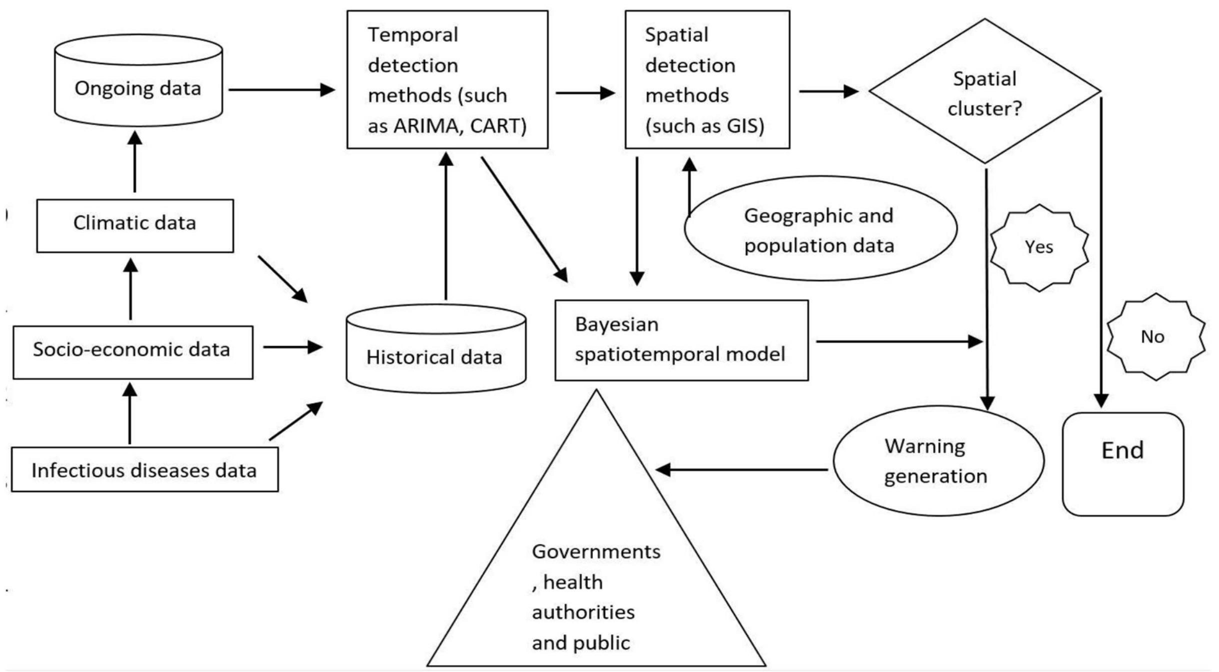

FIGURE 2
Hypothesized framework of a dynamic spatiotemporal model for infectious disease surveillance using internet search data.

disease surveillance using big data, which provides possible research directions for future study (Figure 2).

Conclusion

Internet search data hold the potential as a free, easily accessible data source to access large community fraction of health-related data to reflect disease activity and generate timely disease information by targeting people in the early phase of the disease process (72). Ongoing evaluation, validation, and verification of internet search data-based surveillance with epidemiological and clinical data by users, developers, and agencies will greatly improve the utilization of this new surveillance approach for infectious disease detection and tracking. This study provides the necessary groundwork and critical appraisal of the use of internet search data and spatiotemporal analysis approaches. This study also provides future directions to researchers to investigate the combination of internet search data with spatiotemporal analysis in a wider range of infectious disease surveillance in more regions worldwide.

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

HS and YZ contributed to the conceptualization, methodology, and writing—review and editing. GG and DW contributed to the data curation and funding acquisition. All authors read and agreed to the published version of the manuscript, participated in data collection, preliminary analysis, early drafting of the manuscript, made substantive contributions to the development and revision of the manuscript, contributed to the article, and approved the submitted version.

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Conflict of interest

HS, YZ, GG, and DW were employed by Popsmart Technology (Zhejiang) Co., Ltd.

Publisher's note

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Blockchains as a means to promote privacy protecting, access availing, incentive increasing, ELSI lessening DNA databases

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Not all blockchains are created equal, and many cannot accommodate all of the primary characteristics of big data: Variety, Velocity, Volume and Veracity. Currently, public blockchains are slow and clunky, it can be expensive to keep up with the velocity of genomic data production. Further, the transparent and universally accessible nature of public blockchain doesn't necessarily accommodate all of the variety of sequence data, including very private information. Bespoke private permissioned blockchains, however, can be created to optimally accommodate all of the big data features of genomic data. Further, private permissioned chains can be implemented to both protect the privacy and security of the genetic information therein, while also providing access to researchers. An NFT marketplace associated with that private chain can provide the discretized sale of anonymous and encrypted data sets while also incentivizing individuals to share their data through payments mediated by smart contracts. Private blockchains can provide a transparent chain of custody for each use of the customers' data, and validation that this data is not corrupted. However, even with all of these benefits there remain some concerns with the implementation of this new technology including the ethical, legal and social implications typically associated with DNA databases.

KEYWORDS
blockchain, ELSI (ethical, legal, and social implications), DNA database, big data, privacy

Introduction

There are millions of human genome sequences (both whole genome and partial) online as a result of various public and private efforts. That number grows daily (1). Online genomic information is increasingly pervasive due in part to the rapid fall in sequencing and storage costs. Concomitantly, direct to consumer (DTC) companies have been selling ever cheaper sequencing opportunities, providing a range of mostly recreational services with varying degrees of scientific validity. Additionally, on the research side, there are many government-funded efforts that collect genomic data from study participants (2–4). One of the largest and most prominent, the All of Us program, is a US government directed personalized health initiative that aims to collect genomic data from up to 1,000,000 US citizens (5).

When the DTC genomics company 23andMe sold access to collected genomic information, they underscored the value of access to these troves of genomic information (6). However, both the potential to deanonymize data to identify private and compromising genetic-based information about people, and the potential to use public genomic databases to also seek out and convict criminals has created a chilling effect on the sharing of genomic data. Many who have submitted or are considering submitting their genetic information to both public and private databases are concerned that their information could be used to put them or a close relative behind bars.

In a worst-case scenario, this expansive amount of publicly accessible DNA information can lead to what the late United States Supreme Court Justice Antonin Scalia referred to as a "genetic panopticon." (7) Like Jeremy Bentham's proposed prison of constant surveillance, the ability to easily access genetic information that can be relatable to you, either directly or through relatives, creates a reality where our genetic information, when publicly accessible can inform or incriminate anytime and without our consent.

A simple-minded solution would be to store genetic sequencing data offline, encrypted or otherwise in some mostly inaccessible fashion. However, the value of that genetic data to society would be significantly diminished. This dichotomy between simple and easy access to genetic information for research purposes and the need for genetic information to be inaccessible for privacy purposes has long vexed research in this space. Blockchain technology could be part of the solution.

Blockchain platforms are typically immutable ledgers sealed with cryptography and decentralized, with the data siting on thousands if not millions of independent machines or nodes within the blockchain network. Blockchain technology provides a novel storage solution that could allow for continued access to genomic resources while potentially also preventing the misuse of genomic information collected from both governmental and private sources. More than the privacy implications, storing genomic sequences on the blockchain could provide substantial gains in access and usability.

Their potential notwithstanding, there are numerous concerns associated with employing blockchain technology for genomics research. Storing so much data– simply the raw genomic data would comprise at least a gigabyte or more of information– is not necessarily feasible or cost-effective on many public blockchains, like the Bitcoin or Ethereum chains, owning to the massive costs to store so much data. Storing the data off-chain might be more feasible, but then many of the benefits derived from blockchain technology are minimized, such as decentralization and immutability, to degrees.

Nevertheless, in spite of the practical concerns with employing blockchain, in addition to the aforementioned academic research, there are numerous companies that are employing blockchain for genomic and other health-related information (8). Consider, for example, a company like DNAtix which aims to compress DNA sequences by up to 99% of the original size (9), to facilitate the use of public chains. Other companies might consider other possibilities like bespoke private chains. We discuss them herein as well as the ethical, legal and social concerns associated with using either public or private blockchains to store genomic and associated information.

What is wrong with the current situation?

In the research world, databases for genomic information have goals that may sometimes come into conflict. Researchers need data to be accessible, transparent, reliable and informative and standardized. On the other hand, data is often private and revealing and needs to be inaccessible to those lacking the required permissions. Even those that have permission, may need different versions and different accessibility of the data, depending on many factors, including the nature of their research. And there is always the concern that data, even if permission is legitimately granted, can be misunderstood and misused, or leaked.

Individuals who sequence their genome either for research or for recreational uses are often keen to learn about the results of that research. In other circumstances, sequenced individuals do not want to learn about the outcomes of relevant research, particularly if there isn't anything that can be done to ameliorate the future concern. In some situations, the researchers arguably have an ethical obligation to inform sequenced individuals of actionable medical information gleaned from the data, in some situations they might have an ethical obligation not to inform the sequenced individual, and in some situations, they may have an obligation to inform the extended family of the individual. In addition to the enormous ethical burden, the administrative costs of tracking those that want to, need to, or don't want to be informed of findings can be overwhelming, especially for smaller research endeavors. Further complications can arise when sequenced individuals will allow research to be conducted on their genomes in some areas, but not others. This limitation can complicate access to data when informed consent is required for each new research direction. All of this can inhibit sharing and access to data.

Other concerns associated with standard genetic databases include: (i) data corruption or database failures can limit the usability and reliability of data; (ii) access to DNA databases can be expensive, and researchers can benefit from reliable access that is priced according to their needs; and, (iii) ostensibly anonymized DNA and its associated private information can be accessed without an individual's consent even though that information can often be deanonymized. There remains a fundamental question as to whether a DNA sequence can ever remain truly anonymous; studies have shown that even purportedly anonymous genomes can allow, at least to some extent, the determination of the donor's identity (10–12).

The law often moves glacially slow in response to evolving technologies. Laws and regulations lag behind the innovations in DNA sequencing and analysis (13) and any current enforcement of privacy policies and protection of DNA data are still in their developmental phases.

In summary standard DNA databases have been unable to deal adequately with all of these and other governance issues (14). As such, a technological solution that can provide usable access without impinging on the sequenced individual's ethical rights is needed. That technical solution can be found in blockchain technology.

Blockchains

Since time immemorial ledgers have formed the backbone of most economies, recording contracts and payments for buying and selling of goods or the exchange of assets. These ledgers started out as records on clay tablets, later on paper, ultimately forming the books supporting modern accounting. Over the last decades these records have moved into the digital realm which made the current complex global economic system possible. Innovation in data keeping continues even today as ledgers are shifting to a global network of computers which is cryptographically secured and decentralized commonly known as a distributed ledger technology (DLT) or blockchain technology. The pseudoanonymous Satoshi Nakamoto described and created the first model of the blockchain (15).

Blockchain can be understood as a decentralized distributed digital database. Until recently, digital databases were designed to centralize information (16). The blockchain though, uses a network of independent computers to maintain a shared database across many nodes (17). Succinctly: when new entries into the database are made, they are automatically broadcast across the blockchain's decentralized network, creating redundant and exact copies. Blockchains claim to be trusted databases, with this trust maintained by open secure computer code and encryption running on all of the decentralized and distributed nodes.

More technically, a blockchain is a set of agreed upon protocols and cryptographic methods that enable a network of computers to work together to securely record data on a shared open database. Every transaction of information is registered and timestamped; all other participants can see that registration. Metaphorically, a blockchain may be considered as a series of blocks of data that are securely chained together. The chain of blocks are linked and secured using cryptography (18). New blocks within a blockchain are formed as contributors create new data. These blocks are encrypted and given a hash value that represents a unique identifier of the data within that block (19). This hashing works *via* a standard algorithm being run over the block's data to compress it into an alphanumeric string. This hash value can be recalculated from the underlining file, confirming that the original contents have not changed. Any minor change within the data will result in a substantially different alphanumeric string—but the reverse is not possible: given just the hash value you cannot recreate the data contained in the block.

All blocks of data which are formed after the first block are securely chained to the previous one *via* the hashing system. Thus, once recorded, the data in any given block cannot be altered afterwards without the alteration of all subsequent blocks across a majority of the identical blocks residing across all the nodes within the network. This hashing and linking of blocks make canonical blockchains resistant to modification of their data. The records are effectively immutable as they cannot be deleted or changed without a consensus of the majority of nodes within the change. Without this majority agreement, a consensus algorithm runs across all nodes hosting the blockchain to make sure that there are no lone outlier records within the network that do not match other versions within the network, for example, due to data corruption. As such, data stored on the blockchain is generally considered incorruptible.

Another principle characteristic of canonical blockchains is that they are distributed systems. This means there is no centralized organization to maintain and verify the entries on the database. Instead, this database is maintained by a large number of computers that are, in some blockchain systems, incentivized to provide computing resources by earnings some form of tokens in exchange. Any computer that is connected to the blockchain network can perform the task of validating the transactions taking place in the network. Validated information is ultimately saved on all the computers nodes in the network providing a greater degree of reliability and protection against data corruption: While each computer node in the network cannot be unwaveringly trusted individually, the system provides a mechanism for creating consensus between the distributed nodes, resulting in the necessary trust and reliability.

Immutable database—tamper proof

To successfully and intentionally tamper with the blockchain you would need to alter all the encrypted blocks on the chain going forward from the one you altered so that all the aforementioned hashes reflect the underlying data. In a true distributed public chain this would require that the interlocuter take control of more than 50% of the peer-to-peer network. Only then, when more than half of the participants in the network have the altered record will it become the consensus of the chain. On a blockchain of almost any substantive size this would be difficult to do. On larger worldwide networks it is effectively impossible. Of course, this only protects on-chain data. Storing information off the chain and linking to an on-chain identifier will not protect that off-chain data from bad actors or data corruption. Further, on chain data is only truthful with regard to the time of entry and in some specialized cases like the bitcoin blockchain, the number of bitcoins owned by the various users. The blockchain, however does not attest to the veracity of the underlying data—i.e., anyone can easily submit false data to the blockchain, as there are no barriers to this.

Blockchain taxonomy: public and private blockchains/permissioned and permissionless blockchains

While blockchain technology was initially introduced to the world as a mechanism to enable Bitcoin, it has become increasingly recognized that this system is secure enough to work as a ledger for limited access databases for governments and for private financial institutions. To accommodate the varied institutions that use blockchains there are numerous types of blockchains. These include permissioned and permissionless and private and public chains. Most recognize the public blockchain versions, such as the Bitcoin and Ethereum blockchains. These are ostensibly ownerless entities run by consensus of the nodes. There is no centralized or trusted authority. These chains are also permissionless. In permissionless blockchains, anyone can download the necessary software, become a node within the blockchain and have access to all of the canonically transparent information. Nodes can read, write and/or audit the blocks of data. In public blockchains, in principle, any of the nodes can be the originator of the information in the block.

Permissionless chains are often public and privately owned chains are often permissioned, but that needn't be the case.

Nodes in permissionless blockchains are typically anonymous or at least pseudonymous. These types of blockchains stake their trustworthiness and reliability on the hope and belief that colluding bad actors control less than 50% of the nodes. Any changes to the blockchain software protocols are consensus driven.

Public blockchains lack a trusted intermediary by design and rely on their consensus and validation software run over numerous independent nodes for validation. That validation can sometimes be expensive and energetically wasteful depending on the type of validations used. One prominent type of validation is proof of work. This validation stems in part from miners that compete for fees, that fee is funded by those completing transactions on the chain. At the time of writing, the Ethereum public permissionless blockchain only just implemented software changes that will switch the chain from proof of work to proof of stake. Whether this will significantly increase the speed of transactions, reduce the cost of using the Ethereum platform, and reduce its environmental impact remains to be seen (20).

Permissioned chains are closed to only those nodes that are granted permission through invitation. Private and permissioned blockchains are often used for enterprise applications and are often much faster and more efficient than public and permissionless chains. Private blockchains can employ a trusted intermediary to mediate the operation of the network, which is often considerably smaller than public networks, although private chains can also incorporate mining operations for validation. Private and permissioned blockchains, their centralized authorities notwithstanding, still often operate on decentralized distributed ledger system. In some cases, the centralized authority may maintain a primary copy of the ledger and permissioned users can set up nodes with access to some but not necessarily all of the ledger data.

While all nodes are typically equal in permissionless chains, in a permissioned chain or in a private chain, some nodes may have more rights and capabilities than others; the central authority can choose the degree and nature of transparency for the data for each user. Private and permissioned chains can also be run by a closed consortium wherein some or all the members themselves represent the trusted intermediary. Hybrids of the permissioned and permissionless blockchains also exist. They may be relatively open in terms of the ability for the public to become a node, but they have a trusted intermediary in a central authority.

Genetic information on blockchains

Given the concerns and problems associated with standard DNA databases described above, there are many advantages to saving and storing genomic information on a blockchain. This paper will focus principally on private/permissioned blockchains as public blockchains raise their own difficult privacy concerns given their transparent nature. They are also typically slow and expensive and the amount of data that can be stored on the chain is inherently restricted; they are not necessarily better DNA data storage options than standard databases.

Private permissioned blockchains on the other hand can be constructed such that they can host large amounts of data on chain rather then simply pointing to the data that resides elsewhere. Hosting the data on chain can allow for greater security and reliability: with multiple copies of the database hosted in various nodes, the chain can rely on a consensus algorithm to maintain a dataset that reflects the majority of nodes and not the minority of corrupted nodes. Versions of private chains for storing genetic information have already been described (21).

A private blockchain further allows for data to be stored safely and securely while still allowing for infinitely-discriminating access to permissioned users. Each user can be granted their own tailored access to the data in terms of things like timeframe of use, nature of the data provided, amount of the data requested, off-chain usability of the data and more. Moreover, private chains relying on a trusted intermediary don't necessarily require the slow and expensive validation steps of public blockchains. Their software protocols are also easily adjustable and adaptable by a central authority when necessary.

A private blockchain can be designed with the specific needs of the genomics research community. For example, each block can represent a single individual and all the associated data, including genomic and phenotypic information. Alternatively, data for a single induvial can reside on multiple blocks, as its added, and yet still be associated with the sequenced individual *via* a unique identifier stored either in the chain, or off chain. The second option allows for updates and additions to the data while still maintaining cryptographically ensured immutability of the data.

Permissioned users can be allowed to either add and/or view data on the chain depending on the centralized authority. Reading, writing, and accessing of the data can be recorded and cryptographically timestamped within the blockchain itself providing a more reliable chain of custody of the data as well as keeping track of who uses and submits data to the chain.

An NFT marketplace for genomic data

Consider the following technical solution for empowerment of sequenced individuals while creating access to data for researchers.

Each sequenced individual is indexed within the blockchain *via* a unique identifier. Their genomes and medical information that reside throughout the private blockchain, added periodically as more data becomes available, are all tied to that identifier. At least one non-fungible token (NFT)–a unique, often standardized cryptographic asset associated with data on the blockchain, comprising some data or metadata—for each sequenced user is created to transparently represent each individual identifier within the database. That NFT can be anonymous or not, depending on the database or the sequenced individual, although to protect the genomics of the extended family the NFT ought to be anonymized, keeping in mind that at minimum, the NFT will be associated with an IP address or a wallet, likely the wallet or IP address of the sequenced individual.

More broadly, NFTs were initially designed to create scarcity where there was none. Consider digital art online. In the non-digital art market, value is partially associated with the rarity of the art. With online art there is no scarcity as the art can usually be reproduced infinitely, often without the permission of the artist, with no noticeable loss of quality. Consider the canonical example of an image that has been online for years, copied thousands if not hundreds of thousands of times. In these cases, a digital artist is faced with the possibility that collectors will not pay for this art if it is freely available online to everyone else. The NFT was created to artificially create the scarcity component for art. While there may be millions of copies of the art, there is only one (or more) unique, non fungible tokens associated with the art. The NFT is linked *via* the coded smart contract within the NFT to said art by way of a unique identifier.

The NFTs need not confer any actual rights vis-à-vis the original digital art, or any item, digital or corporal, for that matter, that is linked to the NFT. Rather the NFT represents only a unique link to that object. Moreover, they need not confer any ownership rights over an image or digital object that are often otherwise continued to be freely copied and used online.

More simplistically, the NFT is a cryptographic token that represents some relationship between the owner of the token and the item that the token represents. Arguably, an NFT is metaphorically an authenticated signature associated with a piece of art.

More technically, NFTs are smart contracts (specifically built upon the ERC-721 standard that dictates details within the contract such as ownership security and other metadata) that represent a bundle of ownership rights associated with an object, typically a digital object and often a piece of art, although NFTs can be employed to tokenize ownership of art and real-estate in the non-digital world. Rarely do NFTs confer undiluted ownership, and often NFTs will retain ownership rights for the creator of the NFT, e.g., the artists, such as pass-through royalties.

While NFTs as a collectable or investment product have seen their market erode substantially (22), NFTs remain valuable tools to identify and track information as it is traded among the blockchain. NFTs need not contain the information they represent, only code that can be used to identify and locate the information or digital file.

In our case, the NFT is associated with genetic, phenotypic and/or medical data. The token is a unique connection to that data, and the holder of the token can be granted some rights in that data, including access and manipulation. Moreover, the flexibility of the NFT smart contract standard allows the incorporation of other data within the NFT associated with genomic information. This data can include information regarding a user's privacy preferences, research-area preferences, informed consent and other relevant legal information. Alternatively, rather than storing this information on chain in the NFT, it can also be stored off the blockchain, albeit associated with the unique identifier within the NFT.

Off chain data can be stored on distributed files systems like the IPFS, the interplanetary file system or centralized databases. Notably, off chain data can also be more easily modified than data in an NFT, as might be necessary with regard to evolving preferences and informed consents. However, at minimum, the computer code residing within the NFT should provide anonymized basic relevant information about the sequenced user, including information like gender, basic medical history including disease, and other information that might be important to a biomedical researcher seeking out sequences to include in their research. Regardless of what data is stored in the NFT, the NFT will spell out the immutable connection between the genomic and medical data and the metadata on the NFT.

Researchers keen on researching a particular disease or condition, for example, can purchase the relevant NFTs on a purpose-built genomic research marketplace. The purchasing of the NFT would trigger a smart contract that would provide the researcher with access to genomic sequence data, demographic and health data of the individual. That data can be unencrypted, or even encrypted, perhaps employing asymmetric encryption techniques to grant that access.

Each NFT can be designed to create limitations associated with the sale of the information, including limits on using the data relating to time, or nature of the research. The smart contract could also automatically send a percentage of the sale price of the NFT to the sequenced individual. In this way, not only would the sequenced individual be compensated for their data, they would also have an idea as to who is using their data and for what purposes. The marketplace as well as the centralized trusted intermediary would also have this information. The centralized trusted intermediary would also have the ability to deanonymize the sequenced individual as well as restrict or open up access to the said sequenced individual.

NFTs could also be created by the owners of the private blockchain to reflect aggregated sequence information, such that an NFT could be purchased by a researcher that would provide access to all genomes identified within the blockchain containing a particular sequence at a particular locus, or particular expression data for a particular gene. In this way, researches can gain access to a limited but relevant dataset. These transactions as to what data was obtained for what purported use at a particular time can all be recorded on or off the blockchain. Those who wished to revisit and validate research could simply call up the same NFTs purchased by the original researcher with the exact information and redo the analysis. These NFTs could be created ex nihilo to reflect the nature of the research, e.g., the research queries, being performed on the genetic and phenotypic data in the database.

Sequenced individuals could even set the price for their associated NFTs reflecting their actual desire to be part of research. Market forces would likely drive down the average costs of those NFTs. Users could also set different prices for their NFTs depending on the public or private nature of the research, perhaps making academic research more affordable than commercial research. Knowing that their data was included within a particular study, the sequenced individuals could also follow up on the research to seek out actionable information, if any. Each transaction with their NFT would be immutably recorded on the blockchain.

This NFT marketplace could be restricted to qualified individuals and institutions so purchasers of the NFTs would not be able to be anonymous. Similarly, secondary sales of the NFTs would have to be limited if not outright prohibited, as there would be concerns that data would be used by secondary non-qualified researchers. The NFT code could also include time limits on the use of the data to prevent subsequent unauthorized misuse, as well as restrictions as to which IP addresses could access the data represented by the NFT. The system could also use IP addresses to automatically provide cheaper pricing to institutions in developing nations or to IP addresses associated with educational research institutions.

In a more ambitious project, sequenced individuals themselves could use their own NFTs to run analyses on their data. Thus, as a further incentive to provide their data to this secured system, individuals could access various programs and applications that would run analyses on the data. Much of these analyses would have to be recreational in scope given concerns of misinforming the public, but an individual could also use their NFT associated with their genomic data to grant access to their physician to assess the genome for more medically actionable information.

NFTs need not be the only tokens associated with this database endeavor. Just as bitcoins are tokens granted to bitcoin blockchain miners, the private blockchain could incentivize miners within their system as well. Tokens would be granted in exchange for validation. In this case, the token represents the value of accessibility to the genomic data in the database. The tokens can be provided in exchange for access rights on the blockchain, including storage, data access, and information access. These tokens provide both utility as well as a potential investment to support the private chain endeavor.

Regardless as to how access to a private blockchain is mediated, the technology can allow for limited and controlled access of genomic and associated medical and demographic data that is reliable and distributed amongst many nodes, preserving accuracy and accessibility. However, when implementing blockchain technology for genomic sequence information we need to be cognizant of the many potential, ethical, legal and social considerations. Some of these issues are generalizable to all types of databases, not necessarily blockchain. We will endeavor to cover those issues specific to blockchain.

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Similar efforts to employ blockchain and NFT technology for genomics research

Numerous papers have suggested that blockchain technology can provide some of the solution (23). Our solution however is a bit different. Consider for example Musamih et al. (24). The paper provides a broad description of the various uses of NFTs in healthcare, including the ability to employ encryption to help deal with privacy concerns. For example, the paper discusses issues relating to digital twins in healthcare, which we have discussed earlier, here (25), here (26), and here (27). The paper also suggests saving data both on and off chain as well as employing private chains, which we suggest employing as well. However, the paper suggests that control of the data be relegated to the patient. We disagree. While the patient can price the NFT to limit access, or can include limitations on the use of the data, once a researcher purchases access to the patient's data, they have control, as described herein. Further, the paper describes full access to the metadata of the blockchain with regard to the NFT. Here we suggest that in private chain, the patient can choose who can access that metadata and to what degree. Additionally, in Musamih et al., the authors suggest that the patient need not monetize the NFT. We disagree. Each use of the NFT ought to be charged, if for no other reason then that the fees that the NFT exchange collects can be used to help fund the entire endeavor. Allowing some NFTs to not charge for access might also skew research toward those genomes that are free to access. This might further limit access to minorities and underrepresented populations who historically might be poorer and need to monetize their NFTs whereas wealthier and perhaps non-underrepresented populations might need the funds less/ This can bias the data. As such, in our proposal, we suggest that it is best to set a minimum proposed default fee per NFT that we hope all users will use, to reduce bias.

Another similar effort describes the company Genobank.io (28). As per their paper and their website, Genobank will employ end-to-end encryption on the biosample and test results flow both to and from the patient. Genobank similarly claims to be employing a private blockchain, albeit one that is decentralized and immutable. As we discuss herein, we suggest that both or these classical characteristics of blockchains may not be best for the genomic and healthcare records themselves, as this data can be sometimes variable and/or may need to be updated to reflect new and/or better data collection. Genobank also aims to have the genomic data stored in a cryptocurrency wallet, i.e., off-chain. We discuss both the pros and cons of saving data off chain and support both possibilities on a private blockchain. Moreover, as per Genobank's description of their services, the data seems to be held locally by the patient. We disagree with this system as it creates inefficiencies in the process; or system has the data help centrally either within the blockchain or off-chain, but associated with data on the blockchain. This will provide greater efficiencies, especially dealing with the potentially millions, of genomes that could be stored within the system. Finally, the paper focusses on the privacy policies under CCPA, the California Consumer Privacy Act (29). Subsequent to the paper's publishing, California signed the Genetic Information Privacy Act into law. The law took effect in January 2022 and was intended in part to provide particular legislation for genomic privacy. GIPA is directed toward direct to consumer (DTC) genetic testing companies. Given this limited focus, its not clear that all data stored in our proposed platform would qualify for GIPA protection, and as an extension, CCPA, this will especially be the case in a truly decentralized system where no one entity can be found to be liable for privacy infringements.

Technical implementation of the blockchain for various potential user groups

Privacy is of utmost importance with regard to genomics and health care records, especially, keeping in mind that the disclosure of an individual's genomic data has implications for that individual's immediate and even extended family (30). To some degree, private corporations have already begun to consider the privacy aspects relating to putting genomes on the blockchain (31).

In the proposed platform, we envision at least three potential distinct user groups: (i) patients, their doctors and their families; (ii)researchers, both academic and industry, and, (iii) to a very limiting degree, the general public. Each of these groups are accessing the platform for different needs and purposes and will be availed different opportunities to use the platform depending on those needs and purposes, potentially at different price points depending on characteristics like geographical location and nature of the institution accessing the data.

However, ultimately the goal is to provide the most efficient usability whilst still endeavoring to protect the privacy of the data in the platform for each user group. In addition to providing usability, efficiency and privacy, however, the system is further intended to provide incentives to the first group, the patient group, to submit as much data as possible to the database, as the more data that is provided the more useful the database is to researchers. In this case, while we have described the use of NFTs to provide a monetary incentive, others have suggested some form of security or other representative financial instrument within the larger database as an incentive for populating the database (32).

Public permissionless blockchains are not necessarily designed to provided discriminating access to data; defining characteristics of a public permissionless chain are transparency and accessibility. As such, with each node gaining access to the entire dataset, and with no barriers to entry to become a node, the privacy of an individual within such a blockchain cannot be sufficiently protected unless all the data is encrypted. As noted prior, encrypting the data limits useability of the data.

Thus, recall that our proposed blockchain platform is a private permissioned one. As such, a trusted intermediary can designate the nature and amount of data that can be provided to each user group, as well as the amount and nature of the data that will be accessible to the various nodes supporting the decentralized database. For example, while a researcher (group II) may have access to anonymized data of each individual in the dataset, only a patient (group I) or their physician or their family can access actual names of relatives represented in the patient history. Groups II and II might have access to thousands if not hundreds of thousands of individuals within the dataset, however, Group I would only have access to their own data. Another example, Group III, the general public, including perhaps law enforcement upon production of a warrant, or professional genealogists, might be granted access to the genomic data, and some demographic data, but not the medical and clinical history data.

To further protect the privacy of the individuals in the dataset, the data held in the blockchain can be encrypted, such that even an inadvertent disclosure to an unauthorized individual will still not disclose personal and private information regarding an individual in the dataset. In some cases, one could imagine that the researchers and the public (Groups II and III) might be able to analyze the data *via* homomorphic encryption without the necessary step of decrypting the data and exposing personal and private information (33, 34). Group I, patient, doctor or family might have access to unencrypted data.

Through their minting of NFTs representing their data, the patient can also choose how much information they are willing to share with various group, keeping in mind that that the NFT marketplace that assesses the value of the NFT representing the patient's file will value a more in-depth file. Still, it remains up to the patient to decide on the level of data that they wish to share with other groups accessing the database. More specifically, a patient could mint different NFTs each representing different amounts of data that they are willing to share with third parties.

The trusted intermediary may also include more ethical concerns within their control over genomic data. For example, a patient might be unable to adequately process statistical information relating to their disease risks. In these cases, the trusted intermediary might even limit the type of data that the patient can access given concerns that they might mismanage their own information and make drastic life choices based on misunderstood genomic information (35).

Alternatively, in these cases the data might be released to the patient only through a verified physician or trained genetic therapist. Similarly, a patient may have sequenced and submitted their genomic data for a particular purpose and researchers may have stumbled across an actionable incidental finding, that data might be shared, *via* the blockchain system with the patient's physician, perhaps even automatically *via* a smart contract. At this point it would up to the physician to decide how the information might be best shared, if at all, with the patient and/or their family.

Additional data that might be stored on or off the blockchain and might be made available only to the patient could include a list of the researchers who have gained access to the patient's data and the outcomes, if any of any research done on that data. This could include metadata from the NFT marketplace, describing the type of research done on the datasets.

Typically, all users of an NFT marketplace have access to the historical data associated with the NFT, including past sales. However, as this data could be construed as private –small directed studies that include the data could indicate that there is relevant information related to the disease being studied within that file—the trusted intermediary may by default limit access to this type of metadata. Alternatively, a patient who provides their data and mints an NFT from their clinical and genomic data can request that the transactional history of their NFT, including all potentially privacy infringing metadata be masked from the marketplace.

Information rights

While information rights are relevant for all DNA sequences regardless as to the nature of the database that stores them, storing DNA sequences on a blockchain raises some specific concerns. Individuals who are sequenced arguably have the right to know their genomic sequence, and arguably, the right to limit the use of their information. DNA sequence data should be as accessible and transparent as possible for the individual, and practically, for researchers as well. However, the sequenced individual's right, which stems from their autonomy, is often not absolute. Both in the UK and Israel the law limits an individual's right to know their genetic data by granting medical practitioners the discretion whether to reveal DNA test results in some situations.

Alternatively, in some cases, the right to know one's genetic information is broad, going beyond the sequenced individual. Relatives arguably also have some right to access relevant information culled from the genome of the sequenced individual (36), given the amount of DNA that they share. For example, identical twins share effectively 100 percent of their DNA, parents and siblings share up to 61 percent of their DNA, and even distant third cousins share up to 2.2 percent of their DNA (37). Thus, when one family member undergoes genetic sequencing and analyzing this has an impact and consequences on the rest of his family, even distant cousins (38).

The sequenced individual similarly may have a right to not disclose their sequenced information. The right not to know has been explicitly recognized: Article 10.2 of the European Convention on Human Rights and Biomedicine states: "Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed". The Explanatory Report to the Convention justifies the right not to know by saying that "patients may have their own reasons for not wishing to know about certain aspects of their health" (39). Similarly, the UNESCO Universal Declaration on the Human Genome provides (Article 5c) that: "The right of every individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected." (40) Although some have suggested that this right is limited to the context of the doctor-patient relationship (41).

There can also be duties not to disclose information: Genetic information is often complex and the connections between genetic sequences and disease states is often not straightforward or simple. This can confuse individuals leading to situations known colloquially as the worried well and the walking sick—essentially misunderstanding genetic information can cause an induvial to over-or-under assess the severity of the link between their genetic sequence and a disease. To wit, in Israel, the Genetic Information Law Article 10 rules that only a genetic counselor or an otherwise qualified individual is authorized to give genetic tests results.

With all of these privacy and access limitation concerns, its clear that storing genomic information on a permissionless public blockchain where data can be accessed by anyone all the time can be problematic. On private permissioned chains however, this is of lesser concern. In the example described above, the private chain can be built such that access rights to data can be easily allowed and just as easily revoked. Under the guidance of an ethical committee, the central authority can also decide who can and who cannot gain access to the chain itself, or more specifically to specific sequences.

Information ownership

The issue of ownership of genetic information is perhaps easier to determine with data stored on public blockchains in contrast to private chains. Individual users who store their data *via* public chains arguably are the owners of their own data, as by design, no one owns a public blockchain and no one else can claim ownership or even copyright rights under a theory of compiliations of database copyright. And while public chains are often too expensive and too restrictive to store genomic sequences, they can still be employed to identify and transact information that is stored off-chain in things like distributed databases. Sequenced individuals can store their data in this fashion and even create their own NFTs to share their genomic data, with or without any limitations. Private chains on the other hand are more like private databases, and the issues regarding DNA ownership in private databases are the same whether the database is a distributed ledger or a single excel file on a single computer. Raw genomic data is often argued to belong to the sequenced individual, its not necessarily the case, however for processed information. The ownership question is also relevant for the outputs of genomic research. While researchers arguably own their resulting research, it could be argued that the sequenced individual retains some rights to even the research outputs. In the example described above, any rights that a sequenced individual might claim should be spelled out in smart contracts associated with the transaction. Users who retain too many rights will likely see that their data remains unused.

Information veracity & stewardship

In a decentralized public blockchain the software underlying the chain is designed to be responsible for validating that the data remains uncorrupted. Although once in a blockchain, data is less able to be tampered with, blockchain technology does not natively provide any ability to validate that the data that is created outside the system and then entered into the system is itself reliable. A centralized authority of a private chain could conceivably implement safeguards to police and prevent false information from getting onto the chain, this might be more difficult in a public chain, especially one that is not purpose-built for storing genomic information. In a public chain, liability for error that creeps into the data, for example suggesting that an individual does or does not have a genetic condition, cannot be easily assigned, as there is ostensibly no owner or anyone that can held responsible. On private or permissioned chains, negligence can be assigned to the centralized authority that manages the chain.

Another veracity concern relates specifically to public blockchains wherein anyone could conceivably add their data to the distributed ledger. Unfortunately, without oversight and a centralized system there is no way to confirm that the data was transcribed accurately, or if even the data is legitimate. Moreover, malicious users can upload malware to a public chain hiding within the genomic data that could infect systems using the data. This is a cyberbiosecurity concern (42). Both public and private chains could conceivably run software on their ledgers to make sure that uploaded information isn't clearly infectious code. Further, on bespoke systems designed as a genomic database, the centralized authority could also review the genomic data itself on the system to confirm that the genetic information is what it claims to be and not a problematic sequence that could, if printed as a gene, create havoc (43).

The right to be forgotten

Under the General Data Protection Regulations (GDPR) there is an increasing awareness relating to privacy issues on the internet, including a somewhat novel right to be forgotten. Although not absolute, Article 17 of the GDPR entitles the data subject, e.g., the sequenced individual, to have the data controller erase their personal data, cease further dissemination of the data, and potentially have third parties halt processing of the data (44). Of course this right is limited if there is a contract that obligates the sequenced individual to leave their data on the chain. The right is also limited if the data is anonymized, as it most likely would be on a blockchain. Pseudoanonymized data might still be protected under GDPR. Whether sequence data falls under the concept of anonymized or pseudoanonymized (as it can, apparently be sourced with enough information) will be a limiting factor in the application of the GDPR to genomics on public blockchains because of the immutable nature of the data stored on the blockchain (45). Note however, that Satoshi Nakamoto the pseudoanonymous creator of blockchain technology allowed for the idea of eventually pruning the blockchain of data.

Also, without a central source to contact, there is no data controller who can follow through with the GDPR directives. Although public blockchains could be created to allow for consensus driven implementors of chain governance, including the deletion of GDPR protected data. Immutable chains can deal somewhat with these concerns by storing any truly identifiable information off-chain, allowing those records to be deleted or taken off-line if a GDPR-based request is made.

Private chains can also be designed to allow for changes to the data, albeit at the expense of some of the inherent value associated with using the blockchain technology. Alternatively, private chains can delete the identifier that links the various data sets associated with the sequenced individual if DNA is considered to be fully anonymous. In the example described above, NFTs that are tied to the individuals data can also be pulled from circulation as well, effectively disappearing them from the chain.

Incentive-based economy

Integrating blockchain technology as a key component in DNA storage enables the user a decentralized and rewarding platform for sharing sensitive data (46). Some might argue that the example of NFTs could be used to create perverse incentives that encourage users to share their genetic and medical information in exchange for an economic reward. This creates an ethical conflict between one's privacy and financial interests (47). Similarly, creating a market to purchase access to data can be seen as counter to the ethos of open science. Although access to data is often purchased in scientific research, creating an actual market may be seen as a step too far. However, the idea that one could profit each time someone accesses your sequence data for research might solve an ongoing concern in genomic research, the possibility of payment may create a counter incentive for those that are often otherwise disincentivized to participate, solving an ongoing concern: the limited representation of minorities in the databases (48). Further, the chilling effect on participation in genomic studies coming from some fearing that their accessible data will be appropriated by the criminal justice system could be countered with the possibility of remuneration.

Hacking

With blockchains comprising thousands if not millions of interconnected nodes, there is a concern that hackers could target the weakest links to gain access to the entire network. Whereas in a centralized database the owners of the database need only focus on hardening access to a single site, a large network with distributed copies of the data creates significant cybersecurity concerns, especially when all the nodes in the network may not necessarily be under the oversight of the owner of the blockchain as is the case in a public chain. Private chains can minimize the damage of a hack by limiting the amount of information stored on some nodes, leaving most of the valuable information within a centralized location or a handful of reliable nodes. In these cases, whereas a hack targeted at the infrastructure may be just as problematic as a hack in a public chain, it might be less damaging in terms of lost information.

Biases

In the NFT example described herein, consumers have the ability to select datasets based on desired characteristics of the data and the sequenced individuals. Similarly, the same system was also described as allowing each user to specifically describe the nature of the consent that they were providing for the use of their data. In both instances, there can be concerns that both consumers of data and the sequenced individuals will employ their inherent biases when deciding which demographics they might research or which diseases they will provide consent for, respectively. On paper, this concern could be dealt with through contract; the terms and conditions that could be submitted to both the consumer and the sequenced individual would have to disallow overt biases, although proving actual malice in any perceived biases might be difficult.

Standards

Databases, regardless as to whether they are distributed or not are made more usable by the standardization of the data that they hold. This usability is increased further with standards that are upheld among many databases. In maintaining a genomic database on the blockchain, standards will also need to be set. Standards are also necessary for the creation of a genomic NFT marketplace. Fortunately, users of blockchains and creators of NFTs are already held to standards that seem to be broadly maintained. With regard to genomic data, a consortium of stakeholders should devise relevant standards for the maintenance of data on and off chains, standards for anonymization and maintaining privacy and standards for reidentification, standards for consent, and standards for interaction with those who have been sequenced. This is non-trivial and could take significantly longer than the creation of the underlying infrastructure.

Conclusions

We described how an NFT marketplace based on a permissioned private chain could be implemented to minimize many of the ongoing concerns associated with DNA databases. A number of commercial entities have attempted to create various blockchain or blockchain interacting systems as genomic databases. Many are now offline or have not lived up to the hype. In spite of the current crypto-winter, we believe that ultimately some version of a blockchain genomic database will succeed in providing both easy transparent valuable access to genomic researchers while simultaneously providing sequenced individuals with extensive autonomy to both protect their privacy and also profit off of their data.

Author contributions

Authors are part of the Zvi Meitar Institute for Legal Implications of Emerging Technologies. All authors contributed to the article and approved the submitted version.

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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A European arena for joint innovation in healthcare: The Platform for Innovation of Procurement and Procurement of Innovation (PiPPi)

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By 2000 the European Union (EU) had recognized that its innovation capacity was underperforming in comparison to similar competitors and trading partners. Although the EU has made an effort to stimulate public research and development (R&D) through policy tools like Pre-Commercial Procurement (PCP) and Public Procurement of Innovation (PPI), starting with the 2000 Lisbon strategy and continuing through the 2021 updated Guidance on Innovation Procurement, there has remained a gap in knowledge of and use of these tools, in particular within healthcare. The past decades have seen an explosion in the number and use of digital technologies across the entire spectrum of healthcare. Demand-driven R&D has lagged here, while new digital health R&D has largely been driven by the supply side in a linear fashion, which can have disappointing results. PCP and PPI could have big impacts on the development and uptake of innovative health technology. The Platform for Innovation of Procurement and Procurement of Innovation (PiPPi) project was a Horizon 2020-funded project that ran from December 2018 to May 2022 with a consortium including seven of Europe's premier research hospitals and the Catalan Agency for Health Information. To promote PCP and PPI, PiPPi established a virtual Community of Practice (CoP) that brings together all stakeholder groups to share and innovate around unmet healthcare needs. This perspective presents a brief history of PCP and PPI in Europe with a focus on digital innovation in healthcare before introducing the PiPPi project and its value proposition.

KEYWORDS

health innovation, digital health, innovation procurement, health policy, Community of Practice, university hospital

Introduction

Two decades of innovation and public procurement in the European Union

By the early 2000's the European Union (EU) had recognized that its innovation capacity was underperforming in comparison to similar competitors and trading partners (1). The 2000 Lisbon strategy for Growth and Jobs (2) aimed to address this gap, with a goal of making Europe "the most competitive and dynamic knowledge-based economy in the world, capable of sustainable economic growth with more and better jobs and greater social cohesion." The strategy already highlighted the potential for a digital information society to foster improvements from the individual to the international level. The 2005 revised Strategy explicitly included investment in innovation as a focus area (3).

By this time the value of procurement of research and development (R&D) had already been globally demonstrated in multiple fields and further evidence was emerging especially in connection with societal needs and goals (1) (as opposed to the defense and aerospace sectors, which have always dominated R&D procurement). From 2005–2007 several independent expert reports (4) and European Commission communications (1) came out that specifically highlighted public procurement for R&D as a tool to increase the EU's innovation competitiveness, and formally introduced the pre-commercial procurement (PCP) policy tool as a method for public bodies to procure innovation.

In 2010, following the global financial crisis of 2007–2008, the EU released the Europe 2020 (5) strategy for the next 10 years, "A European strategy for smart, sustainable and inclusive growth," which included the "Innovation Union" as a flagship initiative (6). Member States were directed to engage in public R&D procurement and the EU committed to provide further resources. These resources materialized in the 2011 "Green Paper on Modernisation of EU Public Procurement Policy" (7) and the subsequent 2014 Procurement and Concessions Directives (8). From this time PCP and public procurement of innovation (PPI) were established as tools that could be used by public bodies to buy solutions for identified market gaps. These tools stimulate innovation from the demand side and encourage increased involvement of end-users in the requirements specification and development of solutions, which is a reversal of the more typical supply-side-driven R&D.

However, despite this encouragement and support from the Commission, PCP and PPI continued to be underutilized by Member States. In 2018, the EU issued a new Guidance on Innovation Procurement (9) that built on the 2014 directives. This Guidance was further updated in 2021 (10) in response to the COVID-19 pandemic.

From 2014–2020 the EU directed 80 billion € in funding to identified development goal areas through the Horizon 2020 Programme for Research and Innovation (11). At the time it was the largest such program for international research collaboration, only surpassed by the next iteration, Horizon Europe, starting from 2021. Beyond simply providing funding for innovative R&D, these efforts in fact explicitly provide funding for PCP and PPI actions.

A similar and complementary trend is that of value-based procurement (VBP) (12, 13). The VBP model shifts the goal of procurement from simply low cost per volume to one that considers other outcomes, longer-term results, and wider impacts. This model also emphasizes the need for demand- and supply-side collaboration from the early stages of procurement processes (14). Where PCP and PPI are the European policy tools that public bodies can use for purchasing, VBP is a model that may direct the way the tender is awarded and evaluated.

Of course, it should be considered that diverse opinions on the appropriate balance of public vs. private spending exist (15, 16), and in practice EU member states vary widely in total public expenditure as a percentage of GDP. In 2019, the public spending ratio ranged from over 50% in France, Belgium, and some of the Nordic countries, to ∼35%+ in several Eastern European countries, to 32.8% in Switzerland, and 24.2% in Ireland (17). The real utility of the public procurement tools presented here therefore depends partially on location. However, public investment in R&D is clearly also needed to fully optimize innovation capacity, so these tools represent an important opportunity even within public-private mixes weighted toward the private side.

Innovation procurement in the healthcare context

The healthcare sector is one area where demand-driven R&D has lagged, in particular when considering public hospital activity, and even more so when looking at PCP and PPI actions. However, great potential for fostering healthcare innovation using these policy tools has existed for some time. The EU has used the aforementioned directives and communications, as well as the Horizon funding programs, to steer healthcare actors in this direction. One subfield of healthcare where PCP and PPI could provide great benefits is digital health, both the development of cutting-edge technologies, as well as increasing the adoption of those technologies.

The past decades have seen an explosion in the number and use of digital technologies across the entire spectrum of healthcare. They run the gamut from inexpensive, low-tech solutions to state-of-the-art products that make up significant portions of healthcare costs and budgets. From an organizational perspective, where the latter type of product is more often in question, implementing medical technologies that balance cost and utility is a strategic priority (12, 18).

New digital health R&D has largely been driven by the supply side in a linear fashion (19, 20). An unfortunate side effect of this can be that product uptake, adoption, and diffusion fall short of expectations, which is not uncommon, and is concerning given the large investments in developing and purchasing these products. Collaborative innovation involving all relevant stakeholder groups is still the exception not the norm, so disconnects can exist between the real needs of end-users and the solutions offered by digital technology developers (21, 22). The EU's efforts to increase dialogue between suppliers and purchasers and to stimulate innovation in healthcare through policy tools like PCP and PPI are one macro-level response to this.

Finally, it should also be mentioned that medical procurement and innovation has been greatly influenced by the COVID-19 pandemic. Short-term adjustments included increased procurement efforts for personal protective equipment (23) and medical devices like ventilators (24), as well as EU-level modifications to the formal innovation procurement process in order to streamline and shorten time requirements (25). A greater focus on digital solutions and eHealth models is expected to be a lasting change in the field, however (26–28).

Current state of affairs

Although it is clear that a concerted public policy effort has gone into stimulating innovation performance in the EU, there remains a gap in the actual knowledge and usage of the PCP and PPI tools. A small number of successful models, such as Campania's regional "One Health" approach (29), and isolated examples can be found, primarily of projects funded through the Horizon 2020 program (30), but innovative procurement still remains the exception. This is especially true when considering a subpopulation of university hospitals. Although these organizations themselves produce some of Europe's leading breakthroughs, they are not known for innovative procurement to address the needs of their own employees and patients. Even when it has been done, these actions are rarely cross-border in nature.

This is problematic, especially in the realm of digital health innovations. Healthcare is increasingly both digital and international in nature. It is no longer sufficient to simply purchase off-the-shelf digital solutions that do not meet real needs, just as solution interoperability and data standardization are crucial for long term success. The status quo, however, has not yet adjusted to these modern realities, leaving healthcare with silo-ed stakeholder groups and technology islands.

To explicitly address this gap, the Coordination and Support Action "Platform for Innovation of Procurement and Procurement of Innovation" received Horizon 2020 funding to build a Community of Practice to bring healthcare stakeholders together to better engage in procurement of innovation. Project outputs, including this perspective, represent the compiled results of over 3 years of qualitative and quantitative data collection from internal and external actors, including expert interviews, workshops, surveys, process mapping, literature review, and KPI analysis, among others.

Platform for Innovation of Procurement and Procurement of Innovation (PiPPi)

The Platform for Innovation of Procurement and Procurement of Innovation (PiPPi) was an international consortium project funded by the European Union's Horizon 2020 research framework program that ran from December 2018 to May 2022. The project consortium included Karolinska University Hospital (Sweden), Erasmus MC (the Netherlands), King's College London NHS Foundation Trust (UK), Vall d'Hebron University Hospital (Spain), San Raffaele Hospital (Italy), the Catalan Agency for Health Information, Assessment and Quality (Spain), Helsinki University Hospital (Finland), and the Medical University of Vienna (Austria). The overarching goal of the project was to capture unmet needs of university hospitals and to identify opportunities for innovation in digital health and care services.

Based on the combined experiences and knowledge bases of leading research hospitals, the project produced a toolset to assist healthcare actors to identify unmet needs and successfully elaborate them into a formal project plan for a PCP/PPI. This toolset accompanies the PiPPi Community of Practice (CoP), which is a virtual platform (pippi-platform.eu) bringing together all critical stakeholder groups to facilitate the procurement of innovation and the innovation of procurement. The platform was first made available as a beta release in October 2021 and was officially launched in April 2022. In the first year post-project it will continue to be governed by a related consortium.

Discussion

Platform for Innovation of Procurement and Procurement of Innovation's value proposition rests on several points. First, the platform combines the increasingly popular CoP model with an emphasis on PCP and PPI policy tools to foster healthcare innovation in a way that is unique. A barrier to the use of procurement of innovation at hospitals is low knowledge of and proficiency in using this technique, especially among the key stakeholder groups patients and clinicians. The virtual CoP format allows stakeholder groups to take advantage of modern technologies to network and find commonalities across regions. PiPPi brings stakeholders together to collaborate to understand and define the problems that we all face. The process and related tools that are the results of the project lower the barrier to entry for this type of work.

Second, the CoP provides an opportunity to better aggregate demand and drive the innovation process from the very beginning, which increases the likelihood of successful adoption in the future. As some of Europe's leading research hospitals, the founding members are in a unique position to identify truly unmet needs for which no good market solutions exist and to influence the most beneficial development of solutions.

Lastly and most importantly, the PiPPi project and the CoP have made particular efforts to include patients and clinicians into this process, one which typically excludes these ultimate end-users and beneficiaries. While including a medical expert in technology development is often standard practice, the PiPPi platform provides democratic access possibilities to clinicians of participating institutions. Under the PiPPi model, a clinical champion is a requirement to successfully develop a project plan and move toward PCP/PPI. In addition, the interest of patients and citizens in shaping not only specific interventions, but also the future of healthcare is real and of personal significance, however it is not standard to include these actors until the final stages of testing new solutions. Patient and citizen involvement in unmet need specification is critical to the PiPPi process. During the project a dedicated 12-person Patient and Citizen Advisory Group was established and collaborated on project actions and has advised on sustainable involvement beyond the project end, which will take the form of an overarching patient/citizen working group. The high level of involvement of these stakeholder groups sets PiPPi apart.

Conclusion

By bringing together all stakeholder groups - with particular value seen from the involvement of patients - in a virtual community devoted to sharing expertise and co-creation, the PiPPi platform evolves the state of European innovation procurement. Although the efforts of the last two decades to advance procurement of innovation in Europe have produced underwhelming usage of PCP and PPI, the stakeholder collaboration made possible by the CoP offers great potential for the future. Further scientific research is needed not only to demonstrate the impact of the PiPPi CoP, but also to elaborate the field of innovation procurement.

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

MRA and PAL wrote the first draft of the manuscript. All authors contributed to conception and design of the study, manuscript revision, read, and approved the submitted version.

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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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Digital maturity and its determinants in General Practice: A cross-sectional study in 20 countries

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Background: The extent to which digital technologies are employed to promote the delivery of high-quality healthcare is known as Digital Maturity. Individual and systemic digital maturity are both necessary to ensure a successful, scalable and sustainable digital transformation in healthcare. However, digital maturity in primary care has been scarcely evaluated.

Objectives: This study assessed the digital maturity in General Practice (GP) globally and evaluated its association with participants' demographic characteristics, practice characteristics and features of Electronic Health Records (EHRs) use.

Methods: GPs across 20 countries completed an online questionnaire between June and September 2020. Demographic data, practice characteristics, and features of EHRs use were collected. Digital maturity was evaluated through a framework based on usage, resources and abilities (divided in this study in its collective and individual components), interoperability, general evaluation methods and impact of digital technologies. Each dimension was rated as 1 or 0. The digital maturity score was calculated as the sum of the six dimensions and ranged between 0 to 6 (maximum digital maturity). Multivariable linear regression was used to model the total score, while multivariable logistic regression was used to model the probability of meeting each dimension of the score.

Results: One thousand six hundred GPs (61% female, 68% Europeans) participated. GPs had a median digital maturity of 4 (P25–P75: 3–5). Positive associations with digital maturity were found with: male gender [$B = 0.18$ (95% CI 0.01; 0.36)], use of EHRs for longer periods [$B = 0.45$ (95% CI 0.35; 0.54)] and higher frequencies of access to EHRs [$B = 0.33$ (95% CI 0.17; 0.48)]. Practicing in a rural setting was negatively associated with digital maturity [$B = -0.25$ (95%CI −0.43; −0.08)]. Usage (90%) was the most acknowledged dimension while interoperability (47%) and use of best practice general evaluation methods (28%) were the least. Shorter durations of EHRs use were negatively associated with all digital maturity dimensions (aOR from 0.09 to 0.77).

Conclusion: Our study demonstrated notable factors that impact digital maturity and exposed discrepancies in digital transformation across healthcare settings. It provides guidance for policymakers to develop more efficacious interventions to hasten the digital transformation of General Practice.

KEYWORDS

primary care, quality of care, digital technology, digital maturity, electronic health records, health information interoperability

Introduction

Digital technologies have revolutionized many aspects of modern society — health care is no exception (1). Around the world, the onset of the digital transformation has radically changed the primary care landscape (2, 3) through the widespread computerization and the digitalization of personal health information into Electronic Health Records (EHRs). Simultaneously, the dissemination of electronic medical devices (4), as well as adoption of systems enabling digital drug prescriptions, referrals, billing, scheduling tests and appointments are also major contributors to this change (5). Advances in digital technologies can also be seen from the proliferation of implantable devices which offer real time monitoring of physiological parameters (6, 7), to telemedicine (1) and mobile health—the use of mobile devices to improve health outcomes (8–11). This already ongoing digital transition has been further accelerated as a result of the COVID-19 pandemic (1, 12).

From facilitating communication between providers to improving prevention, achieving early diagnosis and providing timely treatments, digital technologies have demonstrated tremendous potential to improve health care delivery (13, 14). However, they are yet to play a major role among efforts to improve primary health care delivery (15). Nonetheless, the relevance of digital technologies keeps growing in primary care as governments' approaches to this sector continue to move toward the use of more collaborative systems (3). The extent to which digital technologies are employed to promote the delivery of high quality healthcare is known as digital maturity and it is an emerging concept across developed health care systems (16). The digital maturity of health professionals and systems is necessary to ensure a successful, scalable and sustainable digital transformation (17–19).

More than the modernization of medical resources, digital transformation is a complex multidimensional process (8) and therefore digital maturity, as any care intervention, needs to be rigorously evaluated and monitored to ensure successful implementation (16). While there have been studies focused on the assessment of digital maturity in secondary care (20, 21), similar efforts are likewise needed in primary care (3). The importance of exploring digital maturity shortcomings in primary care increases as some of its components such as EHRs have been cited as a contributor to physicians' burnout, particularly GPs' (22). To our best knowledge, digital maturity in primary care has not been previously evaluated.

This study assesses digital maturity — per individual dimensions (i.e., usage, resources and ability, interoperability, general evaluation methodology, and impact) and overall score (sum of all dimensions) — in General Practice across 20 countries. It also evaluates if the characteristics of participants or clinical practices, as well as features of EHR adoption, are associated with digital maturity. Our hypothesis is that the characteristics described above can affect digital maturity. The identification of such factors may contribute to developing more efficacious digital transformation implementation strategies worldwide.

Methods

Study design and setting

This is a cross-sectional study, utilizing an online questionnaire completed by GPs. Ethical approval was granted from the Imperial College Research Ethics Committee (Reference 20IC5956), which oversees health-related research with human participants. The study adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline for cross-sectional studies. The research was conducted by a primary care consortium (inSIGHT Research Group) which gathers health professionals from 20 countries (Australia, Brazil, Canada, Chile, Colombia, Croatia, Finland, France, Germany, Ireland, Israel, Italy, Poland, Portugal, Slovenia, Spain, Sweden, Turkey, the United Kingdom, and the United States).

Study population

Participants were eligible if they were GPs working in the countries above between March and September 2020.

Sample size and recruitment

The sample size is superior to the total number of responses needed to provide a confidence level of 95% and a margin of error of 5% (901), according to the published protocol (23). Recruitment of participants was conducted by national leads who invited GPs working in their country to take part in the questionnaire *via* email and through social media channels, such as Facebook and LinkedIn. Participants were recruited between June and September 2020.

Description of questionnaire

Investigators at the Patient Safety Translational Research Center and Department of Primary Care and Public Health at Imperial College London constructed the questionnaire. It was piloted by the national leads of the 20 inSIGHT Research Group associate countries in May 2020 and edited for national, cultural or organizational adaptations. The questionnaire was originally developed in English, and was translated to French, German, Italian, Portuguese, and Spanish by national leads to stimulate higher participation. The questionnaire was provided to participants through Qualtrics. The research protocol (including the full questionnaire) is available as a published paper in JMIR Research Protocols (23).

Demographic data (gender, age, and country), practice features (setting, number of hours of clinical work per week, number of years of experience as GP and involvement in teaching activities) and characteristics of access to EHRs (availability of EHRs, duration, and frequency of use) were collected. Digital maturity was assessed using the digital maturity framework developed by Flott et al. (Supplementary material), which considers the dimensions usage, resources and abilities (organizational and individual), interoperability, general evaluation methodology, and impact (21). These dimensions were assessed, respectively, by measuring agreement with the statements below.

- Usage: "*Most healthcare providers in our practice use the digital system.*"
- Resources and ability (organizational): "*Our organization is ready to use the digital system correctly.*"
- Resources and ability (individual): "*We have the individual abilities needed to use the digital system correctly.*"
- Interoperability: "*Our digital system has the capability to communicate across services or with other systems.*"
- General evaluation methodology: "*We have best practice digital maturity evaluation methods in place.*"
- Impact: "Our system has a positive impact in terms of outcomes for patients, structure, process or finance."

All dimensions were evaluated by the participant as one of the following options: agree, neutral or disagree. The overall digital maturity score was calculated as the sum of the scores for the six dimensions. Whenever the participant expressed agreement with one dimension, one point was granted, and therefore overall digital maturity scores ranged between 0 to 6.

A full list of the questions included in this work is provided as Supplementary Table S1.

Data analysis

All participants, even those in which some parameters were missing, were used in the analysis. Countries were categorized as European (Finland, France, Germany, Ireland, Italy, Poland, Portugal, Slovenia, Spain, Sweden, and the United Kingdom) and Non-European (remaining). The variable "Setting of practice" was split into "Rural" and "Urban." The option "Prefer not to answer" in the questions regarding age, gender and involvement in teaching activities were treated as missing information.

The normality of distribution of each continuous variable was assessed using the Kolmogorov-Smirnov test (24). This test is one of the most general non-parametric methods for comparing two samples, as it is sensitive to differences

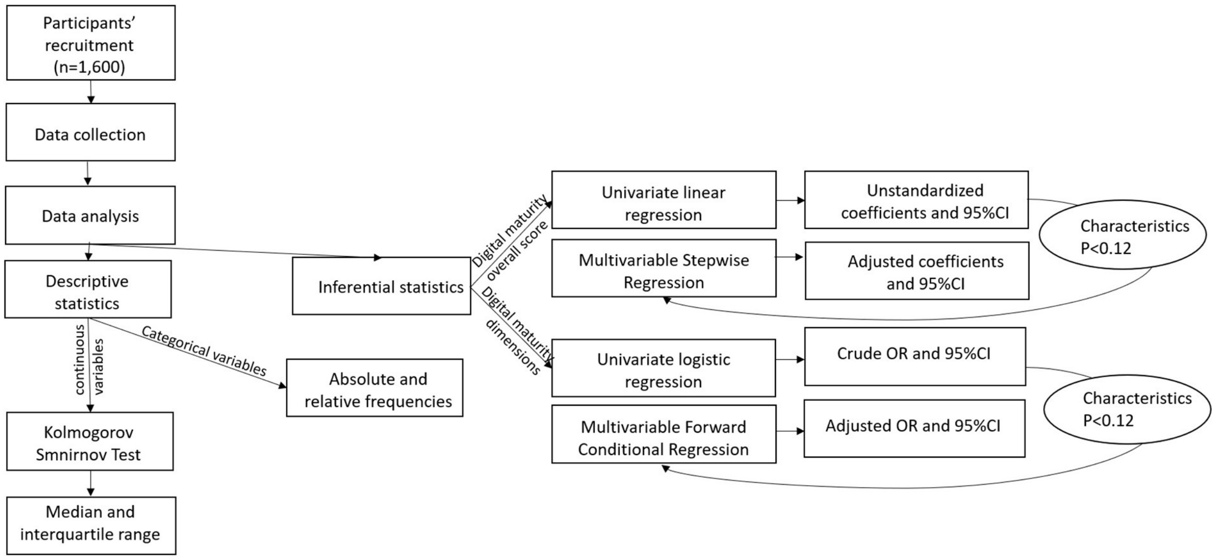

FIGURE 1
Visual representation of methodology. OR, odds ratio; CI, confidence interval; characteristics $P < 0.12$, independent variables whose association with the dependent variable had a P-value < 0.12.

in both location and shape of the empirical cumulative distribution functions of the two samples, therefore was chosen to assess normality in this case. Descriptive statistics were performed using absolute and relative frequencies for categorical variables, and median and interquartile range are presented for continuous variables with skewed distribution. Univariate linear regression was performed to determine the characteristics (i.e., gender, age, country, years of experience as GP, hours of clinical work per week, involvement in teaching activities, rural setting of practice, urban setting of practice, access to EHRs, duration and frequency of use of EHRs) associated with the digital maturity score (25) (continuous variable). Unstandardized coefficients (B) and 95% confidence intervals were calculated. All independent variables associated with digital maturity score with a P-value < 0.12 were included in the first multivariable model iteration. P-value represents the probability of obtaining the observed results, assuming that these characteristics were unrelated to the digital maturity score. The variables for multivariable analysis were chosen through the stepwise method. The models were evaluated using P-values, coefficients of determination (R^2). Similarly, univariate binomial logistic regressions were used to identify characteristics possibly predicting the binomial outcome (0 = neutral/disagree, 1 = agree) of each of the six components of the digital maturity score usage, collective resources and ability, individual resources and ability, interoperability, general evaluation methods and impact (26, 27). Characteristics with P-value < 0.12 at univariate analysis were used in a multivariable logistic regression. The final model was obtained using a forward conditional regression. Adjusted odds ratio and 95% confidence intervals [aOR (95% CI)] were calculated (Figure 1). The models were evaluated using Hosmer Lemeshow tests and Nagelkerke's R-square (26, 27). Data were analyzed using IBM SPSS Statistics 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Participants characteristics

A total of 1,600 GPs were enrolled, mostly female (61%; n = 976), aged between 30 to 39 years old (33%; n = 530) and practicing in European countries (68%; n = 1,081). Most of them had more than 20 years of experience as a GP (31%; n = 431), worked a median of 36 h per week (P25–P75: 28–40), in an urban setting (73%, n = 1,354) and were involved in teaching activities (64%; n = 1,017). Most of them had access to EHRs (95%, n = 1,523), were using it every day (91%, n = 1,379) and for more than 10 years (55%, n = 838). The characteristics of the participants are summarized in Table 1.

Digital maturity and participants' characteristics

Participants had a median digital maturity score of 4 (3–5). The highest three levels of the score accounted for almost 60% of the answers. Among the six dimensions, usage registered the highest percentage of agreement (90%, n = 1,209), followed by collective and individual resources and ability (80%, n =

TABLE 1 Participants characteristics ($n = 1{,}600$).

Characteristics	Total ($n = 1{,}600$)
Gender[a]	
Female	976 (61%)
Male	613 (39%)
Age[b]	
<30 years	101 (6%)
30–39 years	530 (33%)
40–49 years	414 (26%)
50–59 years	325 (20%)
60–69 years	208 (12%)
70+ years	18 (1%)
Country[c]	
European	1,081 (68%)
Non-European	517 (32%)
Years of experience as GP	
<5 years	335 (21%)
5–10 years	360 (23%)
10–15 years	241 (15%)
>15 years	173 (42%)
Hours of clinical work per week, median (P25–P75), hours[c]	36 (28–40)
Setting of practice[c]	
Urban	1,354 (73%)
Rural	1,000 (63%)
Involvement in teaching[d]	1,017 (64%)
Access to EHRs[c]	1,523 (95%)
Duration of use of EHRs[e]	
Only after COVID-19 outbreak	23 (2%)
Before COVID-19 outbreak, but <2 years	111 (7%)
(2–5) years	205 (14%)
(5–10) years	336 (22%)
>10 years	838 (55%)
Frequency of access to EHRs[e]	
Less than 1*month	29 (2%)
At least 1*month	12 (1%)
At least 1* week	27 (2%)
More than 1* week	66 (4%)
Every day	1,379 (91%)

Unless otherwise indicated, values are displayed in n (%).
GP, General Practitioner; P25–P75, percentile 25 to percentile 75.
EHRs, electronic health records.
[a]Eleven GPs with missing information.
[b]Four GPs with missing information.
[c]Two GPs with missing information.
[d]Fifteen GPs with missing information.
[e]Eighty-seven GPs with missing information.

1,073 and 77%, $n = 1{,}035$, respectively), impact (59%, $n = 788$) and interoperability (47%, $n = 633$). Best practice general evaluation methods registered the lowest scores of agreement (28%, $n = 380$). A significant multivariable linear regression model explained the digital maturity score ($R^2 = 11\%$, $P < 0.001$). Being male was associated with a higher digital maturity score [$B = 0.18$ (95% CI 0.01; 0.36)], while practicing in a rural setting was inversely associated with it [$B = -0.25$ (95% CI -0.43; -0.08)]. Additionally, longer duration and higher frequency of use of EHRs were also associated with a higher digital maturity score [$B = 0.45$ (95% CI 0.35; 0.54), $B = 0.33$ (95% CI 0.17; 0.48), respectively]. A detailed overview of the model is provided in Table 2 and a graphic representation in Figure 2A.

Individual dimensions of digital maturity and participants' characteristics

Unadjusted ORs estimating the association between the characteristics of the participants and each of the six dimensions of the digital maturity are presented in Supplementary Table S2. Urban setting of practice was not associated with any dimension, while duration of use of EHRs was associated with all of them.

Adjusted ORs (aORs) represent the multivariable analysis of the predictors of each dimension and are summarized in Supplementary Table S3. The models explained 19% of the variance of usage, 13% of collective resources and ability, 6% of individual resources and ability, 7% of interoperability, 4% of general evaluation methods and 6% of impact. Hosmer Lemeshow tests showed that the models adequately fitted the data ($P = 0.713$, $P = 0.983$, $P = 0.276$, $P = 0.554$, $P = 0.981$, and $P = 0.956$, respectively).

Usage

GPs were less likely to use digital systems if they were using EHRs for a shorter period of time (aOR from 0.09 to 0.52) when compared to GPs accessing them for more than 10 years. Lower frequencies of access to EHRs were also associated with lower odds of use of the digital systems (aOR from 0.18 to 0.43) when compared to accessing them every day. On the other hand, in comparison with GPs practicing for more than 15 years, GPs who started practicing more recently had higher odds of using the digital systems (aOR from 1.58 to 2.42). The number of hours GPs worked in a week were negatively associated with usage of digital technologies [aOR = 0.99 (0.98; 1.00); Figure 2B].

Collective resources and ability

When compared to GPs accessing EHRs for more than 10 years, GPs who started accessing them later were less likely to express having collective resources and abilities (aOR from 0.14

TABLE 2 Univariate and multivariable linear regression models to explain the digital maturity score.

Characteristics	Univariate analysis		Multivariable analysis	
	B (95% CI)	*P*-value	*B* (95% CI)	*P*-value
Gender (Ref = Female)	0.27 (0.08; 0.45)	0.005	0.18 (0.01; 0.36)	0.042
Age	0.18 (0.11; 0.26)	<0.001		
Country (Ref = Non-European)	0.26 (0.07;0.45)	0.008		
Years of experience as GP	0.21 (0.13;0.28)	<0.001		
Hours of clinical work per week	−0.01 (−0.01; 0.01)	0.864		
Rural setting of practice	−0.15 (−0.34; 0.40)	0.114	−0.25 (−0.43; −0.08)	0.005
Urban setting of practice	−0.03 (−0.28; 0.22)	0.797		
Involvement in teaching activities	0.19 (−0.01; 0.38)	0.056		
Access to EHRs	0.28 (−0.18; 0.74)	0.229		
Duration of use of EHRs	0.53 (0.44; 0.61)	<0.001	0.45 (0.35; 0.54)	<0.001
Frequency of access to EHRs	0.57 (0.42; 0.72)	<0.001	0.33 (0.17; 0.48)	<0.001

Ref, reference; B, unstandardized regression coefficient; 95% CI, 95% confidence interval; GP, General Practitioner; EHRs, electronic health record.

to 0.54), as well as GPs who access EHRs less frequently (aOR from 0.39 to 0.85) when compared to GPs accessing them every day (Figure 2C).

Individual resources and ability

Being male was positively associated with reporting individual resources and ability [aOR 1.33 (95% CI 1.00; 1.80)], while practicing in a rural setting was negatively associated with it [aOR 0.67 (95% CI 0.51; 0.88)]. GPs who started accessing EHRs more recently were less likely to acknowledge individual resources and abilities (aOR from 0.47 to 0.77), when compared to GPs accessing them for more than 10 years. GPs who accessed EHRs less frequently were also less likely to acknowledge individual resources and ability (aOR from 0.20 to 0.55) when compared to GPs accessing them every day (Figure 2D).

Interoperability

In comparison with non-European GPs, Europeans were more likely to identify interoperability in the digital system they used [aOR = 1.42 (1.11; 1.80)]. In contrast, GPs who started accessing EHRs more recently were less likely to identify interoperability (aOR from 0.28 to 0.51) than those who have been accessing them for more than 10 years (Figure 2E).

General evaluation methods

Being European was associated with lower odds of practicing the best digital systems evaluation methods [aOR 0.68 (0.52; 0.88)]. Likewise, having started to access EHRs more recently was associated with lower odds of having best practice evaluation methods in place (aOR from 0.27 to 0.65; Figure 2F).

Impact

Males had higher odds of reporting digital system's impact (aOR1.35), as well as younger GPs (aOR 3.41–5.30) when compared to being 70 or more years old. On the other hand, in comparison with GPs who started to access EHRs over than 10 years ago, GPs who started accessing them more recently were associated with lower odds of recognizing impact of the digital systems they used (aOR from 0.33 to 0.62). Similarly, when compared to GPs with every day access to EHRs, GPs with less frequent accesses were less likely to identify impact as an asset of the digital systems (aOR from 0.16 to 0.86; Figure 2G).

Discussion

Principal findings

GPs had an overall good digital maturity score. While overall usage was the most acknowledged dimension of the digital maturity evaluation framework (90%), interoperability (47%) and use of best practice evaluation methods (28%) were dimensions which received a lower score, highlighting the potential for improvement in these areas.

Being male, having used EHRs for longer periods of time, and higher frequency of access to EHRs, were all positively associated with self-reported digital maturity. On the other hand, practicing in rural settings was negatively associated with digital maturity. No significant associations were found with age, country, years of experience as GP, hours of clinical work per week, urban setting of practice,

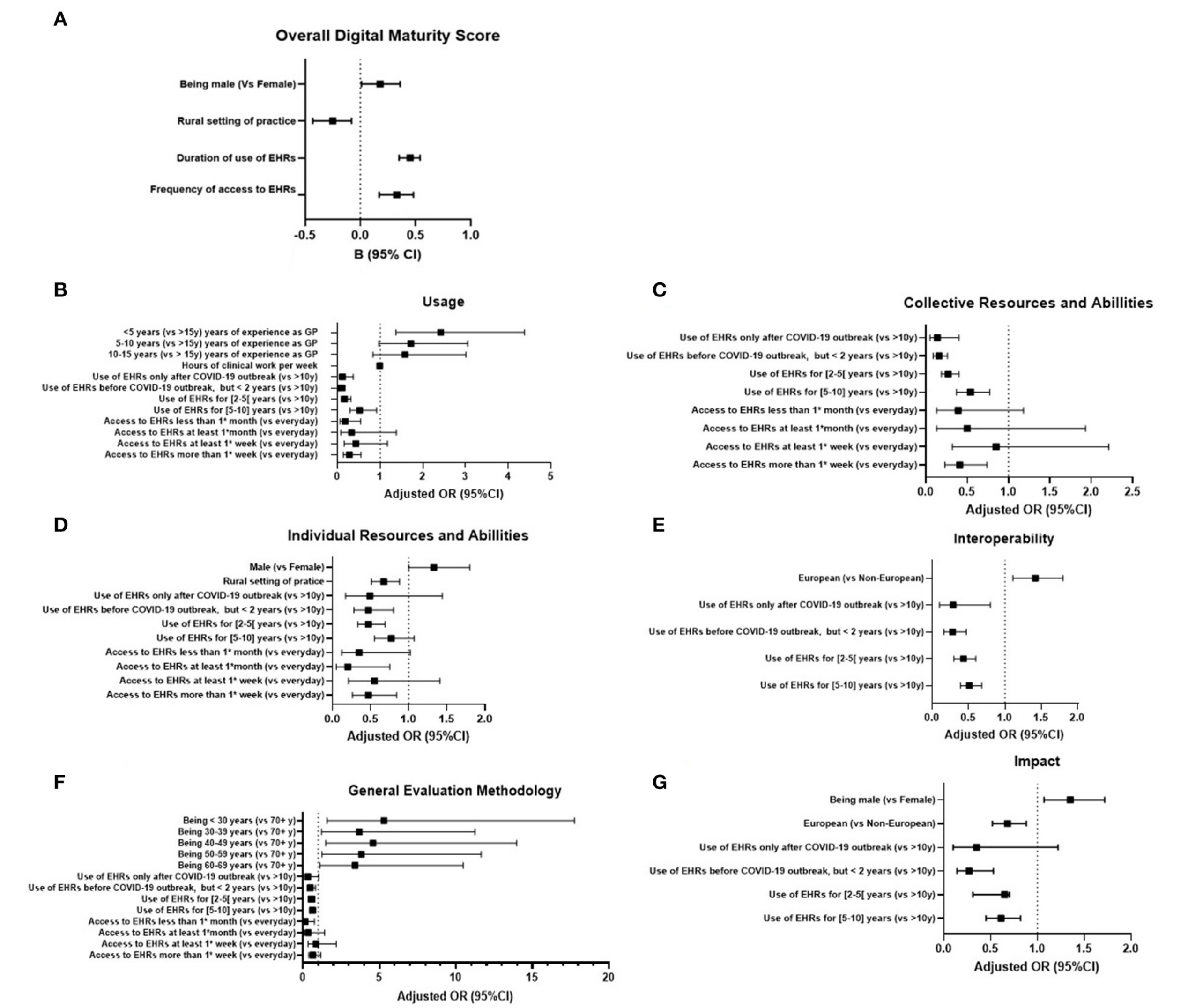

FIGURE 2
Forest plots of multivariable analysis for characteristics associated with overall digital maturity **(A)** and its dimensions-usage **(B)**, collective resources and abilities **(C)**, individual resources and abilities **(D)**, interoperability **(E)**, general evaluation methodology **(F)** and impact **(G)**. *B*, beta; OR, odds ratio; CI, confidence interval; vs, in comparison with.

involvement in teaching activities, and having or not access to EHRs.

All six dimensions of digital maturity may be explained by distinct characteristics, with shorter durations of use of EHRs being negatively associated with all of them.

Comparison with previous literature

There has been an increase in the number of studies focused on developing digital maturity evaluation tools (28, 29). Although a considerable amount of research on this topic has been recently published, to our knowledge, there are no studies reporting the usage of such tools in primary care.

The World Health Organization has already recognized investment in resources, strategies for maximizing impact, standardized evaluation metrics and interoperability of systems, as key to the success of digital transformation (30). Interestingly, we found interoperability and general evaluation models to be the most prevalent shortcomings of digital systems maturity. Previous evidence regarding the determinants of digital health transformation in integrated care in Europe showed that although the importance of interoperability is well understood, the maturity of its implementation at present remains poor (31), a finding which is consistent with our findings. However, comparisons between studies should be interpreted with caution given the different tools used to assess digital maturity.

O'Donnel et al. conducted a systematic review on GPs attitudes toward EHRs which included 33 articles based on the American, European and Asian countries. It is concluded that the perception that EHRs can improve patient safety and quality of care common among GPs. Nevertheless, concerns regarding the impact of adynamic, rigid functionalities of EHRs in GPs' productivity were also raised (32). These findings are congruent with ours, since interoperability and best evaluation methodology—a necessary tool to enable positive changes in the systems to be made—are highlighted as the most prevalent digital maturity shortcomings despite the good overall digital maturity score.

Previous studies on the analysis of digital maturity determinants in secondary care focused on investigating whether availability of resources was related to digital maturity. In hospitals, investment in hardware and software was positively associated with higher levels of digital maturity (33). However, the effects of demographic factors, practice characteristics and adoption of EHRs features on digital maturity is less well documented in the literature.

Zaresani and Scott (33) have suggested that physicians who used digital health technology were more likely to be male. In the present study, being male was positively associated with digital maturity, but this information should be interpreted with caution due to the possibility of the existence of other confounding factors.

Gheorghiu and Hagens conducted a study in Canada to study the adoption of interoperable EHRs across different jurisdictions. They concluded that jurisdictions where physicians accessed interoperable EHRs more often were also the ones where they have already been doing so for longer periods of time. The authors used the frequency of end users' access to EHRs as a method of gauging the systems' maturity (34). Corresponding in our study, GPs accessing EHRs more frequently were associated not only with higher overall digital maturity, but also with better scores on usage, collective resources and abilities, individual resources and abilities and impact of the digital systems they used. The duration of use of EHRs was also associated with better overall digital maturity and with each of its six dimensions.

Regarding clinical practice in rural areas, this was negatively associated with the maturity of digital systems. Although there was sparse evidence specifically exploring the impact of the practice setting on the digital maturity of health systems, existing studies noted that rural areas often remain left behind in terms of broadband coverage and other forms of digital connectivity, as well as lower rates of digital adoption and skills (35).

Strengths and limitations

This study has several strengths. To the best of our knowledge, it is the first study focusing on the evaluation of digital maturity indicators across patient pathway in primary care and the exploitation of its determinants across distinct countries in the perspective of GPs. Participants were GPs working from 20 different countries worldwide, with diversified resource management policies in primary care. A comprehensive set of participants' demographic characteristics, practice characteristics and features of EHRs adoption was collected and analyzed, which allowed us to explore their role in digital maturity.

However, this study also has some limitations that should be acknowledged. It is based on a non validated questionnaire, which gives no guarantees that the collected variables are truly measuring digital maturity. The questionnaire was disseminated online *via* email and social media channels and therefore a potential selection bias cannot be excluded. For example, we can hypothesize that GPs that were more prone to answer the online questionnaire were those working with higher digital maturity. This can possibly explain that 55% of the participants were using EHRs for more than 10 years and 91% were accessing them every day. Additionally, the lack of translation of this questionnaire to the official languages of all 20 inSIGHT Research Group member countries might have presented an obstacle to its enrollment in certain countries. Nevertheless, this data collection methodology enabled us to gather data from 20 countries in a short period of time, proving it to be prompt, economical, and safe to use. Due to its cross-sectional design, this study only enabled us to assess digital maturity during a specific period. It would be important to reproduce this online questionnaire in the future, to allow deductions on the digital maturity temporal evolution to be made.

Additionally, it is important to stress that the framework used to assess digital maturity was developed in 2016 and the employment of digital technologies in health has been rapidly changing since then. However, this tool was a result of a systematic search about the best methods and metrics for evaluating digital maturity and allowed us to perform a patient-centric evaluation focused on identifying how digital maturity can be most significantly refined in the health sector. The choice of evaluating digital maturity at the primary care level only was made since the focus of our work was in fact general practice. Future studies should consider the utilization of the entire framework across four levels (home, community, primary and secondary care) since the evaluation of the digital maturity of health services is dependent on a sector-wide patient understanding (11).

Finally, most GPs included in this study were female (61%), European (68%), involved in teaching activities (64%). Therefore, any attempts to generalize these findings to populations with different characteristics need to be approached with caution.

Implications for research and policy

Our study provides an initial overview of the factors that impact digital maturity and highlights discrepancies in digital transformation across healthcare settings. Future research should evaluate how specific characteristics and features of different healthcare systems, and countries, impact the various aspects of digital maturity and its overall score. Robust comparisons across countries will need to adequately adjust for these factors, and their potential impact as mediators or confounders to robustly support learning from best practices. Additionally, future research should address and measure, other aspects of digital maturity in primary care, beyond the scope of EHRs interoperability.

Conclusion

This is the first international study performed in general practice providing important results for putting into practice in different levels. This work generates evidence on the level of digital maturity in primary care. It demonstrates interoperability and best practice evaluation methods of the digital systems as common digital maturity shortcomings in primary care, which prioritizes the need for these two dimensions to be addressed by stakeholders in order to improve digital maturity across health systems. Our results identified a negative association between practicing general medicine in a rural setting and the level of digital maturity, highlighting discrepancies across various healthcare settings which can slow overall digital transformation.

Therefore, our findings can help to inform key stakeholders in digital health, mainly to policymakers, in developing more bespoke and effective strategies to hasten and take the best advantage of the ongoing digital transformation in General Practice.

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 Imperial College Research Ethics Committee (Reference 20IC5956). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FT, CJ, and AN wrote the first manuscript. All authors reviewed the manuscript and approved the version submitted for publication.

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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.

The handling editor ME declared a past collaboration with the authors.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.962924/full#supplementary-material

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Data-based modeling for hypoglycemia prediction: Importance, trends, and implications for clinical practice

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Background and objective: Hypoglycemia is a key barrier to achieving optimal glycemic control in people with diabetes, which has been proven to cause a set of deleterious outcomes, such as impaired cognition, increased cardiovascular disease, and mortality. Hypoglycemia prediction has come to play a role in diabetes management as big data analysis and machine learning (ML) approaches have become increasingly prevalent in recent years. As a result, a review is needed to summarize the existing prediction algorithms and models to guide better clinical practice in hypoglycemia prevention.

Materials and methods: PubMed, EMBASE, and the Cochrane Library were searched for relevant studies published between 1 January 2015 and 8 December 2022. Five hypoglycemia prediction aspects were covered: real-time hypoglycemia, mild and severe hypoglycemia, nocturnal hypoglycemia, inpatient hypoglycemia, and other hypoglycemia (postprandial, exercise-related).

Results: From the 5,042 records retrieved, we included 79 studies in our analysis. Two major categories of prediction models are identified by an overview of the chosen studies: simple or logistic regression models based on clinical data and data-based ML models (continuous glucose monitoring data is most commonly used). Models utilizing clinical data have identified a variety of risk factors that can lead to hypoglycemic events. Data-driven models based on various techniques such as neural networks, autoregressive, ensemble learning, supervised learning, and mathematical formulas have also revealed suggestive features in cases of hypoglycemia prediction.

Conclusion: In this study, we looked deep into the currently established hypoglycemia prediction models and identified hypoglycemia risk factors from various perspectives, which may provide readers with a better understanding of future trends in this topic.

KEYWORDS

diabetes mellitus, hypoglycemia, prediction, data-based algorithms or models, machine learning

1. Introduction

Diabetes mellitus is a chronic disease characterized by high blood glucose caused by the inability to produce or effectively use insulin. Maintaining blood glucose within the normal range may help prevent or delay the development of diabetic microvascular or macrovascular complications (1–4). However, intensive glycemic control increases the frequency of hypoglycemia while decreasing the risk of long-term complications (5). Hypoglycemia is usually defined as a blood glucose concentration of <70 mg/dL. Counterregulatory response and impaired cognitive function are two physical changes brought on by hypoglycemia (6–8). In addition to impaired behavioral functions such as fear of hypoglycemia (9), depression (10), and dyskinesia (11, 12), hypoglycemia can also result in fatal cardiovascular events (13).

Clinically, hypoglycemia can be classified as mild (MH) or severe (SH) depending on whether third-party assistance is required during hypoglycemia episodes or if there is a loss of consciousness (14). The frequencies of MH and SH episodes in patients with type 1 diabetes (T1D) have been estimated to be 1.6 and 0.029 episodes per person-week, respectively (15), and the incidence of SH was approximately 0.44 episodes per person-year in insulin-treated patients with type 2 diabetes (T2D) (16). Furthermore, hypoglycemia is more common in patients with diabetes who are hospitalized (17, 18). SH is extremely dangerous and is more likely to occur in patients on long-term insulin therapy (5). The counterregulatory response is critical in preventing MH from progressing to SH. However, in individuals with recurrent hypoglycemia, the frequency of hypoglycemic warning symptoms tends to decrease gradually, leading to impaired awareness of hypoglycemia (IAH) and the occurrence of asymptomatic hypoglycemia (19, 20), and IAH, in turn, increases the risk of SH (21, 22), eventually forming a vicious cycle.

Clinical attention is also given to nocturnal hypoglycemia, exercise-related hypoglycemia, and inpatient hypoglycemia. In T1D patients known as "fragile diabetes", nocturnal hypoglycemia (NH) accounted for 55% of hypoglycemia when a blood glucose concentration <54 mg/dL (23–25), and this proportion increased to 75% in pediatric patients (26). Patients may be unable to detect episodes of NH in time while sleeping, which may predispose them to IAH in the long run or even result in "dead-in-bed syndrome". Aside from the benefits of physical activity, such as improving cardiopulmonary adaptability, blood lipid levels, and lowering the risk of long-term cardiovascular events in patients with diabetes (27–29), it may also cause post-exercise hypoglycemia due to increased insulin sensitivity in the short term (30), resulting in avoidance of exercise due to fear of hypoglycemia. Furthermore, symptoms of early hypoglycemia in T1D patients may be masked by physical activity, which may increase the frequency of SH in this population (31). The frequent occurrence of iatrogenic hypoglycemia in hospitalized patients is also not negligible. A systematic review has shown that intensive glucose control increases the risk of inpatient hypoglycemia (32). It was estimated that patients hospitalized for diabetes or hyperglycemia experience an average of two hypoglycemic events per week, with the majority occurring during the night (33). Worse still, inpatient hypoglycemia was associated with a variety of negative outcomes, including increased mortality and serious cardiovascular events (13).

Hypoglycemia prediction is crucial in clinical practice. Many studies have emerged in the last decade that used conventional approaches based on physiological and clinical parameters to predict hypoglycemia (34). These approaches were typically trained using retrospectively collected demographic data, laboratory test results, glucose-lowering agents, and other indicators that may be associated with hypoglycemia obtained from electronic health records in a certain period (35, 36). And the most commonly used statistics were linear regression, logistic regression, Cox hazards regression, and other operations tailored to the problem at hand.

Machine learning (ML) advances, on the other hand, and the need for more accurate hypoglycemia prediction has resulted in data-driven predictive models. Benefiting from the rapid development of continuous glucose monitoring (CGM), the risk of hypoglycemia could be simply predicted by specific parameter calculations such as low blood glucose index (LBGI) (37, 38). Complex CGM-based hypoglycemia predictions were used to develop and improve the artificial pancreas (AP) algorithm, which alerts users when blood glucose levels drop or hypoglycemia is imminent (39). Data-driven algorithms and ML models improve hypoglycemia prediction (40). CGM glucose data are frequently used for ML model establishment due to their continuity and bulkiness.

According to the prediction horizon (PH), such models can be divided into short-term (<180 min), mid-term (180 min to 24 h), and long-term (several days, months, or even years). Undoubtedly, the prediction efficiency of CGM-based models would decrease with the extension of PH. Since glucose autocorrelation usually disappears after 30 min (41), and 30 min is the minimum time interval for effective patient intervention to prevent accidents, current CGM-based hypoglycemia prediction models set PH at 30 min or above. In brief, current hypoglycemia prediction models are mostly based on clinical parameters, CGM data, or a combination of both. The predictive accuracy varied with the study population, outcome definition, PH definition, modeling technique and model training and validation approaches (42). As for clinical data-based models, large sample size and sufficient data processing are frequently required to ensure the accuracy and reliability. Such models typically collect clinical hypoglycemic events for risk stratifying and further hypoglycemia-associated feature selection, followed by internal or external validation of model generalizability. The PH of such models tends to be broad, ranging from predicting short-term hypoglycemic events like inpatient hypoglycemia to long-term hypoglycemic events like SH events months later. It is important to note that a shorter PH may be more useful for prompt clinician intervention, whereas a larger PH increases the prevalence of an outcome and consequently model performance, but may be less useful as a decision support tool (42).

Felizardo et al. (34) conducted a systematic review of data-based algorithms and models in blood glucose prediction, which could be considered an extension of the work of Oviedo et al. (43). They only looked at ML approaches to prediction, and the relevant literature was from before June 2020. Nonetheless, no study comparing conventional and data-based hypoglycemia risk prediction has been discussed and compared from a more holistic clinical perspective to our knowledge. In this study, we investigated the currently established hypoglycemia prediction models and identified hypoglycemia risk factors from various perspectives, which may provide patients and clinicians with a better understanding of future trends in this topic. Our review will be discussed from three perspectives: (1) an overview of currently established hypoglycemia prediction models; (2) dividing the selected studies into five hypoglycemia prediction parts: real-time hypoglycemia, MH/SH, NH, inpatient hypoglycemia, and other hypoglycemia (postprandial, exercise-related), explored hypoglycemia risk factors and illustrated prediction approaches from clinical and ML perspectives, respectively; (3) a comprehensive evaluation and comparison of current hypoglycemia prediction models, with clinical implications and insights into future trends.

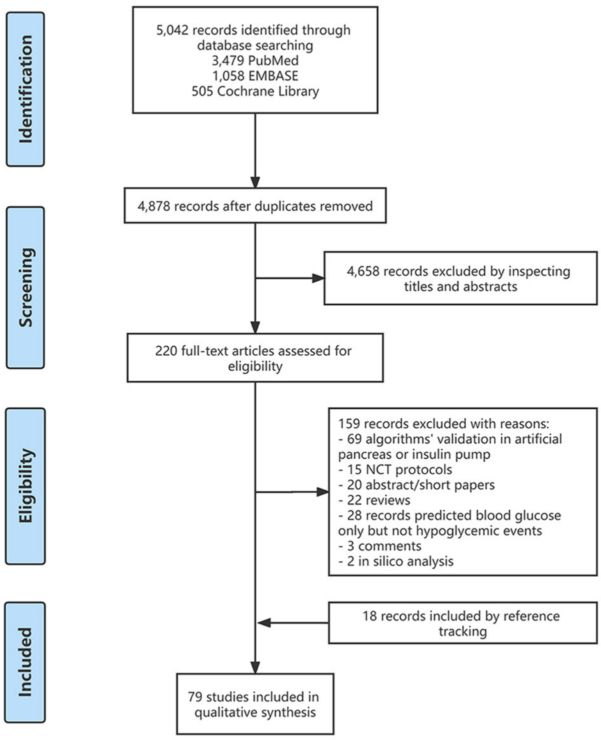

FIGURE 1
Flow diagram of the selection process.

2. Methods

2.1. Search strategy

We searched the PubMed, EMBASE, and Cochrane Library databases for relevant literature from 1 January 2015 to 8 December 2022. The search keywords were "diabetes", "hypoglycemia prediction", "hypoglycemia warning", "hypoglycemia detection" and "hypoglycemia estimation". A total of 5,042 records were found, with 61 of them being relevant to our topic. In addition, we manually added 18 records related to the included records after full-text reading and reference tracking. Figure 1 depicts the flow diagram of detailed literature inclusion.

2.2. Inclusion and exclusion criteria

To include as many relevant records as possible to increase the reliability of our review, we included the records which met the following conditions: (1) the study population were patients with abnormal glucose tolerance or diagnosed with diabetes, regardless of the age of the patients and the type of diabetes; (2) the original data used for the analysis of factors related to hypoglycemia in the records and the establishment of predictive algorithms or models were the patient basic data, medication regimen, laboratory test results and blood glucose measurement results (self-monitoring of blood glucose [SMBG] or CGM results) or other indices retrieved from the real-world studies, clinical trials or cohort studies; (3) the main results of the record were detailed and were exact correlations, algorithms or models related to hypoglycemia prediction. We excluded the following types of records: (1) the research topic was the algorithm proposal or improvement of hypoglycemia warning in AP or CGM products; (2) NCT protocols; (3) abstract/short papers; (4) reviews; (5) blood glucose concentration predictions only but not hypoglycemic events; (6) comments; (7) *in silico* study.

2.3. Data extraction and quality assessment

Data were extracted from the full text and supplementary information of eligible records according to pre-established literature classification criteria. For each study, the following data were carefully extracted: first author, year of publication, use of database features (study population, sample size, type of input clinical data for modeling, source of input glucose data for modeling, modeling approach), type of hypoglycemia prediction (real-time hypoglycemia, MH/SH, NH, inpatient hypoglycemia, other hypoglycemia [postprandial, exercise-related]). Then, the algorithms or models used, the performance, as well as the significance of model performance metrics were tabulated in detail according to the type of hypoglycemia prediction.

2.4. Research emphasis

1) An overview of the currently established prediction model of hypoglycemia;
2) divided the selected studies into five hypoglycemia prediction parts: real-time hypoglycemia, MH/SH, NH, inpatient hypoglycemia, and other hypoglycemia (postprandial, exercise-related), explored the risk factors of hypoglycemia and illustrated prediction approaches from the perspective of clinical and machine learning, respectively;
3) a comprehensive evaluation and comparison of current hypoglycemia prediction models, extraction of clinical implications, and insights into the future trends in this topic.

3. Results

3.1. Eligible studies

Of the 5,042 records obtained after the initial search, 220 records remained after the primary screening of titles and abstracts and were assessed for eligibility, and 159 records were excluded after full-text review, as follows: (1) 69 records were related to the validation of algorithms in the AP or insulin pump; (2) 20 records were without full text; (3) 15 records were protocols for randomized controlled trials; (4) 22 records were reviews; (5) 28 records only predicted blood glucose concentrations but not hypoglycemic events; (6) three records were comment, and (7) two records were *in silico* studies (Figure 1). Furthermore, we added 18 relevant studies through reference tracking. As a result, the total number of studies included was 79: 15 studies on real-time hypoglycemia prediction (19.0%), 24 studies on MH/SH prediction (30.4%), 13 studies on NH prediction (16.5%), 17 studies on inpatient hypoglycemia prediction (21.5%), two studies on exercise-related hypoglycemia prediction (2.5%), and three studies on postprandial hypoglycemia prediction

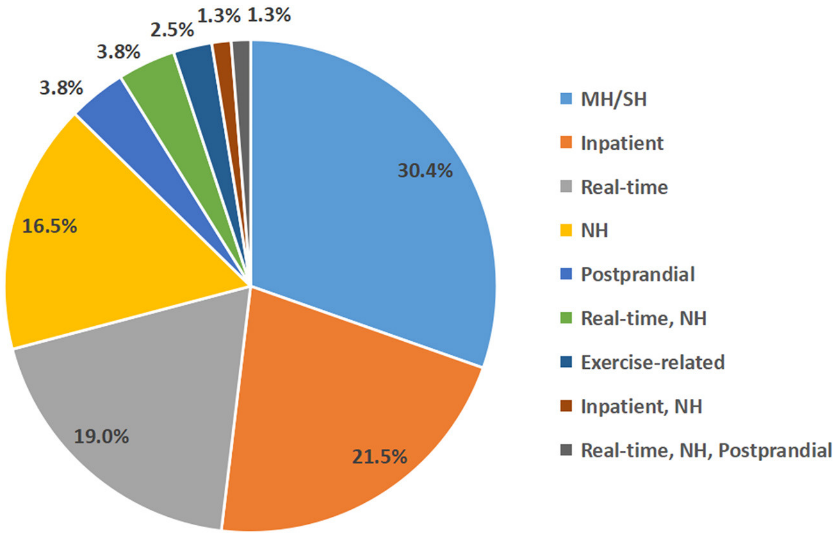

FIGURE 2
The prediction type and proportion of selected studies.

(3.8%), three studies on real-time and NH prediction (3.8%), 1 study on real-time and inpatient hypoglycemia prediction (1.3%) and 1 study on real-time, NH and postprandial hypoglycemia prediction (1.3%) (Figure 2). Details of all included articles are summarized in Table 1.

3.1.1. Study participants

Patients with T1D and T2D made up the majority of the participants in the chosen studies, with 31 of them (39.2%) only including T1D patients. The sample sizes of among studies varied significantly: Six studies with a maximum of 10 participants (7.6%), 22 studies with 11 to 100 participants (27.8%), 19 studies with 101 to 1,000 participants (24.1%), 16 studies with 1,001–10,000 participants (20.3%), 13 studies with 10,001–100,000 participants (16.5%) and two studies more than 100,000 participants (2.5%) (Figure 3). The study subjects were from all age groups.

3.1.2. Inputs

One of the most important strategies for successful hypoglycemia prediction is the selection of appropriate inputs. Thirty-eight of the 79 included studies (48.1%) used CGM data or CGM-derived indices to predict hypoglycemia. Demographics information, insulin use, laboratory tests results, comorbidities, and a history of hypoglycemia were all widely included in clinical hypoglycemia prediction models. Furthermore, other blood glucose-related factors such as carbohydrate intake or meal information (13/79, 16.5%) and physical activity or exercise (7/79, 8.9%) were also included. In addition to the aforementioned factors, 12 studies (15.2%) used physiological parameters such as heart rate, near-infrared light, skin impedance, skin temperature, sweating, and sleep to develop hypoglycemia prediction models (Table 2, Figure 4).

3.1.3. Prediction horizon (PH)

PH is the time period that the model has to forecast the outcome in the future. Prediction windows ranging from 15 min to hours, days, or even months have been reported. It is natural to anticipate a decrease in prediction power as the PH increases due to the limited number of available confounding factors in the data used to train the model. A shorter PH may be more useful for prompt clinician intervention, whereas a larger PH increases the prevalence of an outcome and consequently model performance, but may be less useful as a decision support tool (42). An increase in PH, on the other hand, improves clinical usability of prediction services by extending the time required to take the necessary action during a critical situation, but at the expense of clinical accuracy. According to the aforementioned PH division, 21 studies were short-term forecasting (26.6%), 21 studies were mid-term forecasting (26.6%) and 19 studies were long-term forecasting (24.1%).

3.1.4. Modeling approaches

Various classes of ML techniques have been used in general dynamic system modeling, regression, and prediction services. However, for hypoglycemia prediction in the present study, logistic regression (LR) were the most used techniques (28/79, 35.4%), as shown in Figure 5. Random forest (RF), one of the tree-based models, was the second most used approach (14/79, 17.7%). Support vector machines (SVM) was the third most used algorithm (10/79, 12.7%). Autoregressive and neural networks in various forms ranked as the fourth most used techniques (8/79, 10.1%). XGBoost and support vector regression (SVR) ranked as the fifth (6/79, 7.6%) and sixth most used technique (5/79, 6.3%). Long-short-term memory (LSTM) (4/79, 5.1%), naïve Bayes (3/79, 3.8%), Adaboost (2/79, 2.5%), k-nearest neighbors (k-nn) (2.5%) and other techniques were also used in hypoglycemia prediction.

TABLE 1 An integrated analysis of the selected studies.

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Gerstein et al. (44)	IFG/IGT, T2D	12,537 participants, ≥ 50 years	Demographics, Lab data, GLA, comorbidities		Cox regression		Hypoglycemia ≤ 54 mg/dL, ≤ 36 mg/dL			MH/SH
Bordier et al. (45)	T2D	987 participants, ≥ 70 years	Demographics, Lab data, GLA, comorbidities, COM, mental questionnaires results		LR		Hypoglycemia < 60 mg/dL			MH/SH
Cariou et al. (46)	T1D, T2D	4,424 participants, ≥ 18 years	Demographics, Lab data, GLA, comorbidities, COM, previous HYPO episodes	SMBG	LR		Hypoglycemia < 70 mg/dL			MH/SH
Cichosz et al. (47)	T1D	21 participants, 58 years	Heart rate variability	CGM	Pattern classification	20 min	One single SG < 70 mg/dL (5 min)	10-fold cross validation	AUC = 0.96, Se = 100%, Sp = 91%	Real-time
Ganz et al. (48)	T2D	7,235 participants, ≥ 18 years	Demographics, GLA, previous SH/healthcare/medication		LR		Hypoglycemia ≤ 40 mg/dL			MH/SH
Inzucchi et al. (49)	T2D	1,699 participants, 59.4 years	CGM parameters	CGM	Correlation					MH/SH
Samuel et al. (50)	T2D	NR	GLA, HbA1c, diabetes duration, GFR, BMI		Mathematical model		Hypoglycemia < 70 mg/dL, 50 mg/dL	External		MH/SH
Sonoda et al. (51)	T1D, T2D	123 participants, 65.9 years	Social factors, lifestyle factors, Lab data, GLA		LR		Hypoglycemia < 70 mg/dL, ≤ 49 mg/dL			MH/SH
Sudharsan et al. (52)	T2D	163 participants, 52.8 years	Medication	SMBG	RF, SVM, k-nn, naïve Bayes	24 h, the 8th day	Hypoglycemia < 70 mg/dL	Cross validation	24 h: Se = 91.7%, Sp = 69.5% 8th day: Se = 90.4%, Sp = 91.1%	MH/SH
Ling et al. (53)	T1D	16 participants, 14.6 years	ECG	SMBG	ELM-based NN	3 min	Hypoglycemia < 60 mg/dL	Random subsampling	Se = 78.0%, Sp = 60.0%	NH
Sampath et al. (54)	T1D	34 participants, 18–65 years	CGM parameters	CGM	Aggregating ranking	Nighttime	Hypoglycemia < 70 mg/dL	External	Se = 77.0%, Sp = 83.4%	NH
Tkachenko et al. (55)	T1D	34 participants, 18–65 years	CGM raw data and parameters	CGM	Aggregating ranking	Nighttime	Hypoglycemia < 70 mg/dL	Random subsampling	Se = 73.4%, Sp = 87.8%	NH
Klimontov et al. (56)	T2D	83 participants, 65–80 years	CGM parameters	CGM	LR	Nighttime	Hypoglycemia ≤ 70 mg/dL		Acc = 75.6%, Se = 84.0%, Sp = 62.1%	NH

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TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Karter et al. (57)	T2D	206,435 participants, ≥ 21 years	Demographics, insulin/SU use, history of HYPO-related utilization, prior year ED use		Recursive partitioning	1 year	Hypoglycemia-related ED or hospital use	Internal, external	Internal validation: c-statistic = 0.83, external validation 1/2: c-statistic = 0.81/0.79	MH/SH
Schroeder et al. (58)	T1D, T2D	70,438 participants, 59.8 years	Demographics, diabetes type, Lab data, GLA, comorbidities, COM, previous HYPO events		Cox regression	6 months	Hypoglycemia < 70 mg/dL	External	External validation 1/2: c-statistic = 0.80/0.84	MH/SH
Stuart et al. (59)	T1D, T2D	9,584 participants, > 16 years	Demographics, Lab data, comorbidity score, GLA, previous type of admission		LR	Hospital stay	Hypoglycemia < 70 mg/dL	Bootstrapping	AUC = 0.733	Inpatient
Ena et al. (60)	DM	1,400 participants	Demographics, Lab data, comorbidities, GLA		LR	Hospital stay	Hypoglycemia < 70 mg/dL	External	Validation: AUC = 0.71	Inpatient
Sakurai et al. (61)	T2D	50 participants, 64 years	Demographics, Lab data	SMBG, CGM	Mathematical formula		Lowest nocturnal blood glucose		$R^2 = 0.90$	NH
Chow et al. (62)	T2D	10,251 participants, 62.8 years	Demographics, GLA, comorbidities, previous HYPO events, other medication		Cox regression	5 years	Hypoglycemia ≤ 50 mg/dL	5-fold cross validation	Validation: c-statistic = 0.782	MH/SH
Torimoto et al. (63)	T2D	294 participants, 62.2 years	Demographics, COM, Lab data, GLA, CGM parameters	CGM	LR		One single SG < 70 mg/dL (5 min)			MH/SH
Han et al. (64)	T2D	1,676,885 participants, 57.9 years	Demographics, GLA, current smoking, exercise, insulin, comorbidities, fasting glucose levels, previous HYPO events		Cox regression	1 year	SH events identified by ICD-10 codes	Bootstrapping	Validation: c-statistic = 0.866, Se = 80.2%, Sp = 79.7%	MH/SH
Elvebakk et al. (65)	T1D	20 participants, 41.1 years	Sweating, skin temperature, ECG, counter-regulatory hormones, symptoms of HYPO		ROC analysis					MH/SH
Winterstein et al. (66)	DM	21,840 participants, > 18 years	Demographics, GLA, Lab data, oral intake related, service location related, comorbidities	SMBG	LR	24 h	Hypoglycemia < 50 mg/dL not followed by glucose value > 80 mg/dL within 10 min	Bootstrapping	On day 3–5: c-statistic = 0.877	Inpatient

(Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Mathioudakis et al. (67)	DM	19,262 participants, 61.3 years	Demographics, diagnoses, insulin, comorbidities, Lab data, medications, diet order, steroid use, BG readings		LR	24 h	Hypoglycemia ≤ 70 mg/dL, < 54 mg/dL	Internal	≤ 70 mg/dL: c-statistic = 0.77; < 54 mg/dL: c-statistic = 0.80	Inpatient
Cichosz et al. (68)	T1D	56 participants, 68.7 years	Heart rate variability	CGM	Pattern classification	20 min	One single SG < 70 mg/dL (5 min)	Internal	AUC = 0.95	Real-time
Elvebakk et al. (69)	T1D	20 participants, 41.1 years	ECG, near-infrared and bioimpedance spectroscopy	SMBG	Probabilistic model					MH/SH
Jaggers et al. (70)	T1D	10 participants, 13–17 years	Physical activity intensity	CGM	LR		Two consecutive SG < 70 mg/dL (10 min)			NH
Li et al. (71)	DM	38,780 participants, 57 years	Demographics, Lab data, previous HYPO events, GLA, comorbidities, COM, insurance		LR, CART, RF	2 years	Hypoglycemia < 70 mg/dL	10-fold cross validation	AUC = 0.89 for LR model, AUC = 0.88 for CART model, AUC = 0/90 for RF model	MH/SH
Oviedo et al. (72)	T1D	10 participants, 41 years	Insulin, carbohydrate intake, BG level at mealtime	CGM	naive Bayes, AdaBoost, SVM, ANN	6 h	Three consecutive SG < 70 or 54 mg/dL (15 min)	5-fold cross validation	< 70 mg/dL: Se = 49.0%, Sp = 74.0%; < 54 mg/dL: Se = 51.0%, Sp = 74.0%	Postprandial
Oviedo et al. (73)	T1D	10 participants, 41 years	Insulin, carbohydrate intake	CGM	SVM	6 h	Three consecutive SG < 70 or 54 mg/dL (15 min)	5-fold cross validation	< 70 mg/dL: Se = 71.0%, Sp = 79.0%; < 54 mg/dL: Se = 77.0%, Sp = 81.0%	Postprandial
Shah et al. (74)	DM	585 participants, 69.9 years	Demographics, previous HYPO events, Lab data, GLA, CKD status		LR	Hospital stay	Hypoglycemia ≤70 mg/dL	External	Validation: c-statistic = 0.642, Se = 77.0%, Sp = 28.0%	Inpatient
Tronstad et al. (75)	T1D	20 participants, 18-60 years	Near-infrared, bioimpedance, skin temperature		PLS, ANN		Hypoglycemia < 72 mg/dL			MH/SH
Vu et al. (76)	T1D	9,800 participants, 45.3 years		CGM	RF	3 h, 6 h	Three consecutive SG < 70 mg/dL (15 min)	10-fold cross validation	3h: AUC = 0.90; 6 h: AUC = 0.84	NH
Reddy et al. (77)	T1D	43 participants, 33 years	Demographics, exercise, glucose, hormone features		DT, RF	During exercise	Hypoglycemia < 70 mg/dL	10-fold cross validaton	Acc = 86.67%, Se = 86.21%, Sp = 86.89%	During exercise
Yang et al. (78)	T1D, T2D	100 participants, 44.8 years		CGM	ARIMA	30 min	Three consecutive SG ≤ 70 mg/dL (9 min)		Se $_{T1D/T2D}$ = 100.0/100.0%; FPR $_{T1D/T2D}$ = 10.7/8.0%	Real-time
Gadaleta et al. (79)	T1D	89 participants		CGM	SVR	30 min	Hypoglycemia ≤ 70 mg/dL	Leave-one-out validation	Se = 75.0%, PPV = 51.0%	Real-time

(Continued)

TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Seo et al. (80)	T1D, T2D	104 participants, > 18 years		CGM	RF, SVM, k-nn, LR	30 min	One single SG ≤ 70 mg/dL (5 min)	5-fold cross validation	Se = 89.6%, Sp = 91.3%	Postprandial
Choi et al. (81)	DM	487 participants, 51.8 years	Demographics, GLA, Lab data, previous BG control		Description					Inpatient
Bertachi et al. (82)	T1D	10 participants, > 18 years	CGM raw data, meals, insulin, heart rate signal, steps, calories burned, sleep period	SMBG, CGM	MLP, SVM	Nighttime	One single SG < 70 mg/dL (15 min)	5-fold cross validation	MLP: Acc = 77.38%, Se = 69.52%, Sp = 78.98%; Acc = 80.77%, Se = 78.75%, Sp = 82.15%	Real-time, NH
Elhadd et al. (83)	T2D	13 participants, 51 years	Demographics, Lab data, physical activity, medication	CGM	LR, RF, XGBoost, SVM	During Ramadan			Acc = 27.9%	MH/SH
Hu et al. (84)	T2D	257 participants	Demographics, Lab data, COM, comorbidities		LR	Hospital stay	Hypoglycemia ≤ 70 mg/dL	Bootstrapping	AUC = 0.664	Inpatient
Jensen et al. (85)	T1D	463 participants, 43 years	Demographics, meal, insulin	CGM	LDA	Nighttime	Three consecutive SG ≤ 54 mg/dL (15 min)	5-fold cross validation	AUC = 0.79, Se = 75.0%, Sp = 70.0%	NH
Khanimov et al. (86)	DM	1,342 participants, 75 years	Nutrition risk screening 2002, admission serum albumin		Cox regression	Hospital stay	Hypoglycemia ≤ 70 mg/dL		Acc = 49.0%, Se = 70.0%, Sp = 46.0%	Inpatient
Khanimov et al. (87)	DM	7,718 participants, 71.8 years	Admission serum albumin, blood osmolarity, Charlson Comorbidity Index		Cox regression	Hospital stay	Hypoglycemia ≤ 70 mg/dL			Inpatient
Li et al. (88)	T1D, T2D	1,921 participants, 59 years		CGM	LR, SVM, RF, LSTM	30 min	Three consecutive SG ≤ 70 mg/dL (15 min)	Internal	Se = 92.05%, FPR = 7.69%	Real-time, NH
Ma et al. (89)	T2D	10,251 participants, 62.2 years	Demographics, Lab data, medications, physical exam findings, mental health results		MMTOP		Hypoglycemia < 50 mg/dL	10-fold cross validation	C-statistic = 0.77	MH/SH
Marcus et al. (90)	T1D	11 participants, 18-39 years		CGM	KRR	30 min	Hypoglycemia < 70 mg/dL	Hold-out validation	Se = 64.0%, FPR = 4.0%	Real-time
Misra-Hebert et al. (91)	T2D	1,876 participants, 64.7 years	Demographics, Lab data, comorbidities, GLA, previous HYPO events		LR	3 months	SH events identified by diagnosis code	Bootstrapping	AUC = 0.89, Se = 82.0%, Sp = 79.0%	MH/SH

(Continued)

TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Misra-Hebert et al. (92)	T2D	47,280 participants, 61.4 years	Demographics, Lab data, comorbidities, GLA, previous HYPO events, insurance type		Cox regression		SH events identified by diagnosis code			MH/SH
Mosquera-Lopez et al. (93)	T1D	124 (31 years), 10 (34 years) participants	Insulin, carbohydrate intake	CGM	SVR	Nighttime	One single SG < 70 mg/dL	External	AUC = 0.86, Se = 94.1%, Sp = 72.0%	NH
Tran-Duy et al. (94)	T1D	27,841 participants, 37.0 years	Demographics, Lab data, COM		Cox regression, LR					MH/SH
Vehí et al. (95)	T1D	10 (41 years), 6 (40–60 years) participants	Insulin, carbohydrate intake, meals, physical activity, CGM parameters	CGM	GE, SVM, ANN	4 h for postprandial, 6 h for NH	Three consecutive SG < 70 or 54 mg/dL (15 min)	k-fold cross validation	Postprandial: Se = 69%, Sp = 80% (70 mg/dL): Se = 75.0%, Sp = 81.0% (54 mg/dL); NH: Se = 44.0%, Sp = 85.9%	Real-time, NH, Postprandial
Weiner et al. (96)	DM	6,745 participants, 55 years	Demographics, Lab data, GLA, COM, comorbidities, previous HYPO events, insurance		LR		Hypoglycemia < 70 mg/dL			MH/SH
Calhoun et al. (97)	T1D	127 participants	Demographics, Lab data, insulin, exercise intensity, daytime hypoglycemia	CGM	RF	Nighttime	Six consecutive SG ≤ 60 mg/dL (30 min)	5-fold cross validation	AUC = 0.622	NH
Ruan et al. (36)	DM	17,658 participants, 66 years	Demographics, medications, vital signs, Lab data, hospitalization procedure, previous HYPO events		XGBoost	Hospital stay	Hypoglycemia < 72 mg/dL, 54 mg/dL	10-fold cross validation	< 72 mg/dL: AUC = 0.96, Se = 70.0%, PPV = 88%; < 54 mg/dL: AUC = 0.96, Se = 67%, PPV = 97%	Inpatient
Elbaz et al. (98)	DM	3,605 (71 years), 6,060 (72.9 years) participants	Demographics, smoking, use of alcohol, comorbidities, Lab data, GLA, other medication		LR	First week of admission	Hypoglycemia ≤ 70 mg/dL	Internal, external	Validation set 1/2: AUC = 0.72/0.71	Inpatient
Wang et al. (99)	T1D	12 participants, 25.6 years	Insulin, carbohydrate absorption	CGM	Ruan model, Hovorka model	30 min	One single SG ≤ 70 mg/dL (15 min)	External	Validation: Acc = 95.97%, PPV = 91.77%, Se = 95.60%	Real-time, NH
Jermendy et al. (100)	DM	8,190 participants	Age, type of diabetes, GLA	SMBG	Description		Hypoglycemia ≤ 70 mg/dL			NH
Kyi et al. (101)	T2D	594 participants, 72 years	Demographics, GLA, hospital treatment factors, Lab data, comorbidities, observed-days		LR	Hospital stay	At least 2 days with capillary glucose < 72 mg/dL	Internal	AUC = 0.806, Se = 84.0%, Sp = 66.0%, PPV = 53.0%	Inpatient

(Continued)

TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Li et al. (102)	T1D, T2D	240 participants, 48.2 years		CGM	ARMA, RLS	30 min	Hypoglycemia ≤ 70 mg/dL	5-fold cross validation	Se = 95.72%	Real-time
Dave et al. (103)	DM	112 participants	Demographics, HbA1c, insulin, carbohydrate intake	CGM	LR, RF	30 min, 60 min	Hypoglycemia < 70 mg/dL	Hold-out validation	30 min: Se = 97.04%, Sp = 95.23%; 60 min: Se = 96.21%, Sp = 95.73%	Real-time
Yu et al. (104)	T2D	200 participants		CGM	Prefix Span	30 min	Hypoglycemia ≤ 54 mg/dL, ≤ 70 mg/dL, ≤ 79 mg/dL	Cross validation	≤ 54 mg/dL: Se = 85.9%; ≤ 70 mg/dL: Se = 80.36%; ≤ 79 mg/dL: Se = 78.07%	Real-time
Prendin et al. (105)	T1D	141 participants, > 18 years		CGM	AR, ARMA, ARIMA, SVR, RF, fNN, LSTM	30 min	One single SG < 70 mg/dL (5 min)	Random subsampling	Se = 82.0%, PPV = 64.0%	Real-time
Wenbo et al. (106)	DM	60 (44.8 years), 30 (24.4 years) participants		CGM	VMD, Kernel ELM, AdaBoost	60 min	Three consecutive SG < 70 mg/dL (15 min)	10-fold cross validation	Se = 94.8%, FPR = 7.7%	Real-time
Mathioudakis et al. (35)	DM	35,147 participants, 66 years	Demographics, diagnoses, insulin, hospitalization procedures, Lab data, medications, BG readings, heart rate		LR, RF, naïve Bayes, SGB	24 h after each glucose measurement	Hypoglycemia ≤ 70 mg/dL	Internal, external	Internal validation: c-statistic = 0.90; external validation: c-statistic: 0.86–0.88	Inpatient
Han et al. (107)	T2D	1,410 participants, 62.0 years	Demographics, medications, glycemic variability, Lab data	SMBG	LR	Perioperative period	Hypoglycemia < 70 mg/dL	Bootstrapping	AUC = 0.715	Inpatient
Witte et al. (108)	DM	38,250 participants, 64.3 years	Demographics, medications, Lab data		XGBoost	7 h	Hypoglycemia < 70 mg/dL	5-fold cross validation	Se = 59.0%. Sp = 98.8%, PPV = 71.8%	Inpatient
Yang et al. (109)	T2D	29,843 participants, 64.5 years	Demographics, medications, Lab data		XGBoost	Hospital stay	Hypoglycemia < 70 mg/dL	10-fold cross validation	AUC = 0.822, Acc = 0.93	Inpatient
Yun et al. (110)	T2D	2,645 participants, 62.8 years	Demographics, smoking, alcohol, physical activity, insulin, comorbidities, previous HYPO events, fasting glucose		ROC analysis	1 year	SH episodes requiring hospitalization or medical care	Internal, external	External validation: c-statistic = 0.878, Se = 83.3%, Sp = 84.7%	MH/SH
Wright et al. (111)	DM	6,279 participants, 57.0 years	Demographics, comorbidities, Lab data, vital signs, hospitalization orders, medications, glucose results		LR, RF, XGBoost	24 h	Hypoglycemia <70 mg/dL within 24 h after insulin use	10-fold cross validation	LR: AUC = 0.81, Se = 44.0%; RF: AUC = 0.80, Se = 49.0%; XGBoost: AUC = 0.79, Se = 32.0%	Inpatient

(Continued)

TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Berikov et al. (112)	T1D	406 participants, 36.0 years	Demographics, previous HYPO events, IAH, insulin, CKD, COM, comorbidities, CGM-derived metrics	CGM	RF, LogRLasso, ANN	15 min, 30 min	Three consecutive SG < 70 mg/dL (15 min)	10-fold cross validation	15 min: AUC = 0.97, Se = 94.5%, Sp = 91.4%; 30 min: AUC = 0.942, Se = 90.4%, Sp = 87.4%	Inpatient, NH
Parcerisas et al. (113)	T1D	10 participants, 31.8 years	CGM raw data, meals, insulin, heart rate signal, steps, calories burned, sleep period	SMBG, CGM	SVM	Nighttime	Three consecutive SG < 70 mg/dL (15 min)	Leave-one-out validation, 5-fold cross validation	Population model: Se = 71%, Sp = 76% (include PA), Se = 70%, Sp = 72% (exclude PA); Individualized model: Se = 77.5%, Sp = 64.5% (include PA), Se = 73%, Sp = 75% (exclude PA)	NH
Wang et al. (114)	T2D	313 participants, 53.6 years	CGM-derived metrics, SMBG-derived metrics	SMBG	ROC analysis	Nighttime	Hypoglycemia < 70 mg/dL		AUC of predicting hypoglycemia using LAGE was 0.587, Se = 66.7%, Sp = 50%	NH
Tyler et al. (115)	T1D	20 participants, 34.5 years	CGM data, CGM-derived metrics, insulin, meal, heart rate, metabolic expenditure, age, height, weight	SMBG, CGM	MARS, LR, ARX	During aerobic exercise (4 h)	Hypoglycemia <70 mg/dL	Hold-out validation, 20-fold cross validation	Population model: Se = 73%, Sp = 76%, Acc = 75% (Hold-out set); Se = 64%, Sp = 56%, Acc = 61% (20-fold CV); Personalized model: Se = 73%, Sp = 90%, Acc = 84% (Hold-out set); Se = 68%, Sp = 61%, Acc = 70% (20-fold CV)	During exercise
Duckworth et al. (116)	T1D	153 participants, 17.5 years	CGM data, CGM-derived metrics, age, sex, prior use of CGM, recent HbA1c	CGM	Heuristic model, LR, XGBoost	60 min	One single SG < 70 mg/dL (5 min)	5-fold cross validation	AUC = 0.998, average PPV = 95.3%	Real-time
Faccioli et al. (117)	T1D	11 participants	CGM data, insulin, meals	CGM	ARX	60 min	One single SG < 70 mg/dL (5 min)	Hold-out validation	PPV = 65%, Se = 88%	Real-time
Park et al. (118)	T1D	9 participants	CGM data, heart rate variability	CGM	SVM	10 min, 20 min, 30 min	Hypoglycemia <70 mg/dL	Hold-out validation	Validation set: Se = 89.7%, Sp = 85.8%, Acc = 87.8% (10 min); Se = 88.0%, Sp = 84.3%, Acc = 86.2% (20 min); Se = 80.1%, Sp = 83.3%, Acc = 81.7% (30 min);	Real-time
Zhu et al. (119)	T1D	49 participants, >18 years	CGM data, carbohydrate, bolus insulin	CGM	FCNN, CRNN, LSTM, ARIMA, SVR, RF	30 min, 60 min	One single SG < 70 mg/dL (5 min)	Hold-out validation	FCNN model: Se = 84.09%, Sp = 65.60% (30 min); Se = 68.58%, Sp = 60.64% (60 min)	Real-time

(Continued)

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TABLE 1 (Continued)

References	Diabetes	Sample	Clinical inputs	Glucose inputs	Algorithms	PH	Outcome definition	Validation approach	Model performance	Prediction type
Zhu et al. (120)	T1D	12 participants, 40.0 years	CGM data, non-invasive physiological data, carbohydrate, insulin	CGM	PKM, ARMA, SVR, ANN, LSTM, CRNN	60 min	Three consecutive SG < 70 mg/dL (15 min)	Leave-one-out validation	ARMA model: Acc = 88.58%, Se = 70.30%, Sp = 90.09%; PKM model: Acc = 87.20%, Se = 86.62%, Sp = 82.59%	Real-time

SMBG, self-monitoring blood glucose; CGM, continuous glucose monitoring; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2D, type 2 diabetes; GLA, glucose-lowering agents; MH/SH, mild/severe hypoglycemia; T1D, type 1 diabetes; COM, diabetic complications; LR, logistic regression; HYPO, hypoglycemia; NR, not recorded; GFR, glomerular filtration rate; RF, random forest; SVM, support vector machine; k-nn, k-nearest neighbor; fNN, feed-forward neural network; ECG, electrocardiogram; ELM, extreme learning machine; NH, nocturnal hypoglycemia; ED, emergency department; DM, diabetes mellitus; ROC, receiver operating characteristics; CART, classification and regression trees; ANN, artificial neural networks; CKD, chronic kidney disease; PLS, partial least squares; DT, decision tree; ARIMA, autoregressive integrated moving-average; LSTM, long-short-term-memory; SVR, support vector regression; MLP, multilayer perceptron; LDA, linear discriminant analysis; MMTOP, multiple models for missing values at time of prediction; KRR, kernel ridge regression; GE, grammatical evolution; ANN, artificial neural networks; ARMA, autoregressive moving average; RLS, recursive least squares; VMD, variational mode decomposition; SGB, stochastic gradient boosting; AUC, area under the curve; Acc, accuracy; Se, sensitivity; Sp, specificity; PPV, positive predictive value; FPR, false positive rate; LogRLasso, logistic linear regression with Lasso regularization; MARS, multivariate adaptive regression spline; ARX, autoregressive model with exogenous inputs; FCNN, fast-adaptive and confident neural network; CRNN, convolutional recurrent neural network; PKM, physiologically-based kinetic model; SG, sensor glucose.

3.1.5. Model validation

Model validation is crucial for algorithm development and performance estimation. External validation is important since internal validation may overestimate model performance on a future cohort of patients (121). There are 12 studies utilizing external validation in the present study (15.2%). Internal validation strategies include re-substitution validation, hold-out validation, k-fold cross-validation, leave-one-out cross-validation, and repeated k-fold cross-validation (122). The most commonly used strategies in the reviewed articles are various forms of k-fold cross-validation (22/79, 27.8%). The K-fold cross-validation strategy involves randomly partitioning the datasets into k equal subsets and using one set as a validation set and the rest for training, repeating the process for each subset. Moreover, random subsampling, bootstrapping, hold-out validation, leave-one-out validation approaches are also used.

3.1.6. Performance metrics

As model evaluation performance measures, the majority of studies used sensitivity, specificity, and area under the curve (AUC). For prediction models based on clinical data, correlation coefficients and c-statistics were also frequently used. In addition, accuracy, positive predictive value (PPV) and false positive rate (FPR) were used as evaluation parameters. Each metric was defined in Supplementary Table S1.

3.2. Real-time hypoglycemia prediction

The CGM system can detect the glucose concentration in the interstitial fluid continuously and comprehensively, laying the groundwork for modern glucose monitoring and the emergence of AP. A CGM system, an insulin pump, and a dosing algorithm comprise AP (123). Algorithms are used to implement individual-based accurate blood glucose prediction. The proposal and improvement of dosing algorithms have gradually evolved into a bottleneck of AP development with the increasing maturity of CGM systems. Accurate prediction of impending hypoglycemia is difficult due to large intra- and inter-subject variability, as well as numerous exogenous factors such as diet, exercise, hypoglycemic drugs, and mood changes that can affect blood glucose levels (124). Following a review of the literature, it was discovered that the current impending hypoglycemia prediction primarily includes physiological models, data-based models, and hybrid models (43). Simply put, the development of physiological models is dependent on an understanding of glucose metabolism in the body. These models, which are often compartment models, simulate glucose metabolism and can be used to study glucose-regulated physiological processes. Data-driven models, on the other hand, rely primarily on CGM data and occasionally on additional signals to simulate the patient's physiological response without involving physiological variables. Hybrid models typically combine a physiological model with a data-driven model. Such models incorporate dietary information and insulin absorption *via* physiological models, as well as massive CGM data, to improve the overall prediction accuracy of this model.

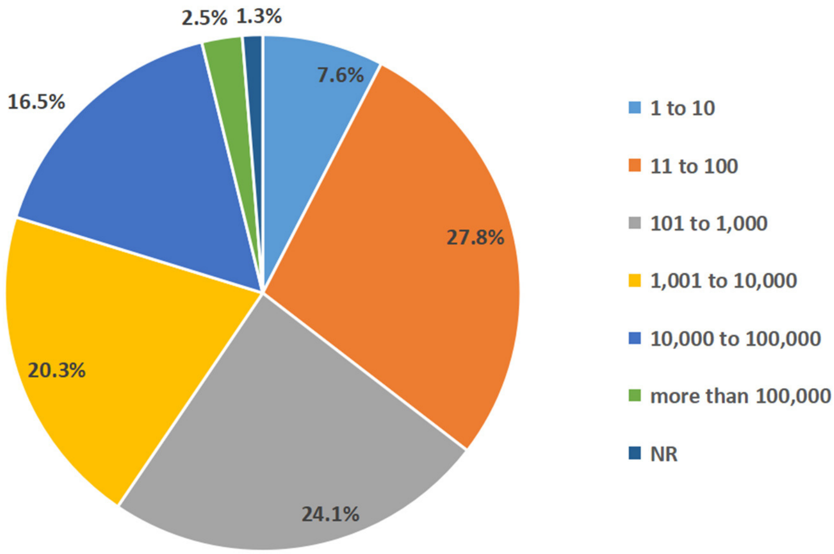

FIGURE 3
The sample size of participants and proportion of selected studies.

TABLE 2 Clinical and glucose inputs for model training.

Input type	References
Demographics data	(35, 36, 44–46, 48, 50, 57–67, 71, 72, 74, 77, 81, 83–85, 89, 91, 92, 94, 96–98, 100, 101, 103, 107–112, 115, 116)
CGM data and parameters	(43, 47, 49, 54–56, 61, 63, 68, 70, 73, 76, 78–80, 82, 83, 85, 88, 90, 93, 95, 97, 99, 102–106, 112–120)
GLA and other medication	(35, 36, 44–46, 48, 50–52, 58–60, 62–64, 66, 67, 71, 74, 81, 83, 89, 91, 92, 96, 98, 100, 101, 107–109, 111)
Laboratory data	(35, 36, 44–46, 51, 58–61, 63, 66, 67, 71, 74, 81, 83, 84, 89, 91, 92, 94, 96–98, 101, 107–109, 111)
Insulin use	(35, 57, 64, 67, 71–73, 82, 85, 92, 93, 95–97, 99, 103, 110, 112, 113, 115, 117, 119, 120)
Comorbidities	(44–46, 58–60, 62, 64, 66, 67, 71, 84, 87, 91, 92, 96, 98, 101, 110–112)
Previous HYPO events	(36, 46, 48, 58, 59, 62, 64, 71, 74, 81, 91, 92, 96, 110, 112)
Carbohydrate intake, meals	(72, 73, 82, 85, 93, 95, 99, 103, 113, 115, 117, 119, 120)
SMBG data and parameters	(35, 46, 52, 53, 61, 66, 67, 69, 82, 100, 107, 113–115)
Physiological signals	(35, 47, 53, 65, 68, 69, 75, 82, 113, 115, 118, 120)
Exercise, physical activity	(64, 70, 77, 83, 95, 97, 110)
Smoking/alcohol consumption	(64, 98, 110)
Mental health condition	(45, 89)

CGM, continuous glucose monitoring; GLA, glucose-lowering agents; HYPO, hypoglycemia; SMBG, self-monitoring of blood glucose.

3.2.1. Only CGM data as inputs for real-time hypoglycemia prediction

This section presents the most recent research on data-based and hybrid hypoglycemia prediction models that only use CGM data as inputs (78, 79, 90, 102, 104–106). AR models were commonly used. Yang et al. (78) proposed an AR integrated moving average (ARIMA) model with an adaptive recognition algorithm. After training with CGM data from 100 subjects (50 T1D + 50 T2D), it was discovered that this model had 100.0% sensitivity in predicting hypoglycemic events, a 9.4% FPR, and an early alert with an average 25.5 min treatment time window to avoid hypoglycemia deterioration. Gadaleta et al. (79) used CGM data from 89 T1D patients to compare current common ML models (static and dynamic) and discovered that the SVR model performed best in terms of prediction accuracy as well as the speed of hypoglycemia detection, with sensitivity and PPV of 75.0 and 51.0%, respectively. Another study comparing linear and nonlinear models laterally found that at a PH of 30 min, the individualized ARIMA model outperformed all linear models in terms of hypoglycemic event detection and prediction accuracy (105). Furthermore, Marcus et al. (90) used a novel patient-specific supervised machine learning (SML) model for hypoglycemia prediction after 30 min and discovered that when the best-fit model was selected for each patient, the hypoglycemia sensitivity was 64.0%, and FPR was 4.0%. Even when only CGM glucose data below 70 mg/dL were included, similar results were obtained. Li (102) and Yu et al. (104) used the model of change detection method and the Winsorization method in conjunction with the autoregressive moving average (ARMA) model and the recursive least squares (RLS) method, respectively. The sensitivity of the former was 95.72%, and the sensitivities of the latter were 85.90, 80.36, and 78.07% when the threshold of hypoglycemia was set at 54, 70, and 79 mg/dL, respectively. Wenbo et al. (106) achieved 94.80% sensitivity for hypoglycemic event prediction at a PH of 60 min using the variational mode decomposition (VMD)-kernel extreme learning machine (KELM)-AdaBoost algorithm. As for sensitivity, the authors of (78) achieved the highest sensitivity at a PH of 30 min (Table 3).

3.2.2. Combining CGM data, insulin, dietary intake and physical activity as inputs

In addition to using CGM data and insulin to predict, carbohydrate intake was also used in models (Table 3). Dave et al.

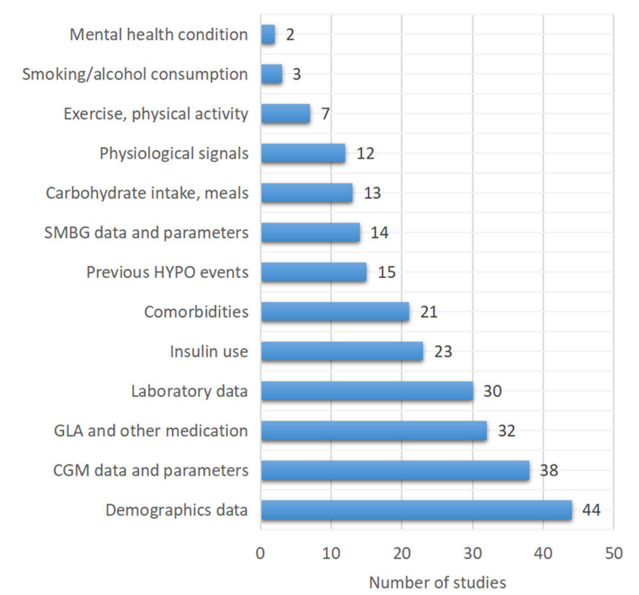

FIGURE 4
The type and number of input parameters used to train the models.

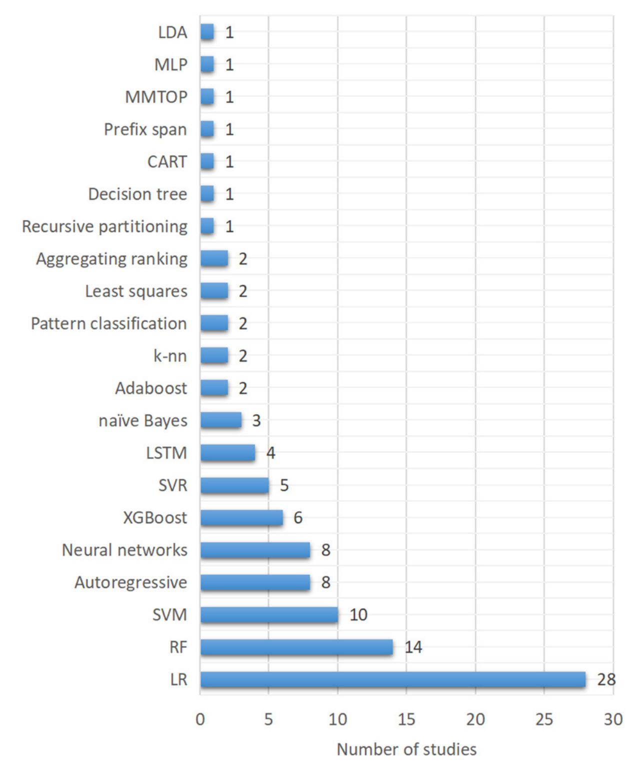

FIGURE 5
Classes of machine learning techniques used in the modeling of hypoglycemia prediction.

(103) confirmed the benefits of including blood glucose-affecting physiological factors in the model by demonstrating satisfactory sensitivity and specificity in hypoglycemia prediction. A recent study indicated a promising predictive efficacy of physiologically-based kinetic model (PKM) which integrated CGM data, carbohydrate intake and insulin usage (120). Additionally, one of the significant factors affecting blood glucose is physical activity (exercise) (125). However, the effect of physical activity (exercise) on blood glucose varies considerably based on many factors, such as the type of activity, amount and intensity of activity, and duration. When compared to studies that only used CGM data as inputs, the contribution of features (meal, insulin, and exercise) other than CGM glucose data is lower but not insignificant; their significance rises for predictions with PH of 60 min (103). Hence, adding clinical factors other than CGM data may allow for improved predictive efficacy, even though overall model performance had not improved to a satisfactory degree.

3.2.3. Non-invasive sensors in hypoglycemia prediction

Aside from CGM data, some researchers have also used non-invasive methods to predict hypoglycemia. Cichosz et al. (47, 68) used CGM and electrocardiograph (ECG) data to predict short-term hypoglycemia events, achieving an AUC of more than 0.96 and a sensitivity of 100% when the PH was set at 20 min. However, the sensitivity and specificity of another NN model for predicting hypoglycemia based solely on ECG signals were only 78.0 and 60.0%, respectively, which could be explained in part by the limited glucose data used in modeling (53). Furthermore, Elvebakk et al. (69) collected physiological parameters such as ECG signals, near-infrared light (NIR), and skin impedance from 20 T1D patients with IAH undergoing hypoglycemic clamp, and they demonstrated that a probability model based on the physiological signals described above could identify 88% of hypoglycemia. Similarly, Tronstad et al. (75) compared the accuracy of partial least squares (PLS) and artificial NN (ANN) in predicting hypoglycemia using NIR signals, skin impedance, and skin temperature data from the same patient source. Their findings showed that the ANN model that combined NIR, skin temperature, and skin impedance outperformed. However, in general, NIR and bioimpedance-based hypoglycemia detection was not very accurate, but it could provide blood glucose trends to some extent.

In summary, current studies aimed at predicting real-time hypoglycemia were mostly short-term. As the PH increased, the prediction accuracy inevitably decreased. Hence, accurate long-term hypoglycemia prediction is extremely urgent. Furthermore, hypoglycemia prediction is gradually shifting from a single signal to a combination of signals to more accurately simulate real-life glucose changes. As shown in Table 3, there was no single technique that could be identified as the most popular model in terms of algorithms. The ML approaches trend revealed that researchers were still experimenting with a diverse set of ML techniques. It can be concluded that there have been some promising results in the field of real-time hypoglycemia prediction, but there is still much room for advancement.

3.3. Mild and severe hypoglycemia prediction

3.3.1. Clinical predictors of hypoglycemia and prediction models based on clinical parameters

Prior to the booming of ML in hypoglycemia prediction, simple predictions based on massive clinical data emerged in this field of study (Table 4). Long duration of diabetes, alcohol consumption,

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TABLE 3 Machine learning approaches for real-time hypoglycemia prediction and best results performed.

References	Participants, type	Inputs	PH (min)	Algorithm	Threshold	Validation	Performance
Gadaleta et al. (79)	89, T1D	CGM	30	SVR	$\leq$ 70 mg/dL	Leave-one-out validation	Se = 75.0%, PPV = 51.0%
Li et al. (102)	240, T1D + T2D	CGM	30	ARMA, RLS	$\leq$ 70 mg/dL	5-fold cross validation	Se = 95.72%
Marcus et al. (90)	11, T1D	CGM	30	KRR	< 70 mg/dL	Hold-out validation	Se = 64.0%, FPR = 4.0%
Prendin et al. (105)	141, T1D	CGM	30	Individualized ARIMA	< 70 mg/dL	Random subsampling	Se = 82.0%, PPV = 64.0%
Yang et al. (78)	100, T1D + T2D	CGM	30	ARIMA	$\leq$ 70 mg/dL		$Se_{T1D/T2D}$ = 100.0/100.0%; $FPR_{T1D/T2D}$ = 10.7/8.0%
Yu et al. (104)	200, T2D	CGM	30	Prefix Span	$\leq$ 54 mg/dL, $\leq$ 70 mg/dL, $\leq$ 79 mg/dL	Cross validation	$\leq$ 54 mg/dL: Se = 85.9%; $\leq$ 70 mg/dL: Se = 80.36%; $\leq$ 79 mg/dL: Se = 78.07%
Wenbo et al. (106)	60, DM	CGM	60	VMD-KELM-AdaBoost	< 70 mg/dL	External	Se = 94.8%, FPR = 7.7%
Cichosz et al. (47)	21, T1D	CGM, HRV	20	Pattern classification	< 70 mg/dL	10-fold cross validation	AUC = 0.96, Se = 100%, Sp = 91%
Cichosz et al. (68)	56, T1D	CGM, HRV	20	Pattern classification	$\leq$ 70 mg/dL	Internal	AUC = 0.95
Park et al. (118)	9, T1D	CGM, HRV	30	SVM	<70 mg/dL	Hold-out validation	Se = 80.1%, Sp = 83.3%, Acc = 81.7%
Dave et al. (103)	112, DM	CGM, INS, CHO	30, 60	LR, RF	< 70 mg/dL	Hold-out validation	Se = 97.04%, Sp = 95.23% (30 min); Se = 96.21%, Sp = 95.73% (60 min)
Faccioli et al. (117)	11, T1D	CGM, INS, CHO	60	ARX	<70 mg/dL	Hold-out validation	PPV = 65%, Se = 88%
Zhu et al. (119)	49, T1D	CGM, INS, CHO	30, 60	FCNN	<70 mg/dL	Hold-out validation	Se = 84.09%, Sp = 65.60% (30 min); Se = 68.58%, Sp = 60.64% (60 min)
Zhu et al. (120)	12, T1D	CGM, INS, CHO	60	PKM	<70 mg/dL	Leave-one-out validation	Acc = 87.20%, Se = 86.62%, Sp = 82.59%
Duckworth et al. (116)	153, T1D	CGM, age, sex, HbA1c	60	XGBoost	<70 mg/dL	5-fold cross validation	AUC = 0.998, average PPV = 95.3%

T1D, type 1 diabetes; T2D, type 2 diabetes; DM, diabetes; CGM, continuous glucose monitoring; HRV, heart rate variability; CHO, carbohydrate intake; INS, insulin.

TABLE 4 Clinical predictors of mild/severe hypoglycemia.

Category of predictors	Predictors of hypoglycemia	Predictors of SH
Demographics	• BMI < 30 kg/m^2 (46), lower BMI (44) • Younger age (44) • Drinking (51, 96) • Longer diabetes duration (63) • Black race (96) • Eating disorder (96)	• Black race (91, 92) • Older age (44, 64, 110) • Female (64) • Current smoker (64) • Drinking (64, 92) • Longer diabetes duration (64, 110) • lower BMI (64, 110)
GLA	• Insulin use $>$ 10 years (46), insulin (96) • 2 injections/day (46) • SU use with antibiotics (96)	• Insulin use (62, 64, 91), intensive glucose control (51, 62) • Multiple OHA use (64) • SU use (91)
CGM parameters	• Higher SD, MAG, MAGE, CV (49, 63), low MBG, higher LBGI (63)	
Other	• Diabetic retinopathy (45), diabetic neuropathy (96) • Low LDL-c level (45) • Altered mini-Geriatric Depression Scale (45) • Previous hypoglycemia (46, 96) • Infection within 30 days (96) • Chronic heart failure (96) • Dementia or falls (96) • HbA1c $\leq$ 6.5% (96)	• Previous SH events (48, 64, 91, 92) • Lack of exercise (64) • Presence of hypertension (44, 64), antihypertensive medication use (62) • CKD (64, 92) • High Charlson score (64) • HbA1c $<$ 7% (91) • High serum creatinine level (44) • Low cognitive function (44) • Depression or other psychiatric disorders (92) • Medicaid insurance (92) • History of CVD (92) • Lower eGFR (110) • Higher albuminuria (110)

SH, severe hypoglycemia; GLA, glucose-lowering agents; OHA, oral hypoglycemic agents; SU, sulfonylurea; CGM, continuous glucose monitoring; SD, standard deviation of glucose; MAG, mean absolute glucose; MAGE, mean amplitude of glucose excursions; CV, coefficient of variance; MBG, mean blood glucose; LBGI, low blood glucose index; CKD, chronic kidney disease; CVD, cardiovascular disease.

eating disorders, low BMI, insulin use, low LDL levels, combined diabetic retinopathy (DR) or diabetic peripheral neuropathy (DPN), depression or dementia, great glycemic variability, infection, and heart failure were identified as risk factors for overall hypoglycemic events (44–46, 49, 51, 63, 96). A long-term SH risk prediction study based on clinical parameters in 1,676, 885 adult T2D patients found that old age, female gender, smoking, alcohol abuse, low BMI, lack of exercise, history of SH, use of insulin or multiple oral hypoglycemic agents, combined hypertension and chronic kidney disease (CKD), long duration of diabetes, and a high Charlson comorbidity index were all important risk factors for the development of SH (64). Several studies have shown an association between insulin use, intensive insulin therapy, previous history of SH, and SH (44, 48, 51, 62, 91). Furthermore, black race, sulfonylurea use, low HbA1c, low serum creatinine levels, and poor cognitive function were also identified as risk factors for SH (44, 91). Hu et al. (84) performed ROC analysis on fasting insulin, fasting blood glucose, and total insulin treatment time of 257 T2D patients receiving intensive therapy and reported an AUC of 0.666 in hypoglycemia prediction. Karter et al. (57) classified 165,148 patients into high, medium, and low-risk groups for SH hospitalization by assessing six factors: number of previous hypoglycemia hospitalizations, insulin use, sulfonylurea use, previous emergency history, CKD stage, and age. Following model validation, they concluded that the proposed SH risk assessment tool was accurate and effective after 12 months of observation. Accordingly, some researchers have used another 6-parameter model (age, type of diabetes, HbA1c, eGFR and previous history of hypoglycemia) to predict the 6-month SH risk (58).

A remarkable cohort study of 27,841 T1D patients followed for an average of 7 years to model T1D health outcomes revealed that male gender, Ln (HbA1c), HDL level, and smoking were risk factors for hypoglycemia (HR = 1.32, 1.63, 1.14, and 1.40, respectively), while Ln (eGFR) was a protective factor (HR = 0.77) (94). Another SH predictive model study based on electronic health record data of 47, 280 T2D patients found that a history of previous hypoglycemia (HR = 4.44), black race (HR = 1.81), Medicaid insurance (HR = 1.35), previous history of cardiovascular disease (HR = 2.35), depression (HR = 1.28), mental disorder other than depression (HR = 1.55), alcohol consumption (HR = 1.55), and CKD (HR = 1.86) were risk factors for SH, while the relationship between sulfonylureas and SH changed with HbA1c: sulfonylurea use was a risk factor (HR = 1.61) when HbA1c was 6%, but it became a protective factor (HR = 0.69) when HbA1c was 9%. Furthermore, the effect of HbA1c levels on SH varied at some extreme values: when the reference HbA1c was 6%, the corresponding HR was 1.59 when an HbA1c level of 5%, however, HR of HbA1c changed to 0.73 when at a level of 7%, and the HR for HbA1c = 9% was 1.39 instead (92).

3.3.2. Application of machine learning to predict hypoglycemia

In addition to clinical models, there were a number of studies that used ML approaches to predict mild and severe hypoglycemia. Ma et al. (89), for example, proposed a model to predict SH that could handle missing data, and they finally included 48 risk factors associated with SH such as demographic data (age, ethnicity, education information), vital signs (diastolic blood pressure, DBP), laboratory test results (creatinine, eGFR, urine protein, UACR) and medication regimens (diuretics, potassium supplements, ACEI, α-blockers, β-blockers, anticoagulants, sulfonylureas, biguanides,

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thiazolidinediones, insulin, etc.) after univariate analysis for relevant variable screening and showed that the average c-statistic of their proposed SH prediction model was 0.77. Predictive modeling also made use of mathematical approaches. Samuel et al. (50) identified four clinical factors associated with MH (BMI, diabetes duration, HbA1c, and GFR) and proposed a mathematical formula for calculating the incidence of MH incorporating these four parameters, but its accuracy was highly uncertain in different populations of patients with diabetes. However, the prediction efficiency of ML was not always superior to that of traditional statistical methods. Li et al. (71) used electronic health records data from 38,780 patients with diabetes to create a prediction model for hypoglycemia and discovered that the ML method (RF) was only 1% more effective than LR in predicting hypoglycemia. A robust recursive partitioning algorithm based SH-related emergency department (ED) use prediction model was proposed based on a large sample size and external validation (57) (Table 5).

3.4. Nocturnal hypoglycemia (NH) prediction

3.4.1. Prediction of NH based on clinical parameters

Age between 10.0 and 19.9 years, diagnosis of T1D, and initiation of insulin therapy were found to be risk factors for NH events (<54 mg/dL, 00:00–05:59) in a study using self-monitoring of blood glucose (SMBG) values and clinical indicators from 8,190 patients with diabetes (100). For NH prediction, CGM parameters had also been adopted in addition to clinical parameters. Daytime (6:00-22:59) mean absolute glucose (MAG) and mean pre-midnight blood glucose levels had predictive value for NH events, according to a cross-sectional study of 83 insulin-treated hospitalized T2D patients (56). Sakurai et al. (61) developed an equation relating age, SMBG values, and basal insulin dose to predict NH. Besides, strenuous physical activity was found to be an important predictor of NH after adjusting for age and gender (70) (Table 6).

3.4.2. Application of ML to predict NH

ML approaches based on CGM data were widely used for NH prediction in addition to clinical factors (Table 7). Tkachenko (55) and Sampath et al. (54) proposed combining predictive risk factors of NH based on CGM data, which both resulted in improved predictive performance. Based on massive nocturnal CGM raw glucose data derived from 9,800 T1D patients, a random forest (RF) model demonstrated an overall NH predictive performance of AUC up to 0.84 (AUC = 0.90 during 00:00–03:00, and AUC = 0.75 during 03:00–06:00) (76). Furthermore, a novel CGM metric-gradient and combining mean sensor glucose enabled the prediction of NH events in patients with diabetes with a sensitivity of 92.05% and a false positive rate of 7.69% (88).

Models that included blood glucose-affecting physiological factors other than CGM data were also widely used in the field of NH prediction. Jensen et al. (85), for example, performed ML feature extraction and ROC curve analysis on basic demographic data, dietary intake, and insulin use combined with CGM data from 463 T1D patients and discovered that the combined extracted CGM indices (linear regression slope of blood glucose during 21:00–24:00, lowest blood glucose value, lowest blood glucose value on the

TABLE 5 Machine learning approaches for MH/SH prediction and best results performed.

References	Participants, type	Inputs	PH	Algorithm	Outcome	Validation	Performance
Sudharsan et al. (52)	163, T2D	SMBG, medication	24 h, the 8th day	RF, SVM	Hypoglycemia < 70 mg/dL	Cross validation	24 h: Se = 91.7%, Sp = 69.5%;8th day: Se = 90.4%, Sp = 91.1%
Karter et al. (57)	206,435, T2D	Demographics, insulin/SU use, history of HYPO-related utilization, prior year ED use	12 months	Recursive partitioning	SH-related ED or hospital use	Internal, external	IV: c-statistic = 0.83, EV 1/2: c-statistic = 0.81/0.79
Li et al. (71)	38,780, DM	Demographics, Lab data, previous HYPO events, GLA, comorbidities, COM, insurance	2 years	RF	Hypoglycemia < 70 mg/dL	10-fold cross validation	AUC = 0.90
Elhadd et al. (83)	13, T2D	CGM, demographics, Lab data, PA, medication	During Ramadan	XGBoost			Acc = 27.9%
Ma et al. (89)	10,251, T2D	Demographics, Lab data, medications, physical exam findings, mental health results		MMTOP	Hypoglycemia < 50 mg/dL	10-fold cross validation	C-statistic = 0.77
Misra-Hebert et al. (91)	1,876, T2D	Demographics, Lab data, comorbidities, GLA, previous HYPO events	3 months	LR	SH events identified by diagnosis code	Bootstrapping	AUC = 0.89, Se = 82.0%, Sp = 79.0%

T2D, type 2 diabetes; DM, diabetes; SMBG, self-monitoring of blood glucose; CGM, continuous glucose monitoring; HYPO, hypoglycemia; Lab, laboratory; GLA, glucose-lowering agents; PA, physical activity; IV, internal validation; EV, external validation.

TABLE 6 Clinical predictors of nocturnal hypoglycemia.

Category of predictors	Predictors
Demographics	• Age (10.0–19.9 years) (100)
	• Type 1 diabetes (100)
GLA	• Insulin treatment (100)
CGM parameters	• Daytime Mean Absolute Glucose (MAG) (56)
	• Pre-midnight mean glucose (56)
Other	• Vigorous intensity physical activity (70)

GLA, glucose-lowering agents; CGM, continuous glucose monitoring.

previous night) and BMI could achieve an AUC of 0.79 for NH prediction (sensitivity: 75%, specificity: 70%). Furthermore, Bertachi et al. (82) confirmed the importance of combining physical activity with CGM data to predict NH events: the specificity of predicting NH was significantly improved to 91.9% when additional information such as heart rate, number of steps, calorie expenditure, and sleep were added. Calhoun et al. (97) discovered an association between NH and bedtime BG, exercise intensity, daytime hypoglycemia, HbA1c, and active insulin (insulin on board, IOB). Vehi et al. (95) established an ANN model that included CGM data, exercise and sleep information from six T1D patients and had a 44.0% sensitivity and an 85.9% specificity in predicting NH. Another study of NH prediction using a SVR model based on CGM data found that blood glucose values at bedtime, age, and mean blood glucose 1 h before bedtime were related to the occurrence of NH, and the AUC of this model to finally predict NH events was 0.86 (sensitivity: 94.1%, specificity: 72.0%) (93).

It can be seen that the most popular approaches for NH prediction in our reviewed articles were RF and SVM. The RF model including CGM, demographics data, INS and other clinical indicators of 406 T1D patients established by Berikov et al. (112) achieved a better performance at a PH of 30 min. Whereas a SVR model taking CGM, insulin use and carbohydrate intake information into consideration showed satisfactory AUC (0.86) and sensitivity (94.1%) for a longer prediction window (93).

Seventy-five percent of hypoglycemic events associated with coma or seizures occur at night, as warning autonomic symptoms caused by hypoglycemia are frequently insufficient to awaken the patient (126). Since NH events are urgent and harmful to patients, current NH prevention focuses primarily on accurately predicting upcoming NH events and alerting using modern glucose monitoring technology and AP to urge medical staff or patients to take prompt action. The findings of our literature review also highlight recent significant advances in the field of NH prediction using ML, however, these algorithms and models must still be validated in a large sample and tested in real-world applications in the future.

3.5. Inpatient hypoglycemia prediction

A recent electronic health record-based risk prediction study for iatrogenic hypoglycemic events included 35,147 hospitalized patients (mean age, 66 years) who received at least 1 U of insulin and completed four finger stick records (35). Demographic data, diagnostic information, inpatient procedure, laboratory test results, finger blood results, and therapeutic drugs were among the 43 types of data extracted from electronic health records. They revealed that basal insulin dose, CV of finger stick blood values, previous hypoglycemic events, nadir glucose value, body weight, and mean blood glucose in the first 24 h of hospitalization were the most important predictors of hypoglycemia. The c-statistic was 0.90 of internal validation and was 0.86–0.88 of external validation (35). Stuart et al. (59) used multivariate LR to develop a prediction model from hospital admissions of 9,584 patients with diabetes, finding that ethnicity (black and Asian), older age (≥75 years), type of admission (emergency), insulin and sulfonylurea use could all predict the occurrence of hypoglycemia in hospitalized patients. A study of 9,665 patients with diabetes using modeling and validation revealed that older age, nasogastric tube or gastrostomy tube feeding, a higher Charlson comorbidity index, admission for vomiting, combined acute renal failure, and insulin use were risk factors for inpatient hypoglycemia (98). In addition to age and insulin, emergency department history in the previous 6 months, oral hypoglycemic agent use without inducing hypoglycemia, and severe CKD were all associated with inpatient hypoglycemia (74). Furthermore, a study of 21,840 adult patients with diabetes found that male patients were more prone to hypoglycemia on the first day of hospitalization, while glucose variability, low body weight, low creatinine clearance, insulin and sulfonylurea use were common risk factors for hypoglycemia (66). Frail patients treated with insulin or with insufficient nocturnal glucose monitoring were predisposed to inpatient hypoglycemia (81). Low serum albumin levels, in addition to the aforementioned risk factors, were also identified (86, 87) (Table 8).

The use of ML approaches in inpatient hypoglycemia prediction was summarized in Table 9. It can be seen that the most popular approaches for inpatient hypoglycemia prediction in our reviewed articles were LR and XGBoost. A study that used ML to mine electronic health records data from 17,658 patients with diabetes revealed the superiority of ML: when compared to the traditional LR method (AUC = 0.75), the AUC of the XGBoost model could reach 0.96 in identifying hypoglycemic events (36). However, considering of the sample size and model validation, the study carried out by Mathioudakis et al. (35) using stochastic gradient boosting (SGB) achieved the best performance in a narrow PH (24 h after each glucose measurement).

3.6. Other hypoglycemia predictions

Prediction of postprandial and exercise-related hypoglycemia was also included in our review. Oviedo et al. (73) used a SVM algorithm to predict postprandial hypoglycemia within 240 minutes after meal in 10 T1D patients receiving sensor-augmented pump (SAP) therapy, and they found that the sensitivity and specificity for prediction of mild hypoglycemia < 70 mg/dL were 71.0 and 79.0%, respectively, and those for severe hypoglycemia < 54 mg/dL were 77.0 and 81.0%, respectively. Seo et al. (80) compared four ML models and discovered that the RF model had 89.6% sensitivity and 91.3% specificity in predicting hypoglycemic events after 30 min of meal absorption (Table 10).

Meanwhile, our research focused on exercise-related hypoglycemia. Prevention of hypoglycemia during exercise is a

TABLE 7 Machine learning approaches for NH prediction and best results performed.

References	Participants, type	Inputs	PH	Algorithm	Threshold	Validation	Performance
Sampath et al. (54)	34, T1D	CGM raw data and parameters	Nighttime	Aggregating ranking	< 70 mg/dL	External	Se = 77.0%, Sp = 83.4%
Tkachenko et al. (55)	34, T1D	CGM raw data and parameters	Nighttime	Aggregating ranking	< 70 mg/dL	Random subsampling	Se = 73.4%, Sp = 87.8%
Klimontov et al. (56)	83, T2D	CGM raw data and parameters	Nighttime	LR	≤ 70 mg/dL		Acc = 75.6%, Se = 84.0%, Sp = 62.1%
Vu et al. (76)	9,800 T1D	CGM	3 h, 6 h	RF	< 70 mg/dL	10-fold cross validation	3h: AUC = 0.90; 6h: AUC = 0.84
Jensen et al. (85)	463, T1D	CGM, demographics, INS, CHO	Nighttime	LDA	≤ 54 mg/dL	5-fold cross validation	AUC = 0.79, Se = 75.0%, Sp = 70.0%
Mosquera-Lopez et al. (93)	134, T1D	CGM, INS, CHO	Nighttime	SVR	< 70 mg/dL	External	AUC = 0.86, Se = 94.1%, Sp = 72.0%
Calhoun et al. (97)	127, T1D	CGM, demographics, Lab data, INS, PA, daytime HYPO	Nighttime	RF	≤ 60 mg/dL	5-fold cross validation	AUC = 0.622
Parcerisas et al. (113)	10, T1D	CGM raw data, PA, CHO, INS, heart rate signal, steps, calories burned, sleep period	Nighttime	SVM	< 70 mg/dL	Leave-one-out, 5-fold cross validation	Population model: Se/Sp = 71/76% (include PA) Individualized model: Se/Sp = 73/75% (exclude PA)
Bertachi et al. (82)	10, T1D	CGM raw data, CHO, INS, heart rate signal, steps, calories burned, sleep period	Nighttime	SVM	< 70 mg/dL	5-fold cross validation	Acc = 80.77%, Se = 78.75%, Sp = 82.15%
Li et al. (88)	1,921, T1D + T2D	CGM	Nighttime	LSTM	≤ 70 mg/dL	Internal	Se = 92.05%, FPR = 7.69%
Vehí et al. (95)	16, T1D	CGM, INS, CHO, PA	6 h	ANN	< 70 mg/dL	k-fold cross validation	Se = 44.0%, Sp = 85.9%
Wang et al. (99)	12, T1D	CGM, INS, CHO	30 min	GIM	≤ 70 mg/dL	External	Validation: Acc = 95.97%, PPV = 91.77%, Se = 95.60%
Berikov et al. (112)	406, T1D	CGM, demographics, previous HYPO, IAH, INS, CKD, COM, comorbidities	15 min,; 30 min	RF	< 70 mg/dL	10-fold cross validation	15 min: AUC = 0.97, Se = 94.5%, Sp = 91.4%; 30 min: AUC = 0.942, Se = 90.4%, Sp = 87.4%

T1D, type 1 diabetes; T2D, type 2 diabetes; CGM, continuous glucose monitoring; INS, insulin; CHO, carbohydrate intake; PA, physical activity; HYPO, hypoglycemia; IAH, impaired awareness of hypoglycemia; CKD, chronic kidney disease; COM, diabetic complications; Lab, laboratory; GIM, glucose-insulin mixture model.

TABLE 8 Clinical predictors of inpatient hypoglycemia.

Category of predictors	Predictors
Demographics	• Advanced age (59, 74, 98)
	• Ethnicity (Black and Asian) (59) • Low body weight (66)
GLA	• Insulin (35, 59, 60, 66, 74, 98, 101) • SU (59, 66, 101)
Other	• CV of blood glucose (35, 66) • Any previous hypoglycemia (35, 60) • Hospital day number (35) • Nadir blood glucose level admission (35) • Type of admission (Emergency) (59) • Feeding with nasogastric or percutaneous gastrostomy tube (98) • High Charlson comorbidity score (98, 101) • Vomiting as a cause of admission (98) • Acute renal failure (98), severe chronic kidney disease (60, 74) • Emergency department visit 6 months prior (74) • Number of hospitalization days (60, 101) • Low creatinine clearance (66) • Frailty (81) • Low serum albumin (86, 87)

GLA, glucose-lowering agents; SU, sulfonylurea.

major challenge in diabetes. Providing predictions of glycemic changes during and following exercise can help people with diabetes avoid hypoglycemia. Reddy et al. (77) pointed out the most important features in the RF model for exercise-related hypoglycemia prediction: an average heart rate above 121 beats/min in the first 5 min of exercise, an increase in energy expenditure and a blood glucose value below 182 mg/dL at the beginning of exercise tended to increase the likelihood of hypoglycemia. Another unique dataset representing 320 days and 50,000 + time points of glycemic measurements collecting in adults with T1D who participated in a 4-arm crossover study evaluating insulin-pump therapies was used to develop adaptive, personalized ML algorithms to predict exercise-related glucose changes (115). Their personalized algorithms based on LR algorithm achieved high accuracy (84%) and specificity (90%) in predicting hypoglycemia during and following 4-h exercise sessions.

4. Conclusions

Hypoglycemia is a huge obstacle to achieving optimal glucose control in patients with diabetes, posing a great challenge to the healthcare system while potentially harming the patient's cardiovascular system and brain. Prediction of hypoglycemia is critical in clinical practice. In this study, we comprehensively reviewed the literature on hypoglycemic risk factors or hypoglycemic prediction that have been published in recent years and elaborated on the research progress in the prediction of various types of hypoglycemic events that are most concerned in clinical practice from various perspectives. Before the explosion of machine learning for hypoglycemia prediction, simple prediction based on large sample-sized clinical data proliferated due to clinical need over the last decade. We concluded the summary table of risk factors for different types of hypoglycemic events by extracting hypoglycemic risk factors from various studies. As a result, we discovered that age, insulin dose, sulfonylurea use, prior history of hypoglycemia, and combined CKD were the main risk factors for hypoglycemic episodes in clinical practice, but that under certain conditions, advanced age or younger age, different levels of HbA1c, and sulfonylurea use had different effects on hypoglycemia. This necessitates clinicians to assess the patient's condition before making an accurate judgment and decision.

The implementation of CGM systems, insulin pumps, and AP in clinical practice provides technical support for the prevention of hypoglycemic events. With the booming field of ML, hypoglycemic prediction models incorporating several other major factors affecting blood glucose such as insulin dose, carbohydrate intake, and physical activity have sprung up based on the massive amount of blood glucose information carried by CGM. However, the PH of current studies is <240 min. Furthermore, the predictive performance of hypoglycemia varied with sample size, training data type, and ML method used. Furthermore, any predictive model and prevention strategy must be validated in a variety of clinical settings to determine whether there will be subsequent hypoglycemia reductions and improvements in clinical outcomes. In conclusion, while there have been some promising results in the field of hypoglycemia prediction, there is still much room for improvement.

Hypoglycemia in patients with diabetes is influenced by multiple factors, such as insulin administration, carbohydrate intake, physical activity, previous blood glucose readings, stress, age, BMI, duration of diabetes, pancreatic islet function, comorbidities, alcohol consumption, and smoking. To more accurately estimate the risk of hypoglycemia, an ideal predictive model for hypoglycemia should consider all pertinent confounding factors jointly. In this review, demographics data and CGM readings were the main types of model inputs used. CGM glucose values, for instance, were the most frequently used feature when performing real-time and nocturnal hypoglycemia predictions. Systems using ML can be trained to forecast future hypoglycemic events based on a person's historical glucose levels. The majority of these models used time series prediction techniques with glucose data that contains precise timestamps corresponding to real glucose values. Additionally, some models also considered the effects of insulin, carbohydrate intake, and physical activity on hypoglycemia. In our study, patients manually recorded their dietary information using paper diaries or electronic diaries. This information included the frequency and timing of each meal and was typically estimated as carbohydrate (grams). Nevertheless, some researchers have attempted to automate the process of dietary data recording. In most cases, ML model integration was done directly using carbohydrate amounts (in grams), figuring out how many calories were in food, or using compartmental models to predict how much glucose is absorbed from the gut into the blood. Besides, the type, quantity, and intensity of physical activity, as well as its duration, all affect hypoglycemia differently. Data on physical activity can be gathered manually or automatically by wearable devices. A wide range of physical activity data, including the intensity of activity, the total energy expended over a specific period of time, a standard table of caloric use during exercise, task metabolic equivalent (MET) were taken into consideration. According to the current results, the most useful features are still the information carried by CGM, such as the original blood glucose value and hypoglycemia-related CGM parameters. When compared to studies that only used CGM data as inputs,

TABLE 9 Machine learning approaches for inpatient hypoglycemia prediction and best results performed.

References	Participants, type	Inputs	PH	Algorithm	Outcome	Validation	Performance
Stuart et al. (59)	9,584, T1D + T2D	Demographics, Lab data, comorbidity score, GLA, previous type of admission	Hospital stay	LR	Hypoglycemia < 72 mg/dL	Bootstrapping	AUC = 0.733
Ena et al. (60)	1,400, DM	Demographics, Lab data, comorbidities, GLA	Hospital stay	LR	Hypoglycemia < 70 mg/dL	External	Validation: AUC = 0.71
Winterstein et al. (66)	21,840, DM	SMBG, demographics, GLA, Lab data, oral intake related, service location related, comorbidities	24 h	LR	Hypoglycemia < 50 mg/dL not followed by glucose value > 80 mg/dL within 10 min	Bootstrapping	On day 3–5: c-statistic = 0.877
Mathioudakis et al. (67)	19,262, DM	Demographics, diagnoses, insulin, comorbidities, Lab data, medications, diet order, steroid use, BG readings	24 h	LR	Hypoglycemia ≤ 70 mg/dL, < 54 mg/dL	Internal	≤ 70 mg/dL: c-statistic = 0.77; < 54 mg/dL: c-statistic = 0.80
Shah et al. (74)	585, DM	Demographics, previous HYPO events, Lab data, GLA, CKD status	Hospital stay	LR	Hypoglycemia ≤ 70 mg/dL	External	Validation: c-statistic = 0.642, Se = 77.0%, Sp = 28.0%
Hu et al. (84)	257, T2D	Demographics, Lab data, COM, comorbidities	Hospital stay	LR	Hypoglycemia ≤ 70 mg/dL	Bootstrapping	AUC = 0.664
Ruan et al. (36)	17,658, DM	Demographics, medications, vital signs, Lab data, hospitalization procedure, previous HYPO events	Hospital stay	XGBoost	Hypoglycemia < 72 mg/dL, 54 mg/dL	10-fold cross validation	$AUC_{72/54}$ = 0.96/0.96, $Se_{72/54}$ = 70.0%/67.0%, $PPV_{72/54}$ = 88%/ 97%
Elbaz et al. (98)	9,665, DM	Demographics, smoking, use of alcohol, comorbidities, Lab data, GLA, other medication	First week of admission	LR	Hypoglycemia ≤ 70 mg/dL	Internal, external	Validation set 1/2: AUC = 0.72/0.71
Kyi et al. (101)	594, T2D	Demographics, GLA, hospital treatment factors, Lab data, comorbidities, observed-days	Hospital stay	LR	At least 2 days with capillary glucose < 72 mg/dL	Internal	AUC = 0.806, Se = 84.0%, Sp = 66.0%, PPV = 53.0%
Mathioudakis et al. (35)	35,147, DM	Demographics, diagnoses, hospitalization procedures, Lab data, medications, BG readings, insulin	24 h after each glucose measurement	SGB	Hypoglycemia ≤ 70 mg/dL	Internal, external	Internal validation: c-statistic = 0.90; external validation: c-statistic: 0.86–0.88
Han et al. (107)	1,410, T2D	SMBG, demographics, medications, glycemic variability, Lab data	Perioperative period	LR	Hypoglycemia < 70 mg/dL	Bootstrapping	AUC = 0.715
Witte et al. (108)	38,250, DM	Demographics, medications, Lab data	7 h	XGBoost	Hypoglycemia < 70 mg/dL	5-fold cross validation	Se = 59.0%. Sp = 98.8%, PPV = 71.8%
Yang et al. (109)	29,843, T2D	Demographics, medications, Lab data	Hospital stay	XGBoost	Hypoglycemia < 70 mg/dL	10-fold cross validation	AUC = 0.822, Acc = 0.93
Wright et al. (111)	6,279, DM	Demographics, Lab data, comorbidities, glucose results, medications, hospitalization orders	24 h	LR	Hypoglycemia <70 mg/dL within 24 h after insulin use	10-fold cross validation	AUC = 0.81, Se = 44.0%;

T1D, type 1 diabetes; T2D, type 2 diabetes; DM, diabetes; Lab, laboratory; GLA, glucose-lowering agents; SMBG, self-monitoring of blood glucose; INS, insulin; HYPO, hypoglycemia; CKD, chronic kidney disease; COM, diabetic complications.

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TABLE 10 Machine learning approaches for other hypoglycemia prediction and best results performed.

References	Participants, type	Inputs	PH	Algorithm	Threshold	Validation	Performance
Postprandial hypoglycemia							
Oviedo et al. (115)	10, T1D	CGM, INS, CHO, blood glucose level at mealtime	6 h	NB, AdaBoost, SVM, ANN	< 70 mg/dL, < 54 mg/dL	5-fold cross validation	< 70 mg/dL: Se = 49.0%, Sp = 74.0%; < 54 mg/dL: Se = 51.0%, Sp = 74.0%
Oviedo et al. (66)	10, T1D	CGM, INS, CHO	6 h	SVC	< 70 mg/dL, < 54 mg/dL	5-fold cross validation	< 70 mg/dL: Se = 71.0%, Sp = 79.0%; < 54 mg/dL: Se = 77.0%, Sp = 81.0%
Seo et al. (81)	104, T1D + T2D	CGM	30 min	RF	≤ 70 mg/dL	5-fold cross validation	Se = 89.6%, Sp = 91.3%
Exercise-related hypoglycemia							
Reddy et al. (86)	43, T1D	Demographics, PA, glucose, hormone features	During exercise	DT, RF	< 70 mg/dL	10-fold cross validation	Acc = 86.67%, Se = 86.21%, Sp = 86.89%
Tyler et al. (109)	20, T1D	CGM/SMBG data, CGM indices, INS, CHO, HR, MET, age, height, weight	During aerobic exercise (4 h)	LR	<70 mg/dL	Hold-out, 20-fold cross validation	Population model: Se/Sp = 73/76%, Acc = 75% (Hold-out set); Personalized model: Se/Sp = 73/90%, Acc = 84% (Hold-out set)

T1D, type 1 diabetes; T2D, type 2 diabetes; CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; INS, insulin; CHO, carbohydrate intake; PA, physical activity; HR, heart rate; MET, metabolic expenditure; NB, naïve Bayes.

the contribution of features (meal, insulin, and exercise) other than CGM glucose data was lower but not insignificant. In contrast to real-time hypoglycemia prediction models, which primarily relied on CGM blood glucose readings, MH/SH and inpatient hypoglycemia predictions were primarily based on the occurrence of hypoglycemic events collected from clinical datasets, and the included parameters were mostly demographics, insulin use, HbA1c or fasting blood glucose levels and previous hypoglycemic events. For such models, the most useful characteristics were those that were clinically closely related to the occurrence of hypoglycemia such as age, insulin, BMI, renal function, previous hypoglycemic events, and comorbidities.

The most effective algorithm in this area is still up for debate, despite the fact that many ML techniques have been widely used for hypoglycemia prediction over the past 10 years. As was already mentioned, the study population, PH, outcome definitions, modeling techniques, and model validation strategies all affect the model performance. Accordingly, it is essential to make sure that all conditions are comparable in order to accurately determine which algorithm outperforms for forecasting a particular hypoglycemic event. The study population of almost every study, according to the literature we reviewed for this study, is unique. Additionally, the inputs used for model development vary from study to study, which makes the horizontal comparison even more challenging. Although comparing sample size and use of external validation under the same PH and outcome under a specific hypoglycemia prediction scenario can yield a relatively well-behaved algorithm, this comparison is partially empirical and lacks direct comparisons of the performance metrics. In light of the present findings of this review, it is challenging to directly compare algorithms.

With the availability of large amounts of clinical data and growing awareness of big data analysis tools, more and more accurate hypoglycemia prediction models can be developed and tested. Future research should concentrate on the discovery of novel algorithms or models to develop more medical devices or decision support systems to prevent various types of hypoglycemic events and other adverse outcomes. Clinical trials will be required before application to assess the economic efficacy and long-term benefits to patients with diabetes.

5. Future directions

The generation of automated and continuous personal data has become possible with the proliferation of commercially available CGM, wearable, and other glucose collection devices for self-monitoring, opening up opportunities for better training ML models with more detailed data. Although integrating CGM with clinical data may improve model performance, widespread implementation of CGM devices in patients with diabetes remains an unsolved problem due to financial and human factor considerations (staff training, time, resources, and other physiological measurement tools that most patients do not have). Furthermore, despite increased research on ML-based prediction models for hypoglycemia over the last decade, achieving a generic model with accurate predictive efficacy under real-world conditions remains difficult due to the complexity of blood glucose dynamics. From the literature reviewed in this paper, most of the study samples came from retrospective datasets and were internally validated only. Thus, there are still great uncertainties in the model's accuracy and generalizability. Although advanced ML methods have been used to address these issues, the majority have yet to be invoked and tested in real-world situations. Future prospective external validation studies are urgently needed to confirm whether these models improve glycemic outcomes.

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

ZZ and LY conceived and designed the analysis. LZ collected the data, performed the analysis, and wrote the paper. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1044059/full#supplementary-material

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Big data in corneal diseases and cataract: Current applications and future directions

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The accelerated growth in electronic health records (EHR), Internet-of-Things, mHealth, telemedicine, and artificial intelligence (AI) in the recent years have significantly fuelled the interest and development in big data research. Big data refer to complex datasets that are characterized by the attributes of "5 Vs"—variety, volume, velocity, veracity, and value. Big data analytics research has so far benefitted many fields of medicine, including ophthalmology. The availability of these big data not only allow for comprehensive and timely examinations of the epidemiology, trends, characteristics, outcomes, and prognostic factors of many diseases, but also enable the development of highly accurate AI algorithms in diagnosing a wide range of medical diseases as well as discovering new patterns or associations of diseases that are previously unknown to clinicians and researchers. Within the field of ophthalmology, there is a rapidly expanding pool of large clinical registries, epidemiological studies, omics studies, and biobanks through which big data can be accessed. National corneal transplant registries, genome-wide association studies, national cataract databases, and large ophthalmology-related EHR-based registries (e.g., AAO IRIS Registry) are some of the key resources. In this review, we aim to provide a succinct overview of the availability and clinical applicability of big data in ophthalmology, particularly from the perspective of corneal diseases and cataract, the synergistic potential of big data, AI technologies, internet of things, mHealth, and wearable smart devices, and the potential barriers for realizing the clinical and research potential of big data in this field.

KEYWORDS
big data, cornea, cataract, clinical registry, artificial intelligence, electronic health record (EHR), mHealth, ophthalmology (MeSH)

1. Introduction

The concept of big data was first introduced in 1990s to capture dataset that are too complex to be stored and analyzed using traditional computer software (Mallappallil et al., 2020). It was previously defined as data that display the characteristics of "3 Vs"—volume, velocity and variety (Mooney et al., 2015). Additional attributes such as veracity and value have also been suggested to fully capture the true nature and values of big data (known as the "5 Vs").[1]

1 https://www.ibm.com/blogs/watson-health/the-5-vs-of-big-data/

In the recent years, the accelerated growth in electronic health records (EHR), disease registries, biobanks, mHealth, Internet-of-Things (IoT), telemedicine, and artificial intelligence (AI) have helped unlock the multi-faceted potential of big data (Chiang et al., 2018; Li et al., 2021; Sahu et al., 2021). Compared to traditional dataset, the wealth of information provided by big data (which are often derived from large-scale or nationwide studies) can facilitate comprehensive and timely examination of the epidemiology, trends, characteristics, outcomes, and prognostic factors of the diseases (Roski et al., 2014; Mallappallil et al., 2020). In addition, the findings help to guide public health policies in terms of risk factors modulation, disease prevention and control, optimization of healthcare service provision, and allocation of research funding targeting more prevalent diseases (Roski et al., 2014).

The multi-dimensional values of big data have been increasingly capitalized in many branches of medicine, including ophthalmology (Cheng et al., 2020; Li et al., 2021). One of the best examples relates to the recent use of big data in understanding the trends and spread of COVID-19, risk factors, treatment outcomes, and morbidity/mortality, which helped inform the clinical practice and public health policies (Haleem et al., 2020; Ting et al., 2020c; Villanustre et al., 2021). Furthermore, big data have enabled the development of highly accurate AI algorithms (which are often data-hungry) in diagnosing a wide range of medical diseases as well as discovering new patterns or associations of diseases that are previously unknown to us (Figure 1) (Ting D. S. W. et al., 2017; Milea et al., 2020; Mehta et al., 2021; Rim et al., 2021; Ting et al., 2021b).

Within the field of ophthalmology, there is a rapidly expanding pool of large clinical registries, epidemiological studies, omics studies, and biobanks through which big data can be accessed (Chua et al., 2019; Tan et al., 2019). In view of the increased availability and accessibility of big data and recent technological advancements, this paper aimed to provide a succinct overview of the availability, clinical applicability and future potentials of big data in ophthalmology, particularly from the perspective of corneal diseases and cataract.

2. Big data in corneal diseases

According to a recent report by the World Health Organization (WHO), corneal opacity represents the 5th leading cause of blindness globally (Flaxman et al., 2017).[2] It is also estimated that $\sim$6 million people suffer from moderate to severe visual impairment secondary to corneal opacity, including non-trachomatous and trachomatous-related cases (see text footnote 2). More importantly, corneal blindness has been shown to be significantly more prevalent in low- and middle-income countries (LMICs), mainly due to limited healthcare resources, higher rate of ocular trauma, poor environmental and personal hygiene, malnutrition, and lower educational level, amongst others (Flaxman et al., 2017; Porth et al., 2019; Ting et al., 2021e). Given the enormity of corneal blindness globally and the significant mismatch between the disease burden and the availability of healthcare resources and workforce, strategic measures are urgently needed.

Within the field of cornea, there is an increasing pool of large corneal registries and epidemiological studies that contains rich resources of big data. These include corneal transplant registries, infectious keratitis studies, genomic studies, large ophthalmology-related registries, EMR-based platforms, and biobanks (Keenan et al., 2012; Chiang et al., 2018; Donthineni et al., 2019). These cornea-related big data enable a better grasp of the prevalence, risk factors, outcomes, and impact of various corneal diseases, which in turn allow for more effective formulations of various therapeutic and preventative strategies in tackling the diseases. In this section, we summarize the main cornea-related big data in various countries and their impact on clinical practice, research and public policies.

2.1. Corneal transplant registries

Corneal transplantation or keratoplasty is the most common type of transplantation performed worldwide (Tan et al., 2012). Currently it remains the main method for restoring corneal clarity and vision in patients with visually debilitating corneal diseases (Tan et al., 2012). However, the persistent shortage of donor corneas has posed significant barriers to successful corneal transplantations (Gain et al., 2016). This has also led to the implementation of various innovative measures, with an aim to improve the eye donation rate (Rithalia et al., 2009; Ting et al., 2016a), utilization of donor corneas (Ting et al., 2016b; Gupta et al., 2018), and reduction of the need for donor corneas (Kinoshita et al., 2018; Ting et al., 2022). In order to tackle this persistent barrier, a wide range of national corneal graft registries and eye banks have been established across the world, including the US, the UK, Europe, India, Australia, and Singapore, amongst others (Table 1) (Tan et al., 2015, 2019; Sharma et al., 2019; Dunker et al., 2021).[3]

The purposes of these national registries and eye banks are manifold. Firstly, it helps standardize the corneal donation-to-transplantation pathway nationally and identify any potential limiting factors, enabling more effective interventions to improve the conversion rate of eye donation and the utilization rate of the donated corneas (Gogia et al., 2015; Ting et al., 2016b; Sharma et al., 2019). Secondly, the prospective database can facilitate examination of the ongoing availability of donor corneas to allow for equal and fair distribution of the donor corneas across the country (Ting et al., 2016b; Gupta et al., 2018) (see text footnote 3).[4] It also helps inform the policymakers and relevant stakeholders on the need for importation (or exportation) depending on the local supply of donor corneas. Thirdly, they provide up-to-date examination of the trends in the types and indications of keratoplasty (Keenan et al., 2012; Park et al., 2015). For instance, various studies have demonstrated a paradigm shift from penetrating keratoplasty (PK) to lamellar keratoplasty [including anterior lamellar keratoplasty (ALK) and endothelial keratoplasty (EK)] over the past decade in many countries. A recent European Cornea and Cell Transplantation Registry study of 10 centers from the Europe, the UK and Switzerland (n = 12913 keratoplasty) demonstrated that Descemet stripping automated endothelial keratoplasty (DSAEK) was the most commonly performed technique (46%), followed by PK (30%) and Descemet membrane endothelial keratoplasty (9%) (Dunker et al., 2021). In addition, the study demonstrated that Fuchs

2 https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment

3 https://restoresight.org/

4 https://www.odt.nhs.uk/statistics-and-reports/

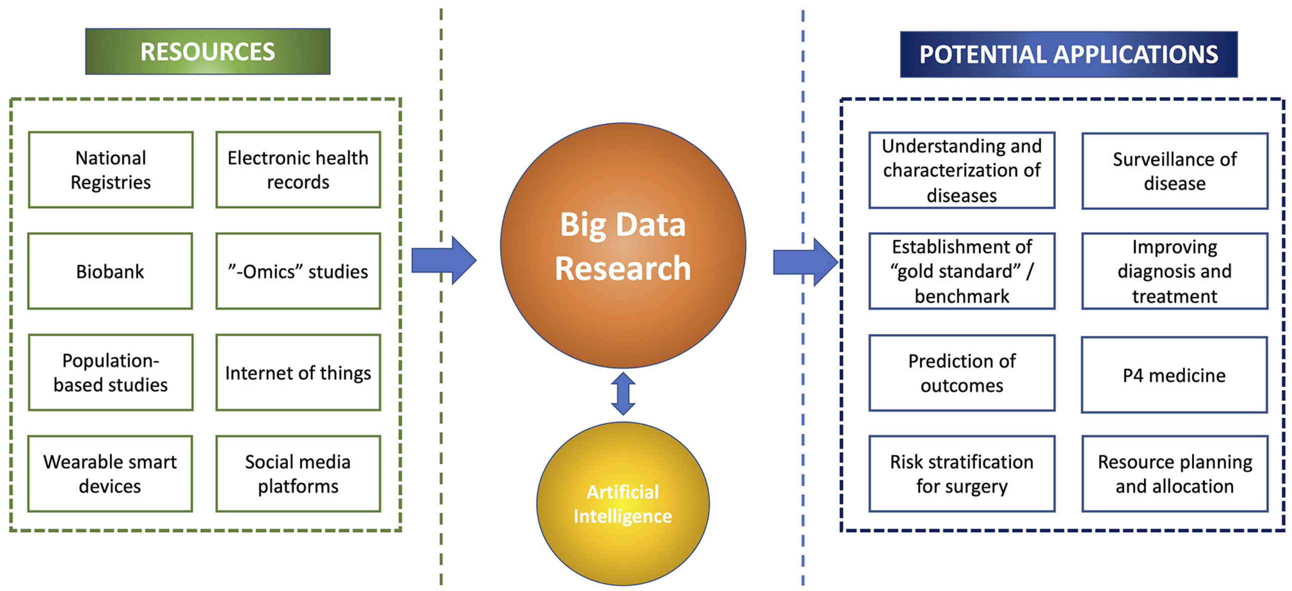

FIGURE 1
An overview of the big data research, including the resources, potential synergism with artificial intelligence, and clinical applications.

endothelial corneal dystrophy (FECD), regraft, pseudophakic bullous keratopathy (PBK), and keratoconus were the main indications for keratoplasty. These common indications were consistently reported in many other national studies conducted in other countries (Keenan et al., 2012; Ting et al., 2012; Park et al., 2015; Tan et al., 2015; Ang et al., 2016c; Fuest et al., 2017). Understanding of the common indications for keratoplasty provides the clinicians and researchers with a clearer picture of how the limited resources (i.e., donor corneas) are being utilized. In addition, more targeted research effort can be channeled toward these higher prevalent corneal diseases to search for alternative therapeutic strategies and reduce the need for donor corneas.

Furthermore, useful information can be obtained from these national corneal transplant registries to understand the risk factors and prognostic factors of keratoplasty, ultimately improving the clinical outcomes (Ang et al., 2011, 2012a, 2016a; Bose et al., 2013). Ang et al. (2016b) observed that patients with FECD and bullous keratopathy achieved a better long-term graft survival following Descemet membrane endothelial keratoplasty (DMEK) when compared to Descemet stripping automated endothelial keratoplasty (DSAEK) and PK. On the other hand, an Australian national study of >15,000 cases of keratoplasty demonstrated that the survival of lamellar keratoplasty (i.e., DALK and EK) fared worse than PK, with some evidence showing the influence of learning curve on the outcome of EK (Coster et al., 2014). Important prognostic factors for graft survival rate, including the indication for graft, number of previous grafts, history of ocular surface inflammation or glaucoma, corneal neovascularization, and postoperative events such as graft rejection or infection, were also identified *via* these national corneal transplantation studies (Williams et al., 2008; Ang et al., 2012b, 2014, 2020; Sibley et al., 2020). Indications such as PBK and infectious keratitis (IK) have been shown to be associated with a worse outcome compared to "low-risk" conditions such as keratoconus and FECD following keratoplasty (Tan et al., 2012), highlighting the need for improvement in the treatment strategy for certain indications (Ang and Sng, 2018).

More importantly, the registries enable examination and monitoring for any significant postoperative adverse events such as infection and endophthalmitis (Chen et al., 2015; Gauthier et al., 2017; Song et al., 2021). Edelstein et al. (2016) previously conducted a study of 354,390 keratoplasty based on the data from the Eye Bank Association of America, analyzing all adverse events following all types of keratoplasty. They observed a higher rate of fungal infection in their study compared to non-US studies and postulated that this might be due to the lack of antifungal agent used in the corneal storage medium in the US (Chen et al., 2015; Edelstein et al., 2016). It was also found that fungal keratitis and endophthalmitis were more common following EK (1.5–3 times higher risk) than PK and ALK, potentially attributed to the increased warming time associated with the preparation of EK tissues in the eye bank (Edelstein et al., 2016). These findings will allow for the refinement of the eye bank protocol in terms of processing and storage of donor corneas, ultimately leading to improved clinical outcome and safety.

2.2. Infectious keratitis databases

Corneal opacity is the 5th leading cause of blindness globally, with IK being the main culprit. IK was previously recognized as a "silent epidemic", and recently, a "neglected tropical disease" status was proposed (Ung et al., 2019). The incidence is estimated to range between 2.5–799 per 100,000 population per year (Ting et al., 2021e). It can be caused by a wide range of organisms, including bacteria, fungi, viruses, and parasites, and polymicrobial infection (Ting et al., 2019b, 2021d; Khoo et al., 2020). In view of its significant impact on human health, healthcare systems and economy, it is therefore not surprising to observe a vast amount of literature on IK, encompassing the epidemiology, risk factors, clinical characteristics,

TABLE 1 Summary of main corneal transplant registries and institutions in the world, categorized by continents.

Countries	Corneal transplant registries (and institutions)
Multi-continent	
Global	Global Alliance of Eye Bank Associations (GAEBA) Pan American Association of Eye Banks
Asia	
China	Beijing Tongren Eye Center Shandong Eye Institute
Hong Kong	Lions Eye Bank of Hong Kong
Japan	Cornea Centre and Eye Bank, Tokyo Dental College Kyoto Prefectural University of Medicine
India	Eye Bank Association of India (EBAI)
Malaysia	National Transplant Registry of Malaysia
Philippines	Santa Lucia International Eye Bank of Manila
Russia	S. N. Fyodorov Eye Microsurgery State Institution
Saudi Arabia	King Khaled Eye Specialist Hospital
Singapore	Singapore Corneal Transplant Study, Singapore Eye Bank
South Korea	Korean Network for Organ Sharing (KONOS) Seoul St. Mary's Eye Hospital
Taiwan	National Taiwan University Hospital
North and South America	
Brazil	Brazilian Association of Organ Transplantation (ABTO)
US	Eye Bank Association of America (EBAA)
UK and Europe	
Europe	European Cornea and Cell Transplantation Registry
France	Centre Francois Xavier Michelet, CHU de Bordeaux, Site Pellegrin
Germany	German Ophthalmological Society (GOS)
Italy	Societa Italian Traplanto Di Cornea (S.I.TRA.C) Veneto Eye Bank Foundation
Netherland	Netherlands Institute for Innovative Ocular Surgery
Sweden	Swedish Registry for Corneal Transplant
UK	UK National Health Service (NHS) Blood and Transplant
Australasia	
Australia	Australian Cornea Graft Registry (ACGR)
New Zealand	New Zealand National Eye Centre
Africa	
Ethopia	Addis Ababa University
South Africa	Pretoria Eye Institute

Adapted from the thesis published by Tan et al. (2015).

causative organisms, management, and outcomes of the disease. Large IK studies published in the recent years are summarized in Table 2 (Lin et al., 2017, 2019; Tan et al., 2017; Khor et al., 2018; Peng et al., 2018; Green et al., 2019; Tavassoli et al., 2019; Asbell et al., 2020; Khoo et al., 2020; Kowalski et al., 2020; Somerville et al., 2021; Ting et al., 2021d).

The clinical and laboratory data captured by these large-scale IK studies enables a better grasp of the microbiological profiles, risk factors, disease impact, and treatment response. So far, from the epidemiological standpoint, these studies have helped unveil the considerable geographical, temporal and seasonal variations in IK, which provide useful guidance to the choice of antimicrobial treatment. For example, *Staphylococci* spp. and *Pseudomonas* spp. were shown to be the most common organisms in the UK, the US and Australia (Tan et al., 2017; Tavassoli et al., 2019; Khoo et al., 2020; Kowalski et al., 2020; Ting et al., 2021d). In addition, several studies (Tan et al., 2017; Ting et al., 2018, 2021d) have identified an increasing trend of moraxella keratitis in the UK over the past decade. In contrast, a recent Asia Cornea Society Infectious Keratitis Study (ACSIKS) of more than 6,000 patients showed that fungal and bacterial infections were the main causes of IK in developing and developed countries, respectively (Khor et al., 2018). More importantly. the study observed ∼50% of the eyes developed moderate visual loss (<6/18 vision), with 46% of the performed therapeutic keratoplasty failed by 6 months' follow-up, highlighting the significant impact on the affected patients.

Studies have shown that the initial severity of the ulcer and presenting visual acuity serve as important prognostic factors for IK (Khoo et al., 2020; Ting et al., 2021a,c). Therefore understanding the risk factors *via* big data research allows for effective implantation of various preventative strategies in reducing the incidence of IK. Contact lens (CL) has been consistently identified as one of the most common risk factors for IK (Cariello et al., 2011; Keay et al., 2011; Ting et al., 2021a). In particular, the risk of CL-related IK was shown to be associated with use of expired CL and overnight CL wear (Sauer et al., 2020). Understanding of these underlying factors allow for better education among the patients and CL wearers. Trauma serves as another important risk factor for IK, particularly in the developing countries (Ganguly et al., 2011; Kaliamurthy et al., 2013). In addition, based on a population-based, cross-section sectional study, [Cornea Opacity Rural Epidemiological (CORE) study] (Gupta et al., 2017), it was found that the use of traditional eye medicine and self-medication was prevalent in the rural regions of India, which could lead to delay in seeking appropriate medical care and exacerbation of corneal diseases and/or infection. These epidemiological studies have helped improve the public awareness and call for new regulatory legislations to address these issues.

Broad-spectrum topical antimicrobial therapy serves as the current mainstay of treatment for IK, though their efficacy is being challenged by the emergence of AMR, observed in several large-scale IK studies (Lalitha et al., 2017; Asbell et al., 2020; Ting et al., 2021e). Clinically, AMR-related pathogens has been shown to negatively affect the outcome and healing time of IK (Kaye et al., 2010). In the Antibiotic Resistance Among Ocular Microorganisms (ARMOR) with data from >6,000 ocular isolates, Asbell et al. (2020) observed that ∼40% of the *Staphylococci* spp. were methicillin-resistant, and many of them were multidrug resistant. On the other hand, various studies in the UK demonstrated a low rate of AMR (<5–10%) against the commonly employed antibiotic regimens used for IK, including fluoroquinolone, cephalosporin and aminoglycoside (Tan et al., 2017; Tavassoli et al., 2019; Ting et al., 2021d). These findings emphasize the wide geographical and temporal variations in AMR for IK and the importance of updated examination in specific regions. Better knowledge of the AMR pattern could also help guide the most appropriate initial treatment for IK in each region.

TABLE 2 Summary of large-scale infectious keratitis study (>1,000 cases) in the world published between 2016 and 2021, in chronological order.

Authors (Year)	Study period	Region	No. of scrapes	Culture positivity (%)	Bacteria (%)	Fungi (%)	Acanthamoeba (%)
Somerville et al. (2021)	2014–2020	UK	3,099	47.2	51.4	0.8	0.2
Ting et al. (2021d)	2007–2019	UK	1,333	37.7	92.8	3.0	4.2
Asbell et al. (2020)*	2009–2018	US	6,091	100.0	100.0	–	–
Khoo et al. (2020)	2012–2016	Australia	1,052	48	64	2.3	–
Lin et al. (2019)	2010–2018	China	7,229	42.8	52.7	57.6	–
Tavassoli et al. (2019)	2006–2017	UK	2,614	38.1	91.6	6.9	1.4
Green et al. (2019)*	2005–2015	Australia	3,182	100.0	93.1	6.3	0.5
Kowalski et al. (2020)*#	1993–2018	US	1,387	100.0	72.1	6.7	5.2
Peng et al. (2018)	1996–2015	US	2,203	23.7	100.0	–	–
Khor et al. (2018)	2012–2014	Asia	6,563	43.1	38	32.7	2.26
Tan et al. (2017)	2004–2015	UK	4,229	32.6	90.6	7.1	2.3
Lin et al. (2017)	2009–2013	China	2,973	46.1	41.9	44.6	13.6

*These studies only included culture-proven IK cases.
#This study also included viral keratitis cases.

2.3. Corneal genomic studies

The increase in large-scale genetic studies, particularly genome-wide association study (GWAS) and genome-wide linkage study (GWLS), has significantly advanced our understanding of many diseases, including corneal diseases, and offer potential novel targets for gene therapy (Riazuddin et al., 2009, 2010, 2013; Baratz et al., 2010; Burdon et al., 2011; Bykhovskaya et al., 2012; Czugala et al., 2012; Li et al., 2013; Lu et al., 2013; Sahebjada et al., 2013; Dudakova et al., 2015; Afshari et al., 2017; McComish et al., 2019). GWAS is an invaluable methodology designed to analyze common genetic variations across the whole genome, particularly single nucleotide polymorphisms (SNPs), by analyzing the genotype-phenotype associations of a disease in case-control cohorts with a large number of individuals. On the other hand, GWLS is a useful tool used to genotype a particular disease by examining families with affected and unaffected individuals (Karolak and Gajecka, 2017; Tam et al., 2019).

FECD and keratoconus are by far the two most commonly investigated corneal diseases. The research focus on these two conditions is primarily driven by the high burden and prevalence of the diseases. Moreover, they represent the most common indications for keratoplasty in many countries (Ting et al., 2012; Park et al., 2015), placing significant burden on the donor corneas. Over the years, GWAS has increasingly been used to identify genetic susceptibility regions in FECD and keratoconus (Iliff et al., 2012; Karolak and Gajecka, 2017). For instance, Hardcastle et al. (2021) recently conducted a multi-ethnic GWAS of keratoconus, including >100,000 individuals, and identified 36 significant genomic loci that were associated with keratoconus. McComish et al. (2019) discovered a novel genetic locus in PNPLA2 at chromosome 11 for keratoconus based on over 6 million genetic variants. Several novel genetic loci for FECD, including *TCF4*, *LAMC1* rs3768617, *LINC00970/ATP1B1* rs1200114, and *KANK4* rs79742895, have also been identified (Afshari et al., 2017). GWLS have also facilitated the identification of a number of important genetic mutations linked to keratoconus, including *TGFBI, TCEB1, CAST*, *COL8A1*, and *LOX* genes (Karolak and Gajecka, 2017). Next-generation sequencing, which enables extensive and deep sequencing of the DNA (Londin et al., 2013), has recently been employed to detect novel mutations associated with many other types of corneal dystrophy (Zhang et al., 2019).

In view of the rapid proliferation of the genomic studies, many genetic banks, databases and web-based resources such as https://www.ncbi.nlm.nih.gov/gtr/ and https://www.omim.org/ have been created to capture and summarize the genomic association of a wide array of human diseases, including ocular diseases. The availability of these results not only help reduce unnecessary duplication of any previously conducted research, which often involves extensive time, effort and funding, but also expedite the discovery and development of new therapeutic targets *via* knowledge- and data-sharing.

2.4. Electronic health record-based registries and biobanks

The rapid emergence of EHR in healthcare systems in the recent years has allowed the capture and analysis of big data by the clinicians, researchers and relevant stakeholders (DesRoches et al., 2008; Day et al., 2015; Evans, 2016). One of the most notable examples in the field of ophthalmology is the Intelligent Research in Sight (IRIS). Registry, which is a US-based ophthalmic EHR registry established by the American Academy of Ophthalmology (Parke Ii et al., 2017; Chiang et al., 2018). In 2016, the IRIS Registry had already captured data from >17 million eye patients, including over a million of patients with dry eye disease (DED), and >35 million ophthalmic visits from 7,200 US-based ophthalmologists, providing valuable information on prevalence, demographic factors, risk factors, management and outcome of a wide range of ocular diseases (Chiang et al., 2018). So far, the IRIS Registry has enabled research in many fields of ophthalmology, including cornea (Anchouche et al., 2021), cataract (Pershing et al., 2020; Owen et al., 2021; Lacy et al., 2022), glaucoma (Chang et al., 2021; Olivier et al., 2021), and retina (Malhotra et al., 2021; Khanani et al., 2022). For instance, Anchouche et al. (2021) included >60,000 patients of chemical and thermal ocular injuries in the US (using the IRIS Registry data) and demonstrated a significant increase in the incidence by 20% from 2013 to 2017 in the US. In a similar vein, Donthineni et al. (2019) demonstrated the value of utilizing EHR-derived big data to estimate the incidence of DED in India as well as the predisposing factors such as age, gender, socio-economic status, and profession. Using the same EHR database of >2 million patients, Das and Basu (2022) were able to identify >20,000 patients who presented with epidemic keratoconjunctivitis and characterized the clinical features and outcomes, enabling more accurate and timely diagnosis and treatment.

Furthermore, there are nationwide databases such as the UK Biobank which also contain extensive clinical, imaging and genomic data related to the eye, including the cornea (Chua et al., 2019). UK Biobank is a large-scale biomedical database and research resource, which contains extensive health, genetic and bioimaging information from >500,000 people in the UK, with regularly update on additional follow-up data.[5] Corneal hysteresis serves as an important biomechanical property of cornea, and it has been shown to influence the measurement of intraocular pressure and risk of glaucoma (Deol et al., 2015). Based on the data of >90,000 participants obtained from the UK Biobank, significant associations between corneal hysteresis and various demographic factors such as age, sex, and ethnicity were detected (Zhang et al., 2019). Khawaja et al. (2019) similarly identified five novel loci that are associated with corneal biomechanical properties, including corneal hysteresis and corneal resistance, which may have important implication on the pathogenesis of keratoconus. In addition, GWAS based on the UK Biobank data enabled the discovery of four novel genetic loci, including HERC2, LINC00340, NPLOC4, and ZC3H11B genes, for corneal astigmatism (Shah and Guggenheim, 2018).

3. Big data in cataract

Cataract is the leading cause of blindness and visual impairment globally, affecting around 94 million of the world population, particularly in the low- and middle-income countries (LMICs) (see text footnote 2) (Flaxman et al., 2017). Currently, ∼20 million cases of cataract surgery are being performed each year (Wang et al., 2016), making it the most commonly performed surgery worldwide. In view of the continuous advancement in the phacoemulsification technology, surgical techniques, biometry calculation for IOL power, and IOL technology, the demand for perfect vision and no/minimal risk of surgical complication continues to rise (Erie, 2014; Ting D. S. J. et al., 2017; Sudhir et al., 2019; Day et al., 2020; Ting et al., 2020a). Furthermore, as cataract surgery is the most commonly performed ophthalmic surgery, it often used as the benchmark for assessing an ophthalmologist's surgical competence, especially during the specialist training or residency program.

To date, many national cataract databases have been established across the world (Table 3). One of the primary aims of these databases is to examine and audit the outcomes of the cataract surgery performed by the surgeons. Secondly, it also helps provide a benchmark for the visual outcome and safety of the surgery for all the cataract surgeons, with adjustment of the experience and complexity of the case-mix. In addition, these big data may also identify important factors that can predict the risk of intraoperative and postoperative complications, including posterior capsular rupture (PCR), retinal detachment, cystoid macular edema (CMO), endophthalmitis, and many others.

One of the most well-known examples is the Swedish National Cataract Register, which is the oldest nationwide cataract registry established in 1992 (Lundström et al., 2002). So far, it has produced >60 publications in the literature, covering many aspects of cataract surgery such as visual and refractive outcomes, posterior capsular rupture, endophthalmitis, postoperative practice pattern, and development of a composite risk-stratification scoring system, amongst others (Farhoudi et al., 2018; Zetterberg et al., 2021; Friling et al., 2022; Ridderskär et al., 2022). The European Registry of Quality Outcome for Cataract and Refractive Surgery (EUREQUO), which is supported by the ESCRS, represents another large-scale database that has so far captured more than 3 million cases of cataract surgery in Europe.[6] This database provides pertinent surgical outcomes as well as the patient-reported outcomes following cataract and refractive surgeries, allowing the operating surgeons to audit their results and implement changes to their surgery (if required) to further improve the clinical outcomes. In addition, the big data obtained from this database (which included >2 million cases) has enabled effective analysis of risk factors for PCR and dropped nucleus during cataract surgery (Lundström et al., 2020; Segers et al., 2022).

TABLE 3 Summary of main cataract registries in the world, categorized by continents.

Countries	Cataract registries (and institutions)
Asia	
China	Shanghai Cataract Operations Database
India	Aravind Eye Hospitals Registry
Israel	Israel Cataract Registry
Malaysia	Malaysia Cataract Surgery Registry
North and South America	
US	Intelligent Research in Sight (IRIS) Registry (supported by the American Academy of Ophthalmology) Medicare Database Paediatric Eye Disease Investigator Group (PEDIG) database Toddler Aphakia and Pseudophakia Treatment Study Registry
UK and Europe	
Denmark	Paediatric Cataract Register (PECARE)
Europe	EUREQUO (supported by the European Society of Cataract & Refractive Surgeons; ESCRS)
Germany	Germany Cataract Registry
Sweden	Swedish National Cataract Register
UK	National Ophthalmology Database (NOD) [supported by the Royal College of Ophthalmologists (RCOPhth)]

5 https://www.ukbiobank.ac.uk/

6 https://www.escrs.org/about-escrs/registries/eurequo/

In the UK, the Royal College of Ophthalmologists (RCOphth), UK, established the DHR-based National Ophthalmology Databases (NOD) in 2009, with an aim to monitor and improve the outcomes in cataract surgery and various ophthalmic conditions, including diabetic eye disease, age-related macular degeneration, glaucoma, and retinal detachment.[7] In 2020, the NOD published the annual report on cataract surgery, which included >200,000 cataract surgery performed by >2,000 surgeons (web). The report highlighted that 86% of the eyes achieved at least 1 Snellen-line improvement in vision postoperatively. The overall PCR rate was 1.1%, with a higher rate (2.4%) in less experienced trainee surgeons and lower rate (0.9%) in consultant surgeons. Within the UK, all ophthalmic surgeons, including consultants and trainees, are required to record the number of cataract surgery performed and the rate of complications (particularly the rate of PCR), The findings from the NOD not only set important benchmarks for all the UK cataract surgeons but also help identify surgeons and trainees who require additional support and training on cataract surgery, particularly if the PCR rate is considerably higher than the national benchmark. These data have also been utilized to stratify the risk of PCR and vitreous loss, enabling the development of effective risk-stratification system to optimize patient selection and safety (Narendran et al., 2009; Day et al., 2015).

As mentioned above, IRIS Registry has showcased its clinical and research values in many fields of ophthalmology. Within the context of cataract surgery, Pershing et al. (2020) demonstrated a 0.04% rate of postoperative endophthalmitis among >8 million cases of cataract surgery and identified important predictive factors such as younger age, need for anterior vitrectomy, and when cataract surgery is combined with other ophthalmic surgeries. In addition, researchers were also able to utilize the IRIS Registry in analyzing and comparing the refractive outcomes and risk of endophthalmitis between immediate sequential and delayed sequential bilateral cataract surgery, which helps inform the clinical practice (Owen et al., 2021; Lacy et al., 2022).

In addition, the recent COVID-19 pandemic has caused an unprecedented surge in the service backlog and number of cases on the waiting list, particularly for cataract surgery (Ting et al., 2020b). With the availability of big data obtained from the EHR, it enables a comprehensive and systematic analysis of the utilization of the clinical and theater space, workflow efficiency (e.g., turnaround time between each cataract surgery), and supply-and-demand matching in terms of available workforce/resources and service backlog, which are useful for strategic planning and allocation of the resources within healthcare services. Big data from large-scale population-based studies also provide invaluable information on the service coverage and health equity (or inequity). For instance, effective cataract surgical coverage (eCSC) is often used as a measure to evaluate the service access to cataract surgery and the outcome of the surgery. A recent population-based study, based on 148 Rapid Assessment of Avoidable Blindness (RAAB) survey data from 55 countries involving ∼500,000 adults aged 50 years and older, reported that eCSC varied considerably between countries, with higher rate in countries with greater income level, highlighting the need for increased efforts to improve access and quality of the surgery in under-resourced countries (McCormick et al., 2022).

7 https://www.nodaudit.org.uk/resources/publications-annual-report

4. Future directions

4.1. Integration of big data and artificial intelligence

The relationship between big data and AI-assisted technologies is highly synergistic and inextricably linked. The enormity and nature of big data usually require advanced computing power, software and algorithms (e.g., machine learning and deep learning-based AI algorithms) to process and analyze the data. On the other hand, development of highly accurate and generalizable AI algorithms often requires the input of big data that satisfy the attributed of "5 Vs". With the rapid development of big data research and digital technologies in the recent years, it is anticipated that AI-power big data analytic platforms, coupled with telemedicine, will shape the future landscape of medicine (Sim et al., 2016; Ting et al., 2019a; Wu et al., 2019). The need for these innovative digital technologies in clinical practice was further heightened by the recent COVID-19 pandemic where all branches of healthcare services, including ophthalmology, have been severely impacted (Babu et al., 2020; Ting et al., 2020b,c, 2021f; Whitelaw et al., 2020; Ho et al., 2021; Kim et al., 2021).

So far, big data-driven AI technologies have demonstrated its clinical potential in many areas of corneal diseases and cataract. These encompass screening and diagnosing a wide array of conditions (e.g., keratoconus, IK, corneal opacity) and cataract, and preoperative planning for refractive surgery, to making automated clinical decisions for various diseases (Rampat et al., 2021). Studies have shown that the diagnostic accuracy of several AI algorithms can be as high as 92–97% in detecting keratoconus and preclinical keratoconus or forme fruste keratoconus (Arbelaez et al., 2012; Smadja et al., 2013; Hidalgo et al., 2016; Issarti et al., 2019; Lavric and Valentin, 2019; Ting et al., 2021b). Automated assessment of the corneal endothelial cell density in normal and diseased eyes as well as corneal guttata, based on AI-assisted algorithms using specular microscopy images and/or retroillumination slit-lamp photographs, have been developed to improve the management and follow-up in patients with corneal endothelial diseases and post-endothelial keratoplasty (Joseph et al., 2020; Vigueras-Guillén et al., 2020; Shilpashree et al., 2021; Soh et al., 2021; Karmakar et al., 2022). A recent study also reported the potential of machine learning algorithms in predicting the 10-year graft survival of PK and DSAEK using random survival forests analysis with highest variable importance factors (Ang et al., 2022). Understanding of the predictive factors allows the clinicians to address any modifiable preoperative factors, select the most appropriate type of keratoplasty for each individual patient, and optimize the long-term graft survival. This will also help reduce the need for regrafting, which has been shown as one of the most common indications for keratoplasty (Ting et al., 2012; Aboshiha et al., 2018).

In addition, several studies have demonstrated the ability of AI algorithms in diagnosing and differentiating the types of IK, and differentiating active IK from healed corneal scar (Liu et al., 2020; Lv et al., 2020; Koyama et al., 2021; Tiwari et al., 2022). These technologies are particularly useful in regions where resources and expertise are lacking. More recently, Li et al. (2020) reported the superior performance of a DL-based AI algorithm in diagnosing a wide range of corneal and conjunctival diseases, including IK, pterygium and conjunctivitis, and cataract based on using slit-lamp photographs. More importantly, the algorithm was able to provide automated clinical recommendation for further management, including clinical observation, medical treatment and surgical interventions. This can greatly reduce the diagnostic and referral time and improve the workflow efficiency within the healthcare system. For acute ocular conditions such as IK, timely diagnosis is crucial in achieving a good outcome; hence an effective AI-powered platform may serve as a novel diagnostic solution, particularly in LMICs.

Automated detection and grading of cataract as well as diagnosis of posterior capsular opacification by AI algorithms have also been described (Xu et al., 2020; Gutierrez et al., 2022). Furthermore, newer generations of IOL calculation formulae, based on big data-powered AI algorithms, have also been developed to enhance the predict accuracy of the IOL power (Ladas et al., 2021; Gutierrez et al., 2022). By using a dataset of ∼5,000 patients, Li T. et al. (2022) recently demonstrated the ability of AI in enhancing the prediction of effective lens position and improving the accuracy of existing IOL formulas, including Haigis, Hoffer Q, Holladay, and SRK/T. Therefore, it is anticipated that the millions of data housed within several national cataract registries can be utilized to train and develop effect AI-based IOL calculation formulae and optimize the visual and refractive outcomes of cataract surgery in the near future.

4.2. Empowerment of big data research by internet of things, mHeath, and wearable devices

The potential of big data research has further been fueled by the recent rapid expansion and development in Internet of Things (IoT) technologies, mobile health (mHealth; a branch of medical and public health practice powered by mobile devices), and wearable devices (Kelly et al., 2020). So far, it has been estimated that more than 2 billion people own a mobile phone globally, with >50 million people utilizing app-based, interactive health self-care and self-triage (Millenson et al., 2018). The scopes and applications of mHealth range considerably from delivering health education, digital therapy, supporting clinical decision making for diagnosis and treatment, to improving clinical outcomes *via* behavioral modification (Rowland et al., 2020). Within the field of cornea, Inomata et al. (2020b) utilized crowdsourced big data, obtained from a mobile app (DryEyeRhythm) of around 3,000 participants, to identify participants with diagnosed and undiagnosed symptomatic DED and determine their associated risk factors. In addition, it was found that depressive symptoms are more common in individuals with DED, enabling an earlier detection and intervention for depression in this cohort of individuals (Inomata et al., 2020a).

Recent advances in wearable devices have also enabled real-time collection of millions of health datapoints (e.g., heart rate, blood pulse, step count, daily activity, etc.) for non-invasive diagnosis and monitoring of various diseases, including cardiovascular diseases, pulmonary diseases, hypertension, and diabetes, amongst others (Guk et al., 2019; Lu et al., 2020). Studies have shown that smart contact lenses (CLs) with biosensing technology are able to detect tear content and metabolites, including glucose and exosomes, which enable real-time non-invasive detection and monitoring of diabetes and cancer (Park et al., 2018; Li S. et al., 2022). The big data obtained from these biosensing technologies may be useful for CL wearers in the future where these smart CLs may help detect any early changes in the tear metabolites and inflammatory cytokines, which may help predict the risk of development of CL-induced DED, inflammatory and infectious keratitis.

In addition, Chen et al. (2021) recently developed a blink-sensing glasses to detect the blinking pattern between DED subjects and health controls. It has been recognized in the recent years that increased digital screen use (either for occupational, recreational or educational purpose) is a significant predisposing risk factor for DED (Mehra and Galor, 2020). Several mechanisms have been proposed, including reduced/abnormal blinking (which can lead to increased tear evaporation and ocular surface inflammation) and damage from the emitting light from the digital screen devices. Therefore, the big data generated from these blink-sensing glasses have the potential of monitoring the blinking patterns and behaviors of the digital screen users (or individuals with DED), which allows for an effective modification of the lifestyle and improves the management of DED.

4.3. Role of big data in predictive, preventive, personalized, and precision (P4) medicine

With the exponential increase in the availability of multi-omics data, large-scale population-based studies, EHR, and digital technologies, it is becoming possible to harness the power of these big data for implementing predictive, preventive, personalized, and participatory (P4) medicine. Instead of treating the patients reactively based on the presenting symptoms and signs, P4 medicine advocates personalizing the care to each individual at an individual molecular, cellular and organ levels, making the treatment more effective and cost-effective (Flores et al., 2013). Furthermore, the combination of real-time health data collected from these wearable smart devices with clinical and "multi-omics" data can potentially improve the understanding and management of certain multifactorial diseases (for instance, DED) where lifestyle and environmental factors play a vital role in the pathogenesis and phenotypic features of the disease (Inomata et al., 2020c).

Recently, Inomata et al. (2021) highlighted the potential of mHealth by using a data-driven multidimensional smartphone-based digital phenotyping strategy to assess and classify DED, which is a highly heterogeneous and multifactorial disease. A wide range of data, including demographics, medical history, lifestyle questions, blink sensing (*via* smartphone cameras and CIFaceFeature for facial detection), and daily subjective symptoms [using the Japanese version of the Ocular Surface Disease Index (J-OSDI)], were collected through the DryEyeRhythm mobile app. Subsequently, through hierarchical clustering heatmap, the authors were able to visualize and classify DED patients into several categories with distinct DED characteristics, illustrating the potential of P4 medicine in managing DED.

The potential of big data in shaping P4 medicine in ophthalmology is huge. For instance, with the increased availability of big data, it will be possible to personalize the choice of IOL for patients who are undergoing cataract surgery and predict those who are most likely to benefit from a certain type of IOL implant (e.g., multifocal vs. monofocal) in the future. One may also leverage the power of big data (and AI) to predict of the risk of postoperative complications following cataract surgery, which helps distinguish the group of patients who are suitable for community follow-up vs. hospital follow-up, thereby relieving the burden on the over-stretched healthcare services. Furthermore, with the combination of phenotypic and genotypic data as well as lifestyle factors (e.g., tendency for eye rubbing), it may be possible to predict the group of patients with keratoconus who are most likely to progress, thereby enabling early prophylactic intervention such as corneal cross-linking to prevent progression and maintain good vision.

4.4. Potential barriers for enabling big data research and its clinical potential

The potential values of big data, EHR, telehealth and mHealth in healthcare have long been recognized by the WHO, which was published as a report by the Global Observatory for eHealth in 2016 (World Health Organization, 2016). However, several barriers exist for translating their potential to real clinical values (Hulsen et al., 2019; Uslu and Stausberg, 2021). One of the main barriers is cost. Establishment and maintenance of these large-scale platforms, registries and EHR often requires substantial financial resources and workforce, which explains the scarcity of big data in under-resourced LMICs. Depending on the scale of the registries and EHR, they can cost the healthcare service from tens of thousands to multimillion dollars to set up and maintain the platforms within the healthcare services (Menachemi and Collum, 2011). Processing and analysis of big data also necessitates advanced computing power, facilities and expertise in order to arrive at clinically meaningful findings and conclusions. Furthermore, considerable expertise, workforce, resources, and facilities, all of which are associated with a high cost, need to be in place to prevent or reduce the risk of EHR system failure, which can significantly disrupt and paralyze the delivery of the healthcare services and cause harm to patients.

In addition to the cost and workforce, there remains a number of significant challenges associated with big data research, including data completeness, accuracy, heterogeneous data sources/platforms, data security, sharing, and visualization (Househ et al., 2017; Dash et al., 2019). Most large-scale EHR systems are designed for delivery of clinical services but not for evidence generation; therefore, capitalization of the EHR-derived big data for clinical research purposes is considerably challenged by the consistency, accuracy, and completeness of data. In addition, many of the systems are usually created for general medical and surgical services, which leads to inaccurate or incomplete data collection for ophthalmic diseases. For instance, many of the ophthalmic diagnoses/codes are not available in the general EHR systems, inhibiting an accurate assessment and analysis of the incidence, characteristics, causes, and impact of ophthalmic diseases presenting to the health services.

Another potential barrier for big data research is data privacy and sharing. Although there has been an increased availability of big data captured through various sources (Figure 1), processing of these data for research purposes are prohibited, unless: (1) the data are fully anonymized; (2) the data owner (i.e., the patients, healthy volunteers, etc.) provide "explicit consent"; or (3) the processing of data are necessary for provision of healthcare services or for public interest (Hulsen et al., 2019). In 2018, the European Union introduced a new set of regulations—the General Data Protection Regulation (GDPR)—to safeguard data privacy.[8] It also places constraints on data sharing where appropriate consent needs to be obtained from the patient before the data can be shared with another organization. In addition, data sharing and management is further guided by the FAIR principles, which include "Findability," "Accessibility," "Interoperability," and "Reusability" (Wilkinson et al., 2016). Therefore, to realize the potential of big data research in ophthalmology, all these highlighted barriers will need to be fully considered and addressed.

5. Conclusions

The continuous growth of IoT technologies, increased acceptability of mHealth, accessibility and affordability of mobile and wearable smart devices, and advancement in AI technologies in the coming years are likely to further expand the potential and applications of big data research in medicine and surgery, including ophthalmology (Wang et al., 2020; Rono et al., 2021; Dow et al., 2022). The establishment of big data resources such as corneal transplant registries, genomic studies, biobanks, and large scale EHR-based registries has so far provided a vast amount of valuable clinical and research information on cataract and a wide range of corneal diseases, ranging from non-sight threatening but functionally debilitating (e.g., DED) to sight threatening conditions (e.g., IK, PBK, keratoconus, etc.). Big data has advanced the understanding of many diseases, provided important benchmark for treatment and surgery, improved treatment outcome, and informed public policies. It is also anticipated that big data research will help propel the field of P4 medicine. However, there is currently a significant deficit and mismatch in the availability and demand for big data in LMICs, highlighting the need for increased effort and work to be invested in the under-resourced countries where blindness secondary to corneal opacity and cataract predominates (Pineda, 2015; Tan et al., 2015).

Author contributions

Study conceptualization and design: DSJT and MA. Data collection and drafting of initial manuscript: DSJT. Critical revision of manuscript: RD, DSWT, and MA. All authors contributed to the data interpretation, analysis, and final approval of manuscript.

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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.

8 https://gdpr.eu/tag/gdpr/

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Fresh takes on five health data sharing domains: Quality, privacy, equity, incentives, and sustainability

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As entities around the world invest in repositories and other infrastructure to facilitate health data sharing, scalable solutions to data sharing challenges are needed. We conducted semi-structured interviews with 24 experts to explore views on potential issues and policy options related to health data sharing. In this Perspective, we describe and contextualize unconventional insights shared by our interviewees relevant to issues in five domains: data quality, privacy, equity, incentives, and sustainability. These insights question a focus on granular quality metrics for gatekeeping; challenge enthusiasm for maximalist risk disclosure practices; call attention to power dynamics that potentially compromise the patient's voice; encourage faith in the sharing proclivities of new generations of scientists; and endorse accounting for personal disposition in the selection of long-term partners. We consider the merits of each insight with the broad goal of encouraging creative thinking to address data sharing challenges.

KEYWORDS

data sharing, data quality, ethics, data privacy, data archives

Introduction

It is widely agreed that sharing health data will translate to benefits for patients and populations and is critical to the advancement of science (Institute of Medicine of the National Academies, 2013; Editorial, 2020; Whicher et al., 2021). The widely cited and endorsed FAIR Guiding Principles provide an invaluable foundation for data management and stewardship (Wilkinson et al., 2016). However, technical, motivational, and policy barriers to sharing health data for secondary research persist [National Academies of Sciences, Engineering, and Medicine (NASEM), 2018]. As public and private entities increase investments in repositories and other infrastructure to facilitate health data sharing, scalable approaches to overcoming these barriers are urgently needed (Institute of Medicine of the National Academies, 2013; Whicher et al., 2021).

Addressing this need, we conducted a modified policy Delphi process to identify and prioritize issues and policy options related to sharing cancer-gene variant data (Majumder et al., 2021). Cancer genomics was the focus of our research given the field's significant efforts to make large-scale data sets available for secondary research with the objective of, among other things, resolving problems concerning variants of uncertain significance (The Clinical Cancer Genome Task Team of the Global Alliance for Genomics and Health, 2017). In the first three Delphi rounds, panelists prioritized issues and generated potential options that we categorized into five domains: data quality, privacy and security, equity, incentives, and sustainability. To broaden the range of perspectives considered by panelists in the final Delphi round, we conducted semi-structured interviews with 24 experts who did not participate in the Delphi process (Table 1). Methods for

TABLE 1 Characteristics of interview participants ($N = 24$).

	n (%)
Gender	
Male	11 (46)
Female	13 (54)
Prefer to self-describe	–
Age, in years	
35–45	7 (29)
46–55	4 (17)
56–65	4 (17)
66–75	2 (8)
Missing data*	7 (29)
Residence	
U.S.	20 (83)
Non-U.S.	3 (13)
Missing data*	1 (4)
Role(s) relevant to health data sharing**	
Data contributors/end-users	4 (17)
Data generators	1 (4)
Data sources	3 (13)
Data facilitators	1 (4)
Professional data users	12 (50)
Policy experts/scholars	10 (42)
Other	3 (13)
Missing data*	5 (21)

*Response was not forced.
**Interviewees were asked to select their role(s) related to cancer genomics commons from the following options: data contributors/end-users=patients, families, and advocacy organizations; data generators=testing laboratories; data sources=databases; data facilitators=data resources, curators, annotators, and variant interpreters; professional data users=genetic counselors, clinicians, and researchers; policy experts/scholars=health and biomedical research policy experts and scholars. Options were select all that apply so total exceeds $N = 24$ (100%).

recruiting interviewees, conducting interviews, and analyzing interview data are described in Supplementary material.

In this Perspective, we describe and contextualize select insights of interviewees on data sharing that we found intriguing and generated rich discussion among our research team (Table 2). Importantly, these insights are not limited to cancer genomics but are relevant to any efforts to share health data. We do not claim that these perspectives have never before been aired, but because they depart (in some cases significantly) from conventional thinking, we refer to them as "fresh takes." Although some might be controversial, we believe each has sufficient merit to justify exploration. More generally, by airing these fresh takes, we aim to encourage consideration of novel approaches to sharing health data.

Data quality: Questioning a focus on granular quality metrics for gatekeeping

The first fresh take focuses on the consequences of sharing data judged to be low quality. The conventional approach is to develop standards by which to designate data as high or low quality with the goal of generating, sharing, and reusing primarily high-quality data. One interviewee, however, worried about generalized use of metrics to expunge or block data from repositories, based on a judgment that they are low-quality according to those metrics, because "all data have warts." Depending on the specific objectives and needs of studies that might reuse data, the interviewee suggested, a data set's particular blemishes might not be significant or even relevant. To help researchers make decisions about reusing data, standards should therefore be developed for characterizing why and how the data were generated, and what they do and do not describe, to promote understanding of their strengths and limitations for specific secondary use contexts.

Consistent with the notion of quality as fitness for use, information systems professionals have described quality dimensions from the perspective of data users that include extrinsic indicators of contextual appropriateness, such as relevance to the task at hand and completeness, in addition to intrinsic indicators, such as accuracy (Wang and Strong, 1996). Medical researchers also recognize that annotation of data facilitates reuse, but data quality frameworks generally focus on development of and compliance with quality standards or metrics. In a systematic review of frameworks for data sharing within consortium-wide platforms for international health research, for example, principles and norms for data sharing included development and implementation of quality standards or threshold metrics (Kalkman et al., 2019). Our interviewee's unconventional insight is that the "play books" of primary researchers—e.g., the rich, narrative descriptions of how the data were originally generated, coded, and interrogated (Bauchner et al., 2016)—are as or even more useful to secondary researchers than granular quality metrics, especially those focused on identifying and quantifying quality "defects" as a basis for exclusion from the data commons. More broadly, it is worth considering whether use of the term "quality" promotes simplistic judgements about data that discourage appropriate reuse.

Privacy: Challenging maximalist disclosures about data sharing risks

The second fresh take concerns research participants' privacy and challenges with keeping their data confidential once shared. Because it is usually impossible to guarantee that data will never come into the possession of unauthorized persons or be used for unauthorized purposes, including reidentification, the conventional wisdom is that disclosing more information about privacy risks is generally better than less. Transparency is also believed to promote trust. One of our interviewees, however, argued that privacy-related disclosures can have the opposite effect by arousing suspicion. By analogy, the interviewee described a neighborhood coffee shop that assures customers its coffee is poison-free. Because customers do not normally wonder whether their coffee is laced with arsenic, the assurance causes customers to worry and ask, "Wait... why do you tell me that it's without poison?" The interviewee therefore advised, "if you want to build trust... don't speak about privacy too much."

A recent study suggests that members of the public who are open to donating their health data for research believe that

TABLE 2 Insights on health data sharing issues shared by interviewees ($N = 24$).

Issue domain*	Conventional approach	Fresh take	Supporting quote from interviews**
Data quality	Standards should be developed for judging data as high or low quality with the goal of generating, sharing, and reusing primarily high-quality data.	Standards should be developed for characterizing data with the goal of understanding why and how they were generated and what they do and do not describe. Appropriateness of reuse depends on context—specifically, alignment of data characteristics with the objectives and needs of specific studies.	"[W]e should be trying to move away from creating data standards for every data point.... [W]e've been trying to do that for two decades and it really has been a fair amount of nonsense. But rather, there should be a very consistent way of describing and characterizing data quality or characterizing data.... I think that quality ascribes judgement, and all data have warts." (9)
Privacy	In relation to research participants and the general public, data holders and managers should be transparent about privacy and security risks because doing so demonstrates respect and helps build trust. More disclosure is generally better than less disclosure.	Emphasizing privacy risks and security protections can breed mistrust. Policy attention should focus on promoting an appropriate level of disclosure, which should take into account psychological impacts.	"[I]f you want to build trust... don't speak about privacy too much.... [I]t goes back to the psychology... Oh, do you want this coffee? This coffee is without poison. And then it's like, Wait, of course, why do you tell me that it's without poison?" (10)
Equity	Patients and their representatives should be included in data governance to help ensure that decisions are responsive to their interests and concerns.	If patients and their representatives are to fulfill the role envisioned for them, power dynamics inherent in decision making processes must be recognized and managed. More broadly, equity initiatives should recognize epistemic equity as an area requiring attention and action.	Patients and their representatives invited to meetings with research funders can be told, "Don't say this or don't say that." Funders might focus on, "We're including a patient advocate, we're having the patient's voice at the table" and not know that the "patient's voice has already been filtered, is already being dominated, if you will." (21)
Incentives	Researchers can be reluctant to share data because doing so is not always in their professional interests. Policy efforts should therefore focus on creating incentives and removing disincentives for sharing.	The culture of newer generations of researchers is to share data. It is unnecessary to devote significant policy attention to incentives and disincentives because this culture will eventually be dominant.	If "you look at people that had got their PhDs within the last 10 years, they're probably much more active in the open science community.... And so, I actually see this as a problem that's going to be taken care of by the natural course of familiarity with a new way of working, which is digital, and that it's correcting itself. And if you say, how do you accelerate it?..... I'd probably answer back: is it worth trying to accelerate, or is it worth just promoting, helping those people that are operating in the new model be successful?" (23)
Sustainability	Partners should be recruited based on expertise, prestige, and resources.	All partners should be critically assessed to ensure that personal dispositions will promote rather than hinder the long-term success of health data repositories for sharing.	It's important to maintain "a pretty hard line on keeping the assholes out.... [T]here are some people who are poison to any consortium and you just can't have them involved...." (8)

*Issue domains identified during modified policy Delphi process (Majumder et al., 2021).
** Interviewee designated by number in parentheses.

transparency about how their data are used would help them trust the data-sharing enterprise (Milne et al., 2021). However, people's views and behaviors around privacy and related trade-offs are more uncertain, malleable, and context-dependent than is often recognized (Acquisti et al., 2015). Indeed, limited attention, "motivated attention" away from unpleasant information, and biased assessments of probability can diminish or even reverse intended effects of privacy-related disclosures (Loewenstein et al., 2014). Further, groups can have different levels of pre-existing concern about privacy that influence how disclosures affect trust. Still, some advocates for disclosure may appeal to considerations such as respect as justification for transparency regardless of any effects on trust (McGuire et al., 2019). In sum, many factors complicate the relationship between disclosures and their impact on trust and accountability (Loewenstein et al., 2014). The nugget of wisdom here is to be curious about and account for human psychology when obtaining consent for sharing health data and beware of unreflective disclosure maximalism.

Equity: Calling attention to power dynamics that potentially compromise the patient's voice

The third fresh take is in the domain of equity. Increasing diversity and sensitivity to the needs and concerns of patients and communities have recently been articulated as priorities in biomedical research (Aguilar-Gaxiola et al., 2022). Consistent with these priorities, some have championed biobank and data repository systems and processes that engage the general public, patients, and patient representatives in data governance (O'Doherty et al., 2011; Kaye et al., 2018; McGuire et al., 2019). But one of our interviewees cautioned that "having the patient's voice at the table" is not in itself sufficient to achieve equity. This is due to inherent power differences between patients and researchers—who may also be treating physicians. We might expect those desperate for help to avoid doing anything that might alienate those researchers. Thus, the interviewee observed, patients might not use their authentic voices—and might even simply parrot what researchers tell them to say—when invited to the table.

The interviewee's concerns are relevant to what Miranda Fricker calls epistemic injustice (Fricker, 2003). Epistemic injustice can occur when a hearer (e.g., physician or researcher) assigns lower credibility to a speaker (e.g., patient or caregiver) as a result of a prejudice stemming from differences of social identity, especially where the differences are characterized by unequal power between the hearer and the speaker (Fricker, 2003). It can also occur preemptively when the speaker remains silent out of fear of not being believed (Lee, 2021). Our interviewee's novel insight is that such silencing can occur out of fear of disrupting existing relationships *as a result* of being believed. Therefore, to protect against the (sometimes unintentional) filtering or dominance of the patient's voice, upstream solutions are needed to better identify and manage relevant power dynamics. For example, data governance can be structured to require the input of many patients and caregivers, rather than just a few.

Incentives: Focusing efforts on new generations of scientists

The fourth fresh take addresses the misalignment of data sharing with researchers' professional incentives. The conventional approach to this well-known problem is to reward data sharing, reduce professional incentives for data hoarding, and enshrine data sharing as an institutional and cultural norm. There are many examples of efforts that have adopted this approach, including the use of sharing badges by journals and data advertising by consortia to enhance the visibility of data sets and reputational credit of their creators (Devriendt et al., 2021). One of our interviewees, however, wondered whether these approaches are necessary given the popularity of open science norms among scientists who have pursued advanced degrees "within the last 10 years." They explained: "I actually see this as a problem that's going to be taken care of by the natural course of familiarity with a new way of working, which is digital, and that it's correcting itself." To those asking how to accelerate this change, the interviewee continued, "I'd probably answer back: is it worth trying to accelerate, or is it worth just promoting, helping those people that are operating in the new model be successful?"

Because incentive-related barriers to health data sharing have proven especially tricky to overcome, the wait-it-out approach endorsed by this interviewee has undeniable appeal. It is also true that there is broad enthusiasm for open science, as evidenced by global initiatives to facilitate access to research data, methods, and products [National Academies of Sciences, Engineering, and Medicine (NASEM), 2018]. Yet, one survey of over 1,300 scientists found that, compared to their older colleagues, younger scientists were less willing to share their research data without restriction, although they were more likely to agree that lack of access to data is a major impediment to progress in science and has restricted their ability to answer scientific questions (Tenopir et al., 2011). Other scholars attribute this finding to competitive pressures that are likely experienced more intensely by non-tenured scientists compared to their tenured colleagues (Fecher et al., 2015). More generally, the literature suggests that incentives and norms should move in the same direction to sustain behavior (Nicholas et al., 2019), and so it does not seem wise to disinvest in incentives for data sharing. Still, the interviewee's insight is useful in thinking about how to maximize the impact of those investments: instead of working to change the behaviors of a resistant old guard, focus on supporting new generations of scientists who might be more receptive to sharing.

Sustainability: Endorsing personal disposition as a partner screen

The final fresh take concerns the financial and human resource challenges associated with maintaining data repositories and sharing programs. A standard approach to promoting sustainability is to partner with individuals and institutions based on their access to resources, as well as their expertise and prestige, which can help attract external funding. But one of our interviewees recommended including an additional screen for personal disposition. Specifically, they explained, it is important to maintain "a pretty hard line on keeping the assholes out." The interviewee elaborated: "[T]here are some people who are poison to any consortium and you just can't have them involved."

Following publication of Sutton's (2004, 2007) landmark *Harvard Business Review* essay in 2004 and follow-on book in 2007, the "no asshole rule" has become well-known in management circles. This rule is intended to protect organizational culture by denying entry (usually in the form of employment) to even high-achieving individuals if they are known to exhibit abusive or other difficult behavior. The interviewee's novel insight was recognizing its relevance beyond business hiring contexts and applying it to decisions about partners in long-term and large-scale scientific collaborations. The move provokes a broader question: what other lessons about long-term operational success might data sharing efforts glean from the business management literature?

Conclusion

Given the intractability of issues associated with developing and sustaining repositories and other infrastructure to facilitate health data sharing, we believe it is worth paying attention to these and other unconventional perspectives. They have the potential to generate new and better solutions by drawing from literature in different fields, highlighting edge and hidden cases, and even reframing the problems. While not every fresh take will ultimately be useful to efforts to promote health data sharing, soliciting and airing them can help ensure that this work is conducted in ways that are open-minded and creative.

Data availability statement

The data presented in this article are not readily available due to the confidential nature of interviewees' participation and consistent with the IRB-approved protocol for this study. Requests to access the data should be directed to guerrini@bcm.edu.

Ethics statement

The studies involving human participants were reviewed and approved by Baylor College of Medicine

Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AM, CG, MM, and JR conceived of and designed this study. CG, MM, RC-D, JB, JG, and AG participated in data collection with support provided by JR and MB. CG, MM, JR, MB, and MS analyzed the data. CG, MM, and JR led the drafting of this manuscript. Funding for this research was obtained by RC-D and AM. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

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Decision-making support systems on extended hospital length of stay: Validation and recalibration of a model for patients with AMI

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Background: Cardiovascular diseases are still a significant cause of death and hospitalization. In 2019, circulatory diseases were responsible for 29.9% of deaths in Portugal. These diseases have a significant impact on the hospital length of stay. Length of stay predictive models is an efficient way to aid decision-making in health. This study aimed to validate a predictive model on the extended length of stay in patients with acute myocardial infarction at the time of admission.

Methods: An analysis was conducted to test and recalibrate a previously developed model in the prediction of prolonged length of stay, for a new set of population. The study was conducted based on administrative and laboratory data of patients admitted for acute myocardial infarction events from a public hospital in Portugal from 2013 to 2015.

Results: Comparable performance measures were observed upon the validation and recalibration of the predictive model of extended length of stay. Comorbidities such as shock, diabetes with complications, dysrhythmia, pulmonary edema, and respiratory infections were the common variables found between the previous model and the validated and recalibrated model for acute myocardial infarction.

Conclusion: Predictive models for the extended length of stay can be applied in clinical practice since they are recalibrated and modeled to the relevant population characteristics.

KEYWORDS

acute myocardial infarction, cardiovascular diseases, length of stay, predictive models, decision-making

Introduction

Europe has been undergoing profound demographic and social changes, the most visible of which are increases in average life expectancy and the increasing number of elderly people (1). The aging of the population, associated with the increase in chronic and degenerative diseases, is a phenomenon that represents a significant economic, health and social challenge for healthcare systems (2).

Among chronic diseases, cardiovascular diseases have emerged as the leading cause of death globally, representing 32.0% of all global deaths in 2019 (3).

In Portugal, diseases of the circulatory system accounted for 29.9% of total deaths (33,624 deaths), in 2019, an increase of 2.1% from the previous year. There were 10,975 deaths from cerebrovascular diseases, 7,151 deaths from ischemic heart disease and 4,275 deaths caused by acute myocardial infarction (AMI) (4), in the group of causes motivated by circulatory system diseases.

In Portugal, there was an 8.1% decrease in the number of hospitalizations for circulatory system diseases compared to 2011, with this decrease being especially relevant in hospitalizations for AMI, which accounted for 10.4% of hospitalizations for circulatory systems diseases (11,510 episodes) in 2016 (5). This shift may be explained by investments in strategic preventive measures and improved diagnosis in the areas of AMI and stroke (5). However, there was an increase in the total number of days patients were hospitalized for AMI between 2010 (91.060 days) and 2014 (95.315 days) (6).

The length of stay (LOS), which refers to the number of days spent in a hospital by each patient (7), is commonly considered to be a measure of efficiency and a proxy for hospital resource consumption (8). It also provides better understanding of patient flow, which is essential to understanding both the operational and clinical functions of a healthcare system (9–11).

Reducing LOS contributes to lower costs and improved outcomes for patients (12), therefore there is a growing interest in the development of models to predict LOS.

The predictive model for extended length of stay (LOSE) by Magalhães et al. (13), has identified specific variables that lead to an increased risk of LOSE in patients with AMI: comorbidities (diabetes with complications, cerebrovascular disease, shock, respiratory infections, pulmonary edema, cardiac dysrhythmia), altered partial pressure of oxygen in the blood (pO2), being aged 69 years or older, and with neutrophils and prothrombin time above level.

Administrative data, which are readily available, relatively inexpensive to obtain, easily accessible, and widely used to assess resource use of hospital systems (14–16), can be used to build the LOS predictive model. The use of administrative data has limitations, such as inaccurate data, coding errors, missing cases, and other inconsistencies; however, it is commonly the only source of information available to observe and analyze clinical issues. It should also be noted that these data could be used to identify quality indicators and benchmark hospital activity (14, 16).

As the prevalence and incidence of cardiovascular diseases in Portugal are significant, as is their weight in hospital management, both in terms of costs, bed occupancy and discharge management, it is imperative and relevant to evaluate the added value of using predictive models in the daily practice of healthcare facilities.

Therefore, the purpose of this study is to determine whether predictive models of LOS at the time of admission developed for small hospital populations can be generalized to larger populations by identifying patients with extended LOS (LOSE).

The specific objectives of the study were to:

- Validate the predictive models for an extended length of stay in a new population with the algorithm previously developed by Magalhães et al. (13), taking into account the set of variables and coefficients determined;
- Recalibrate the model in the new population and verify if the model changes substantially.

Materials and methods

Study population

The study population included patients aged 18 years or older, discharged alive, whose primary diagnosis of admission was AMI (410 ICD-9-CM). To identify the episodes, the codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) were used. Episodes of AMI coded as subsequent diagnosis were excluded, as well as episodes from patients transferred to another hospital. The final sample included 1,531 episodes.

While the Magalhães et al. (13) study used laboratory and administrative data from a Portuguese NHS hospital (~400 beds) in 2010–11, the study population in the current study differs in terms of the period of analysis, sample size, and the hospital from which the data reports.

Data collection

This study used administrative and laboratory data discharges from a National Health Service (NHS) large hospital in Portugal (~1,000 beds), from 2013 to 2015. The anonymized database includes demographic data, such as sex and age, type of admission, primary and secondary diagnosis, and medical procedures (ICD-9-CM), destination after discharge, and analytical results. The study was approved by the hospital's ethics commission (reference 19/16). The data obtained were kept anonymous and confidentiality was ensured. To safeguard the identity of the study population, the hospital guaranteed the anonymity of the data, and the database was made available with encrypted identification codes.

Methods

The study method is 2-fold: first, to validate the prediction of the extended length of stay (LOSE 7 days) on patients with a primary diagnosis of AMI who were discharged alive using the predictive model developed by Magalhães et al. (13), also known in this study as the validated model (VM). Second, the same algorithm used in the Magalhães et al. predictive model was used to recalibrate the model, but the study population focused on patients with LOSE ≥11 days in the sample of patients with the primary diagnosis of AMI. In this study, the recalibration model is referred to as RM.

LOSE was the outcome variable used to promptly identify patients at higher risk of prolonged hospitalization, identifying patients with an adverse result or excessive LOS (value:1). Patients with LOS greater than the 75th percentile (≥7 days in VM and ≥11 days in RM) were considered to have LOSE (5, 16). LOS was defined as the time in days between admission and discharge to the inpatient hospital setting. The different LOSE in the two models corresponds to the use of the same LOSE ≥7 days in the VM (anterior sample model) and the use of the corresponding LOSE on the actual sample ≥11 days in RM.

The model variables determined by Magalhães et al. (13) were: diabetes with complications, cerebrovascular disease, shock, respiratory infections, pulmonary edema, pO2 above level, age group of 69 to 100 years old, cardiac dysrhythmia, neutrophils above level, and the duration of prothrombin above level.

The missing values on laboratory data were handled by applying normal levels, thus using a single imputation procedure (13).

Statistical analysis

A multiple logistic regression based on the previously developed model was used to estimate the coefficients of each variable, and the odds ratio (OR) was used to analyze the coefficients of each variable for VM.

In the RM, a combination of all the independent variables recorded in the population's database under study was used: laboratory results, sex, age, type of AMI and comorbidities.

The final algorithm was created by using the same method as the training model developed by Magalhães et al. (13), so all the data was used to recalibrate the model. Therefore, a simple logistic regression was used to select variables for the multiple analysis. The Wald test was used in this analysis, with a significance level of 25% (p-value < 25%) considered for this phase.

The variable selection methods used for the multiple analysis were stepwise forward and stepwise backward, that presented the best Akaike Information Criterion (AIC) as a reference.

Odds ratios were used to analyze the model coefficients.

The predictive capacity of the models was assessed using the following parameters: predictive efficiency, discriminatory capacity, and calibration.

Results

Descriptive statistics study population

As shown in Table 1, male patients account for 66.4% of 1,531 episodes of patients discharged alive whose primary diagnosis was AMI, while female patients account for 33.6%. 48.6% of the episodes had a LOSE ≥7 days and 26.5% a LOSE ≥11 days.

Of the episodes of patients with LOSE, the AMI NSTEMI-type (29.4%) presented the highest LOS. Of the 31 episodes with shock comorbidity, 28 (90.3%) had an LOSE, followed by patients with pulmonary edema (70.6%) and respiratory infection (60.4%).

Regarding laboratory data, as shown in Table 2, most patients with AMI discharged alive have abnormal levels of lymphocytes (80.6% above level), neutrophils (81.8% above level) and troponin I (86.2% above level). Almost all the results above level are in the episodes with LOSE ≥7 days.

Abnormal level results were found more frequently in patients with LOSE ≥ 11 days in the analysis of albumin (59.1% below level), CK (55.6% below level) and LDH, which showed values 100% below level but with a low frequency (3). For the patients with LOSE ≥7 days

TABLE 1 Descriptive statistics of the study population—Administrative data.

	Discharged alive with principal diagnosis of AMI		LOSE ≥7 days		LOSE ≥11 days	
	N	%	*N*	%	*N*	%
Total	1,531	100	744	48.6	406	26.5
Sex						
Male	1,016	66.4	470	46.3	270	26.6
Female	515	33.6	274	53.2	136	26.4
Type of AMI						
Anterior STEMI	256	16.7	121	47.3	62	24.2
Other STEMI	662	43.2	319	48.2	164	24.8
NSTEMI	613	40.0	304	49.6	180	29.4
Comorbidities						
Anemia	191	12.5	135	70.7	94	49.2
Cancer	63	4.1	29	46.0	16	25.4
Cardiogenic shock	31	2.0	31	100	28	90.3
Diabetes with complications	129	8.4	86	66.7	60	46.6
Diabetes without complications	342	22.3	186	54.4	95	27.8
Cardiac dysrhythmia	379	24.8	232	61.2	141	37.2
Cerebrovascular disease	173	11.3	110	63.6	61	35.3
Pulmonary edema	68	4.4	61	89.7	48	70.6
Respiratory infection	164	10.7	144	87.8	99	60.4
Acute kidney failure	294	19.2	184	62.6	116	39.5
Chronic kidney failure	302	19.7	191	63.2	120	39.7

TABLE 2 Descriptive statistics of the study population—Laboratory data.

Variable	Below level				Above level			
	N	%	LOSE ≥7 days (%)	LOSE ≥11 days (%)	*N*	%	LOSE ≥7 days (%)	LOSE ≥11 days (%)
Albumin	88	5.75	72.7	59.09	3	0.20	66.7	0
Calcium	170	11.10	56.5	38.24	6	0.39	50.0	33.33
Chlorine	51	3.33	58.8	37.25	179	11.69	39.7	19.55
Creatine kinase (CK)	9	0.59	66.7	55.56	471	30.76	49.3	26.54
Creatinine	101	6.60	41.6	17.82	875	57.15	49.8	28.91
Eosinophils	0	0	0.0	0	865	56.50	43.2	23.70
Erythrocytes	570	37.23	56.7	33.16	10	0.65	50.0	20.00
Glucose	14	0.91	50.0	35.71	519	33.90	52.6	27.17
Hematocrit	590	38.54	58.5	33.73	22	1.44	45.5	31.82
Hemoglobin	484	31.61	62.8	37.81	11	0.72	54.5	27.27
Mean globular hemoglobin (HGM)	68	4.44	60.3	27.94	97	6.34	48.5	24.74
International normalized ratio (INR)	0	0	0.0	0	79	5.16	73.4	48.10
Lactate dehydrogenase (LDH)	3	0.20	100	100	813	53.10	91.5	26.69
Lymphocytes	0	0	0.0	0	1,234	80.60	47.7	26.26
Neutrophils	0	0	0.0	0	1,252	81.78	48.2	26.84
Platelets	146	9.54	48.6	28.77	24	1.57	50.0	41.67
Blood oxygen (pO2)	37	2.42	78.4	37.84	59	3.85	61.0	42.37
Potassium	66	4.31	65.2	27.27	82	5.36	61.0	36.59
C-reactive protein (CRP)	0	0	0.0	0	877	57.28	54.5	30.56
RDW-CV	0	0	0.0	0	446	29.13	59.6	35.65
Sodium	94	6.14	68.1	39.36	21	1.37	61.9	38.10
AST	0	0	0.0	0	746	48.73	50.7	27.61
ALT	24	1.57	54.2	20.83	196	12.80	64.8	38.78
Activated partial thromboplastin time (APTT)	9	0.59	55.6	22.22	212	13.85	53.3	32.08
Prothrombin time	1	0.07	0.0	0	147	9.60	69.4	43.54
Troponin I	0	0	0.0	0	1,319	86.15	47.4	25.17
Urea	0	0	0.0	0	414	27.04	64.5	40.58

in LDH (91.5% above level), pO2 (78.4% below level) and Albumin (72.7% below level).

TABLE 3 Performance measures comparison.

Performance measures	Magalhães et al. (13) model	Validation model (VM)
Recall	72%	58%
Specificity	75%	73%
Cut-off	0.24	0.26
AUC	0.828	0.702

Validation model

A Recall (58%) and Specificity (73%), with a cut-off of 0.26, and a discriminatory capacity (area under the ROC curve [AUC] of 0.702) were observed for the population of patients with a primary diagnosis of AMI, who were discharged alive and for the variables defined in the previous model (VM). According to the data presented in Table 3, there is a decrease in the predictive capacity of the VM compared to the results obtained in the model by Magalhães et al. (13). The VM considered LOSE ≥ 7 days.

As shown in Table 4, after testing the VM in the study population, the confidence interval (CI) did not remain the same in relation to the model of Magalhães et al. (13). In addition, differences were also observed concerning clinical variables:

- Total carbon dioxide level in the blood was not tested, since it was not present in the database;

TABLE 4 CI values between the model by Magalhães et al. (13) and the validation model (VM) for AMI.

Magalhães et al. (13) model predictive factors				CI of validation model (VM)
Variables	OR[a]	CI 95%[a]	*p*-value	CI 95%[a]
Age group [69, 100]	3.31	1.9–5.28	0	1.92–5.86
Cardiogenic shock	17.78	1.6–134.02	0.019	2–390.41
Diabetes with complications	37.83	4.12–242.00	0.001	5.71–754.53
Cardiac dysrhythmia	2.97	1.2–6.37	0.019	1.18–7.34
Cerebrovascular disease	18.41	2.12–113.07	0.008	2.97–356.32
Pulmonary edema	7.31	1.38–29.61	0.019	1.58–52.32
Respiratory infections	9.32	1.72–38.47	0.01	2.07–69.29
Neutrophils (above level)	2.03	1.19–3.17	0.009	1.92–5.86
pO2 (below level)	1.7	1.38–3.47	0.222	0.71–3.94
pO_2 (above level)	4.52	1.41–12.01	0.011	1.42–15.15
Prothrombin time (above level)	1.64	1.09–2.67	0.097	0.91–2.92

[a]OR, Odds Ratio; IC, Intervalo de Confiança do OR.

- Chlorine and prothrombin time had the same reference range. However, the range of results was wider;
- The mean platelet volume had the same reference range. However, the range of results was narrower.

Recalibration model

Administrative and laboratory variables with p-value < 0.28 were included in the logistic regression analysis for the population of patients with a primary diagnosis of AMI who were discharged alive and whose LOSE was $\geq$11 days. The variables were age, type of AMI, shock, pulmonary edema, acute renal failure, chronic renal failure, cerebrovascular disease, dysrhythmia, diabetes with complications, anemia, respiratory infection, albumin, calcium, chlorine, creatinine, eosinophils, erythrocytes, hematocrit, hemoglobin, INR, LDH, pO2, potassium, C-Reactive protein (CRP), RDW-CV, sodium, ALT, Activated Partial Thromboplastin Time (APTT), prothrombin time, troponin I, urea.

The explanatory variables of the LOSE were adjusted throughout the tests performed and those that were not significant for the model were removed. Thus, episodes with zero days of hospitalization were also removed, to improve the model's recalibration. The age variable was categorized for individuals aged $\geq$69 years, thus being included in the potentially predictive variables.

Table 5 shows the final variables, resulting from the multiple logistic regression analysis, which are part of the score of the new LOSE model. The variables are age $\geq$69 years, CRP (above level), troponin I (above level), shock, pulmonary edema, dysrhythmia, diabetes with complications, anemia, and respiratory infection. As shown, all variables have positive coefficients except for troponin I.

Variables with a positive coefficient indicate that patients who have this variable have a higher risk of LOSE than those who do not. The opposite is true for variables with negative coefficients.

Patients at greatest risk of LOSE are those who present shock on admission, about 23 times more than those who do not have this comorbidity (OR = 22.96; $p = 0$).

TABLE 5 Predictive factors of LOSE $\geq$11 days for patients with AMI discharged alive.

Variables	Coef.	OR[a]	CI 95%[a]	*p*-value	Pr (>|*p*|)
Age $\geq$69	0.1245	1.48	1.13–1.93	0.004	**
CRP (above level)	0.1826	1.57	1.20–2.06	0.001	**
Troponin I (above level)	−0.8213	0.62	0.44–0.89	0.009	**
Cardiogenic shock	2.0367	22.96	7.67–99.09	0	***
Pulmonary edema	0.8942	4.34	2.45–7.91	0	***
Cardiac dysrhythmia	0.1452	1.54	1.16–2.04	0.003	**
Diabetes without complications	0.1993	1.85	1.22–2.79	0.003	**
Anemia	0.4890	2.31	1.63–3.26	0	***
Respiratory infection	0.9006	3.55	2.46–5.15	0	***

Signif. codes: 0 "***"; 0.001 "**".
[a]OR, Odds Ratio; CI, Confidence Interval; Pr (> ...) – Significance.

Troponin I (above level) was associated with the lowest risk (OR = 0.62; $p = 0.009$). Thus, patients with these values on admission have a lower risk of LOSE $\geq$11 days. The most significant variables (***) are shock, pulmonary edema, anemia, and respiratory infection.

Table 6 shows the comparison of OR values and 95% CI between the model by Magalhães et al. (13) and RM for the study population.

Table 7 compares the performance measures for the population of AMI patients who were discharged alive, comparing Magalhães et al. (13) model, the VM of this study and the RM.

Discussion

The goal of this study was to validate a previous predictive model of extended hospital length of stay (13) and recalibrate it for a

TABLE 6 Comparison of the values obtained for OR and 95% CI between the models.

Magalhães et al. (13) model predictive factors				Recalibration model (RM) predictive factors			
Variables	OR[a]	CI 95%[a]	*p*-value	Variables	OR[a]	CI 95%[a]	*p*-value
Age group [69. 100]	3.31	1.9–5.28	0	Age ≥69	1.48	1.13–1.93	0.004
Cardiogenic shock	17.78	1.6–134.02	0.019	Cardiogenic shock	22.96	7.67–99.09	0
Diabetes with complications	37.83	4.12–242.00	0.001	Diabetes with complications	1.85	1.22-2.79	0.003
Cardiac dysrhythmia	2.97	1.2–6.37	0.019	Cardiac dysrhythmia	1.54	1.16–2.04	0.003
Cerebrovascular disease	18.41	2.12–113.07	0.008				
Pulmonary edema	7.31	1.38–29.61	0.019	Pulmonary edema	4.34	2.45–7.91	0
Respiratory infection	9.32	1.72–38.47	0.01	Respiratory infection	3.55	2.46–5.15	0
				Anemia	2.31	1.63–3.26	0.000
Neutrophils (above level)	2.03	1.19–3.17	0.009				
pO2 (below level)	1.7	1.38–3.47	0.222				
pO2 (above level)	4.52	1.41–12.01	0.011				
Prothrombin time (above level)	1.64	1.09–2.67	0.097				
				CRP (above level)	1.57	1.20–2.06	0.001
				Troponin I (above level)	0.62	0.44–0.89	0.009

[a]OR, Odds Ratio; IC, Confidence Interval.

TABLE 7 Comparison of the performance measures obtained in the models.

Performance measures	Magalhães et al. (13) model	Validation model (VM)	Recalibration model (RM)
Recall	72%	58%	69%
Specificity	75%	73%	68%
Cut-off	0.24	0.26	0.21
AUC	0.828	0.702	0.745
Hosmer-Lemeshow test	0.995	-	0.692

different population, by analyzing administrative and laboratory data from an NHS Portuguese hospital regarding episodes of patients aged 18 years or older, with a primary diagnosis of AMI, discharged alive.

In comparison to the model developed by Magalhães et al. (13), the VM developed in this study lost predictive capacity, the Recall and Specificity valuesropped, as did the AUC. As a result, the model required recalibration in the population under study. Nine predictive variables of LOSE were obtained during AMI model recalibration, using the statistically significant variables. Of these, the variables age, shock, pulmonary edema, dysrhythmia, and respiratory infection were present in the validation model. All variables, except for troponin I, had a high predictive capacity of LOSE, and all of them were statistically significant.

When the Magalhães et al. (13) model was compared to the RM, age, diabetes with complications, dysrhythmia, pulmonary edema and respiratory infection had a lower OR (lower predictive capacity). The variables age, shock, pulmonary edema, and respiratory infection had lower CIs. It is also possible to verify that the variables in the RM presented a higher degree of significance compared to the model by Magalhães et al. (13).

The analytical variables were those that differed the most between the models, and there was no agreement on any of them. This fact can be explained by the data collected in the different hospitals and by the different calibrated values of the results.

The results pertaining comorbidities obtained from the recalibration model were consistent with the data obtained by Elixhauser et al. (17), who identified diabetes with complications and pulmonary edema as comorbidities that increase not only LOS but also mortality and hospital costs. These authors also highlight cancer and renal failure as predictive factors; however, they were not verified in this model.

Furthermore, Swaminathan et al. (9); Magalhães et al. (13) and Kaul et al. (18) suggest that patients with LOSE had a higher prevalence of heart failure, diabetes, renal failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, hypertension, respiratory infections, pulmonary edema, metastatic cancer, coagulopathy, shock, and analytical changes.

The age group over 65 years old is frequently mentioned as being predictive of LOSE and even mortality. For instance, Swaminathan et al. (9); Saczynski et al. (19) and Magalhães et al. (13) conducted studies with elderly populations to test their predictive capacity concerning hospitalized patients with cardiac events.

According to the AMI Risk Score (thrombolysis in myocardial infarction, TIMI), risk stratification is important in predicting disease prognosis. This score serves as a tool to predict death and other cardiac ischemic events. It is composed of seven independent variables: age ≥65 years, 3 risk factors for Acute Coronary Syndrome (ACS), anterior coronary artery stenosis, use of acetylsalicylic acid in the last 7 days, ST-segment deviation of 0.5 mm, symptoms of angina/chest pain in the previous 24 h and presence of an elevated cardiac marker (CK-MB or troponin I) (20). The tested model shares some variables with this predictive model (age and troponin I).

According to the same study, the Hosmer-Lemeshow test (3.56) and the AUC (0.65) for the predictive power of TIMI for unstable angina/ NSTEMI were lower when compared to the AMI RM (Hosmer-Lemeshow test: 0.692 and AUC of 0.745). Thus, the RM for AMI showed better results and a higher discriminatory capacity (AUC) compared to TIMI. However, further studies should be conducted on this evidence, while increasing the sample dimension, allowing the models to evolve to another dimension, namely in the ability to inform not only about LOS and risk of death, but also the decision of the best treatment given the patient's condition (21).

Regarding the analytical variables, CRP, defined as "a marker of acute inflammatory phase response synthesized in the liver" (22), has been associated with the assessment of cardiac risk in intermediate-risk patients (23).

According to the findings in the Potsch et al. (22) study, CRP levels were higher in patients with a primary diagnosis of AMI compared to those who did not have this diagnosis, so CRP values above the level at the time of admission are a useful tool in the identification of patients with more severe chest pain.

Another interesting finding of this study, which corroborated the observed results, is the fact that the measurement of CRP during hospitalization is an important "tool in the prediction of adverse cardiac events during the hospitalization period" (22).

The LOSE value considered is another difference discovered when compared to the previously validated model. LOSE was defined as $\geq$7 days in the model by Magalhães et al. (13). However, LOSE was found to be 11 days in this population, based on the 75th percentile of the total days of hospitalization (13, 24). Because the difference in the cut-off point may have influenced the results obtained, the model must always be adjusted to the existing population.

This number of days, which define LOSE, was also found in a study by Li et al. (25), on national trends in length of hospital stay for AMI in China, where LOS remains considerably high, with an average of 12 days in 2011.

Regarding the performance measures for the population of patients with AMI who were discharged alive, the results obtained in the RM were worse compared to the validation by Magalhães et al. (13) and improved compared to the VM (expected result, since the model was adjusted to the population). Although the AUC decreased slightly, the Hosmer-Lemeshow test showed the greatest decrease in values.

This study had some limitations, namely the difficulty in obtaining studies developed within the scope of LOSE and predictive factors of LOSE, for patients with AMI and cardiac pathologies and also the inclusion of other patient-related data as vital signs and cardiovascular exams results.

The study also made it possible to identify further research opportunities, such as:

- Inclusion of new variables, as is the case of vital signs and cardiovascular exams;
- Elaboration of a more detailed analysis of other cardiovascular pathologies, since all these pathologies have different characteristics;
- Applying this methodology to chronic cardiovascular diseases and even in the rehabilitation care of these patients.

Conclusion

Decision-making support models have proven to be useful in health systems, particularly in hospital management, to achieve the goals of reducing hospitalization time, increasing the number of available beds, and reduce waiting lists. Models that predict the length of stay might be especially helpful to achieve these objectives (10, 16, 26).

This study allowed researchers to conclude that a previous model for predicting LOSE on patients diagnosed with AMI could not be generalized. Therefore, it highlights the need to recalibrate the models to new populations, as the models cannot be generalized to different populations without losing their predictive capacity. However, more research is needed to understand whether these models could be generalized in similar populations and hospitals.

Data availability statement

The datasets presented in this article are not readily available because the data that supports the findings of this study is only available with the permission of the hospital in study. Requests to access the datasets should be directed to teresa.magalhaes@ensp.unl.pt.

Ethics statement

The studies involving human/animal participants were reviewed and approved by Comissão de Ética do Centro Académico de Medicina de Lisboa (Ref. nr. 9/16).

Author contributions

JX and TM designed the study and carried out the data collection. JS wrote and revised the paper. TM coordinated the study and revised the paper. FP is a cardiologist doctor and the data donor and also revised the paper. All authors read and approved the final manuscript.

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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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Constructing big data prevention and control model for public health emergencies in China: A grounded theory study

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Big data technology plays an important role in the prevention and control of public health emergencies such as the COVID-19 pandemic. Current studies on model construction, such as SIR infectious disease model, 4R crisis management model, etc., have put forward decision-making suggestions from different perspectives, which also provide a reference basis for the research in this paper. This paper conducts an exploratory study on the construction of a big data prevention and control model for public health emergencies by using the grounded theory, a qualitative research method, with literature, policies, and regulations as research samples, and makes a grounded analysis through three-level coding and saturation test. Main results are as follows: (1) The three elements of data layer, subject layer, and application layer play a prominent role in the digital prevention and control practice of epidemic in China and constitute the basic framework of the "DSA" model. (2) The "DSA" model integrates cross-industry, cross-region, and cross-domain epidemic data into one system framework, effectively solving the disadvantages of fragmentation caused by "information island". (3) The "DSA" model analyzes the differences in information needs of different subjects during an outbreak and summarizes several collaborative approaches to promote resource sharing and cooperative governance. (4) The "DSA" model analyzes the specific application scenarios of big data technology in different stages of epidemic development, effectively responding to the disconnection between current technological development and realistic needs.

KEYWORDS

big data, public health emergencies, epidemic prevention and control, "DSA" model, emergency management

1. Introduction

Public health refers to "the science and practice of disease prevention and early diagnosis, control of infectious diseases, health education, injury prevention, sanitation, and protection against environmental hazards" (1). Modern public health was born in the 18th century, and with the increasing maturity of human knowledge and practice of public health, there is now a consensus on the definition of public health emergencies–events that have a serious impact on public health, including epidemic of major infectious diseases, animal epidemics, mass illness of unknown origin, grave food and occupational poisoning, etc. Public health emergencies are characterized by suddenness, complexity, severity, etc. (2–4). Since the 21st century, global public health emergencies have occurred frequently: the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 (5), Influenza A (H1N1) outbreak in 2009 (6), Middle East Respiratory Syndrome (MERS) outbreak in 2015 (7), and novel coronavirus (COVID-19) outbreak in 2019 (8). Frequent public health emergencies have caused significant damage to people's lives and health as well as the operation of the economy and society (9). Today, the world is still fighting against COVID-19, at a critical point of great change, differentiation, and adjustment. As of October 12, 2022, the total number of confirmed COVID-19 cases worldwide has reached 626,679,171 with 6,565,147 deaths (10). Faced with such a severe situation, China has adopted policies such as road closures, traffic restrictions, and strict home-staying to prevent the spread of the epidemic. Although these traditional manual approaches have been effective in controlling the epidemic, it has revealed many drawbacks that not only pose challenges to urban management, but also have far-reaching effects on the daily lives of urban residents (11, 12). Therefore, how to adopt new ideas, new technologies, and intelligent responses to improve the scientific nature of the work are top priorities of epidemic prevention and control.

Big Data refers to a huge data set that cannot be effectively processed in a short period of time, with large scale, wide dimensionality, and high scalability. First proposed by Alvin Toffler in 1980 in the book *The Third Wave*, it has 4V characteristics: volume, variety, velocity, and value (13). Big data technology and the governance of public health emergencies have significant applicability: from a policy standpoint, the Chinese state has introduced a series of policies related to strengthening the application of big data technology clusters in the field of public health, and big data has been implicitly reshaping and transforming the external ecosystem of the government. In June 2016, the *Guiding Opinions on Promoting and Regulating the Development of Big Data Application in Health Care* issued by the General Office of the State Council of the People's Republic of China, incorporated the development of big data applications in health care into the national big data strategic layout (14). In April 2018, the General Office of the State Council of the People's Republic of China issued the *Opinions on Promoting the Development of Internet Plus Medical Health* (15), encouraging medical and health institutions to cooperate with Internet companies to strengthen the intelligent monitoring of infectious diseases and other diseases. In February 2020, the Office of the Central Cyberspace Affairs Commission issued the *Notice on the Good Protection of Personal Information Using Big Data to Support Joint Prevention and Control Work* (16), encouraging capable enterprises to use big data to analyze and predict the flow of confirmed and suspected patients, their close contacts, and other highly-relevant populations. In terms of realistic needs, big data technology based on data and algorithms can incorporate the epidemic coverage and surrounding areas into the governance framework presented by data. With its powerful algorithmic logic and calculation rules, it can realize the accurate perception of the external environment to enhance risk diagnosis and early warning capability, which also determines the strong demand for big data technology in the management of public health emergencies (17).

To prevent and control global public health emergencies, most countries rely on institutional public health systems to provide early warning of infectious diseases. This traditional approach faces problems such as insufficient information and delayed response. With the advent of the information society, big data technology provides more diversified information sources and intelligent information processing methods for epidemic prevention and control, which shows great potential for development. The construction of a big data prevention and control model for public health emergencies is of great significance for promoting the deep integration of big data and public health, making up for the shortcomings of the disconnect between big data applications and actual needs, and improving the prevention and control capacity of public health emergencies. Therefore, based on Chinese experience of big data technology development and epidemic prevention and control, this paper conducts an exploratory study on the construction of a big data prevention and control model for public health emergencies using the qualitative research method of grounded theory, aiming to provide references for decision-making and improve the efficiencies of anti-epidemic campaigns. The contributions of this study include the following aspects: (1) The DSA model of big data prevention and control of public health emergencies is constructed in three dimensions: data layer, subject layer, and application layer, which actively responds to the new requirements of the top-level design of the national system in the field of public health. It is an important step to promote the deep integration of big data with public health and improve the technological innovation of epidemic prevention and control. (2) Unblocking channels of information collection, exchange, and transmission. The big data information in public health emergencies has been divided into four categories: "epidemic big data," "healthcare big data," "government open big data," and "Internet big data." It also analyzes the process of how data can realize added-value, and enhances the timeliness and integrity of public health-related information. (3) From a holistic perspective, the correlation and interaction of all necessary elements in epidemic prevention and control are comprehensively analyzed to achieve multi-source information processing and precise information positioning, complete the transformation from group management to individual tracking, and enhance the rigor and accuracy of epidemic prevention and control. (4) The specific application scenarios of big data technology in the incubation period, outbreak period, and recovery period of public health emergencies are analyzed, and macro policy advocacy is applied to epidemic prevention and control, which effectively solves the extreme lack of intrinsic correlation between "policy and practice." It provides a different way of thinking about governance of public health emergencies compared to previous studies.

2. Literature review

The increasing perfection and timely application of big data technologies have changed the perception of information related to public health emergencies in the industry and academia, and have gradually exerted an important influence on the thinking paradigm and approach to crisis response. Experts and scholars at home and abroad have paid great attention to the application of big data in the management of public health emergencies, and a multidisciplinary research situation has been formed, with public health, emergency management, and intelligence science as the main disciplines. From the perspective of public health disciplines, it is mainly about the impact and challenges of big data in the medical field. For example, Pham et al. proposed combining SIR models with Machine Learning and Deep Learning models based on big data technologies that can send timely alert messages to governments and policymakers to act in advance of an outbreak (18). Lopez et al. effectively predicted the epidemiological impact of influenza in Vellore, India, by constructing a big data spatial model (19). Li et al. constructed a false epidemic information identification model to identify reliable information sources based on the analysis of health care big data, which divided the epidemic information screening and public opinion prevention and control research into two modules (20). Bragazzi et al. proposed that big data can help in handling the huge, unprecedented amount of data derived from public health surveillance, real-time epidemic outbreaks monitoring, trend now-casting/forecasting, regular situation briefing, and updating from governmental institutions and organisms (21). Liu et al. established a multi-stage time-delayed SEIR epidemic model based on the classic susceptible, exposed, infected, and recovered (SEIR) epidemic model and epidemic data in Guangzhou, which is suitable for epidemic research in Guangzhou and effectively solves the problem of optimizing the site selection decision for emergency medical facilities for public health emergencies in China (22). From the perspective of emergency management disciplines, the main research is about the mechanism and practice of the role of big data in public health emergencies. For example, Naudé proposed that big data has actual and potential uses in the fight against COVID-19 such as tracking and prediction, diagnosis and prognosis, treatment, and vaccine, which are used throughout the process of Reduction, Readiness, Response, and Recovery in the 4R crisis management theory, and that a careful balance between data privacy and public health needs to be maintained in the future (23). Lee et al. used the issue of mask-wearing as a research topic and applied big data analysis methods to international media reports on COVID-19 pandemic crisis themes conducted a thematic network analysis (24). Zhang H used big data technology to construct a multi-role portrait system model, which can provide data panorama support for epidemic monitoring, early warning, and investigation, and provide new ideas for the prevention and control of infectious diseases (25). From the perspective of intellectual discipline, it is mainly about the construction of intelligent systems and models for public health emergencies in the era of big data. For example, Mohamadou proposed that the intelligence model constructed by combining COVID-19 data such as "medical images, population movements, and case reports" with artificial intelligence can enhance the understanding of disease transmission and evaluation of preventive measures, so as to detect infected patients early and accurately (26). Esposito introduced and compared different data-driven epidemiological intelligence strategies (DDEIS) developed based on DPTT, and analyzed the extent to which DDEIS can effectively achieve the goal of quickly returning to normal cities and minimizing the risk of epidemic recurrence (27). Yin et al. fused the continuous mechanisms of Big Data Intelligent Innovation (BDII) into a complex network, and constructed a three-dimensional collaborative epidemic prevention model to reveal the effectiveness of continuous epidemic prevention under different big data intelligent emergency management policy levels (28).

According to the research results, scholars have made preliminary explorations on the integration of big data and the management of public health emergency governance, ranging from public health risk assessment to emergency capacity-building. However, there are still the following inadequacies: The existing research mainly focuses on the response to public health emergencies, lacking a comprehensive analysis of the interaction between the necessary elements in the emergency governance process from a holistic perspective, which has led to the insufficient application of big data in the management of public health emergencies. The intrinsic connection between macro policy advocacy and practical application is severed, making the deep integration of data, subjects, and applications virtually impossible. Specifically, at the beginning of COVID-19 outbreak, some medical institutions and enterprises in China tried to apply emerging technology with "big data" as the information chain in epidemic prevention and control, such as cloud computing, artificial intelligence, drones, and blockchain. These technologies have played an active role in online medical care, epidemic information processing, and precise management of the mobile population. However, in general, the application of big data technology in the front line of prevention and control is relatively limited at this stage, and the quality and efficiency of epidemic prevention and control work are low due to the lack of crucial technical support, resulting in a depression situation where hundreds of millions of people were home quarantine in China.

Therefore, compared with existing studies, this study aims to address the following questions: How to integrate and optimize the big data technologies currently applied to the prevention and control of public health emergencies, so that the fragmented practical experience can be upgraded into a systematic model, and then guide government departments to carry out accurate and intelligent prevention and control of epidemics? The research on this issue can be broken down into several smaller sub-questions: (1) How to integrate cross-industry, cross-region, and cross-domain epidemic big data information into one systemic framework to fully resolve the deficiencies in disjointed structures, management, and channels? (2) In epidemic prevention and control, what are the differences in demand for information and data among different subjects? How to promote the sharing of information resources and cooperative governance among multiple subjects to avoid the phenomenon of "information island"? (3) What are the practical applications of big data technology at different stages of the management of public health emergencies, from risk prevention, response and disposal to recovery and reconstruction? How to solve the problem that technological development is out of step with real needs?

3. Method and data

3.1. Methodology

The grounded theory originated in the field of sociology and is a scientific qualitative research method first proposed by sociologists Glaser and Strauss to address current scholars' doubts about positivism, and was initially applied to the treatment of dying patients by hospital medical staff. This method collects first-hand materials and data, abstracts and conceptualizes them, and then analyzes, compares, and summarizes them from top to bottom, so as to extract concepts and categories, and deduce and infer the research theory on this basis. In order to make the research theory more representative, the grounded theory research method requires the researcher to be highly sensitive to the data, and the data text must be comprehensive, authentic, and representative.

It is applicable and feasible to apply the grounded theory research method to the study of the construction of big data prevention and control model for public health emergencies. (1) Applicability, first of all, the research object of this paper is "prevention and control of public health emergencies," because the development of epidemics is influenced by many factors from risk prevention, response and disposal to recovery and reconstruction, and the analysis of it needs to be based on the repeated comparison, verification, and generalization of a large amount of textual data. As a more advanced method in qualitative research, the grounded theory is suitable for this research. Secondly, the grounded theory provides a scientific research method to construct theories and discover mechanisms. The spread of public health emergencies is essentially a problem induced by the evolution of spatial and temporal processes, and in this evolutionary process, epidemic data are generally widely distributed and collected through scattered channels, etc. The ability of the grounded theory to explore hidden information and to conceptualize and analyze it is a great advantage in this research. (2) Feasibility, the research on the construction of big data prevention and control model for public health emergencies is rooted in realistic case texts and scientific theoretical achievements, which can effectively avoid the undesirable situation that theory is seriously detached from practice. In addition, the core of the grounded theory lies in the coding and deepening of the original data layer by layer, and it values the study of data. In today's era of big data of information explosion, government, medical institutions, enterprises, media, the public, and other subjects will report a lot of information on epidemic prevention and control, and the information needed for the study is abundant and easy to obtain, so it is feasible to use the grounded theory to study this topic.

The research process based on the grounded theory includes the following steps (29, 30): (1) Determine the research topic, collect primary data purposefully through data survey and literature reading, and eliminate irrelevant data on the basis of ensuring the completeness and comprehensiveness of the data. (2) Data coding is performed on the primary data, concepts are generated from the data through coding, and relevant links between concepts are established to derive theories. The coding process includes open coding, axial coding, and selective coding. (3) Carry out a theoretical saturation test, and the conclusions are generally considered to be theoretically saturated if no new categories can be formed from the original data. (4) Build a theoretical model, and strive for a high degree of integration between the model and its application. This paper analyzes the data with the help of Nvivo 12 software in the process of data sorting and coding. The research process is shown in Figure 1.

3.2. Data sources

Since literature reading is one of the important ways to source data in qualitative research, this paper used "public health," "big data" and "epidemic prevention and control" as keywords to search relevant literature from CNKI, preliminarily selecting 256 papers. After reading and screening the papers one by one, 185 papers with strong relevance were selected as the analysis samples by eliminating the duplicate papers and those with low relevance. In addition, through various channels such as the Chinese General Legal Knowledge Resources Database, Chinese government websites, and the laws and regulations database of Peking University, "medical and health big data" "health science and technology innovation" "Internet medical" as keywords, the search time span was up to January 2022, and the search scope included various policies and measures, regulations, rules, laws and decrees promulgated by the central government (State Council, ministries and commissions) as well as local governments. Initially, 105 policies were selected, and 84 materials were finally screened out by eliminating those policies that were not highly relevant or had lapsed, as shown in Figure 2. The selection of the above textual data was based on the principles of openness, authority, and relevance to ensure the completeness and representativeness of the obtained data to the maximum extent.

4. Data coding and model construction

4.1. Open coding

Open coding is to gradually reduce the original data, get the initial concept and category, and determine the subordinate relationship between them, reflecting the connotation of the original data. In the open coding stage, the researchers are required to adhere to the principle of "believe everything and believe nothing," abandon personal perception and habitual thinking, and ensure the objectivity of the coding results.

In the open coding process, the first step is data decoding: multiple researchers conduct tag construction (here labeled by TX) and concept extraction (here labeled by EX) word by word. If there are differences of opinion, discuss and reach a consensus to eliminate the influence of personal bias on the research results as much as possible. Secondly, the concept categories are summarized by comparing the initial concepts obtained until no new concepts are extracted. Finally, the conceptual categories reflecting the same phenomena are expressed in a more abstract set of concepts, i.e., the initial category (labeled here with IX) is formed. Following this process a total of 251 labels were given in this study, resulting in 53 concepts and finally 36 initial categories, which are coded as shown in Table 1.

4.2. Axial coding

The process of 36 initial categories derived from open coding only ensures the objectivity of the data. The categories are relatively

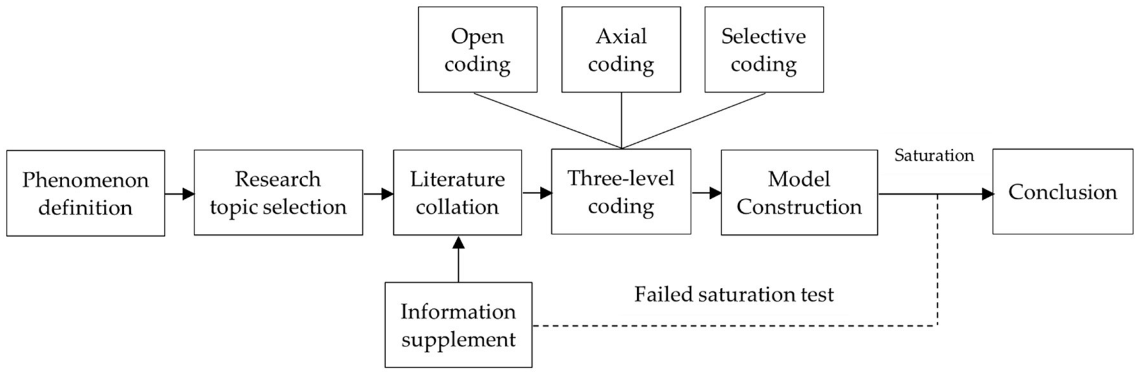

FIGURE 1
Research process based on grounded theory.

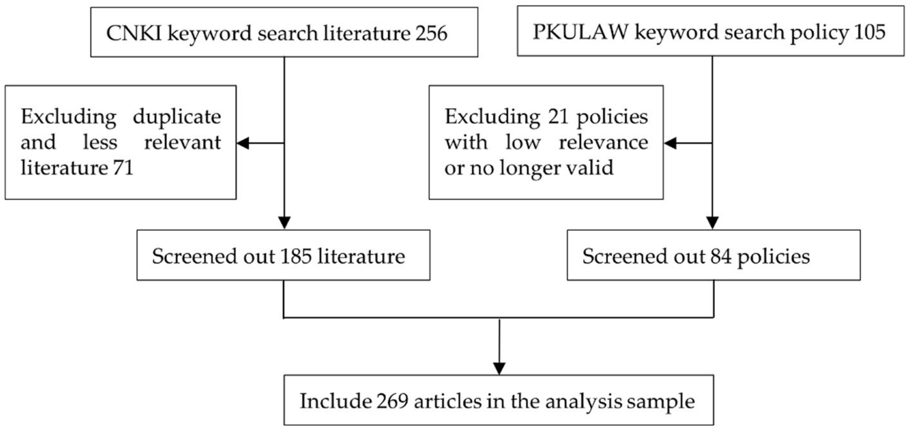

FIGURE 2
Literature and policy text rooting data sources.

independent of each other and difficult to establish connections, so the second step is to perform axial coding. Spindle coding, also known as secondary coding, is a process of further classifying, condensing, and refining the initial categories obtained in open coding. Its main task is to find and establish the relationship between categories, so as to develop the main category and sub-category and complete the transition stage from empirical description to abstract analysis. In axial coding, it should not be limited to the concept category formed by open coding. It is equally important to keep the openness of data and thinking at this stage. Eight main categories are finally summarized through axial coding and coded as MX, which are subject classification, subject information demand, multi-subject collaboration, data type, data value-added, incubation period, outbreak period, and recovery period, as shown in Table 2.

4.3. Selective coding and model construction

By clarifying the association paths between the main categories and the initial categories, the selective coding further abstracts and connotes the main category obtained in the secondary coding, so as to mine and form a leading core category, and finally build a grounded theoretical model that can cover all data. In the process of selecting the core categories, the following principles should be followed: (1) It should cover all phenomena and have more complete and subtle features compared with the main categories. (2) It should be selected based on the category with the highest frequency in the original data. (3) It has connections with all other categories and can be verified with data. (4) It can be developed to form a storyline, and its emergence and development are regular. Through continuous comparative research based on the above principles, the core categories are as follows: "data type" and "data value-added" are the underlying logic of the construction of big data prevention and control model for public health emergencies. These two categories are based on data, so they can be grouped into the core category of "data layer." As the users of data, "subject classification," "subject information demand" and "multi-subject collaboration" promote the digital prevention and control of epidemics, these three main categories can be refined into the core category of "subject layer;" The "incubation period," "outbreak period," and "recovery period" are the key stages of epidemic evolution, and the subjects must closely

TABLE 1 Open coding preliminary categorization.

Tag construction	Concept extraction	Initial category
T_1 Data technology	E_1 Epidemic type	I_1 Government
T_2 Data drive	E_2 epidemic hazard	I_2 Health care big data
T_3 Data environment	E_3 Epidemic scope	I_3 Healthcare resource
T_4 Public data	E_4 Clinical treatment	I_4 Path prediction
T_5 Data openness	E_5 Web crawler	I_5 Data collection
T_6 Data information	E_6 Browse records	I_6 Close contact screening
T... Data standards	E... Health record	I... Data analysis
Data classification	Community epidemic	Risk perception
Big data era	Population migration	Epidemic big data
Multi-source data	Vaccine development	Medical institutions
Data sharing	API interface	Epidemic monitoring
Data center	Vacancy filling	Media
Massive data	Standard treatment	Epidemic traceability
SEIR model	Epidemic evolution	Intelligent medical
Emergency response	Correlation analysis	Clinical data
Database building	Data interpretation	Government big data
Questionnaire system	CDC	Platform data set
Secondary disaster	Research institutes	Program optimization
Epidemiology	Sina Weibo	Information authenticity
Close coordination	Planning coordination	Helping to resume work
Regional distribution	Virus traceability	Visual display
Transmission trends	Isolation and treatment	Medical treatment
Viral variation	Behavioral motivation	Data collaboration
Ecology	Internet consultation	Public
Biogeography	Online drug purchase	Decision collaboration
Pathogens	Regional joint defense	Enterprises
Matrix	Negotiation decision	Epidemic warning
Rodents	Wrong decision	Goal coordination
Reverse tracing	Risk monitoring	Internet big data
Corporate interest	Misdiagnosis	Infected person tracing
Guided care	Treatment pressure	Data processing
Sterilization	Information sharing	Global needs
Relationship graph	Health education	Drug R&D
Education system	Big data profiling	Information timeliness
Place of visit inquiry	Mental health	Government interaction
Analysis report	Knowledge update	I_{36} Information source
Face recognition	Integrity analysis	
Infrared imaging	...	
Posture recognition	E_{53} Lessons learned	
Resumption of work		
...		
T_{251} Online office		

integrate with the application scenarios when using data, so these three main categories can be condensed into the core category of "application layer." In summary, the core problem of this paper can be summarized as the event trail of the "data layer-subject layer-application layer" and formed into a theoretical model, as shown in Figure 3.

4.4. Saturation test

Theoretical saturation test refers to the process of stopping data collection and three-level coding of pre-reserved data to test whether the coding results obtained before are accurate when new concepts or categories cannot be found in the process of data analysis. The purpose of the saturation test includes the following two aspects: (1) To ensure the accuracy and credibility of the coding results and to eliminate the interference of human factors in coding to the maximum extent possible. (2) To ensure that the theoretical model obtained from the exploration has high validity. In this study, 50 research literature and policies were reserved as the data text for the saturation test (the 50 texts were randomly selected from the original data before the study started). Also, the procedure was the same as that for the theory construction in the paper–open coding, axial coding, and selective coding were performed on the text. The final 45 initial concepts can be obtained from the 53 previously constructed concepts, and no new concepts are found; After categorizing the 45 initial concepts, 35 initial categories are obtained. Except that the category of "prevention and control scheme optimization" does not appear, other categories can be found in the previous 36 categories; After axial coding of 45 initial categories, 8 main categories were obtained, and no new categories were mined, and the core categories obtained in the next step were the same. Therefore, it can be determined that the "big data prevention and control model for public health emergencies" constructed in this paper is theoretically saturated.

5. Interpretation of model content

Through the modeling and saturation test of the grounded theory, this study found that the three elements of "data-subject-application" play a prominent role in the digital prevention and control practice of epidemics, and constitute the basic framework of the model, so the model is referred to as the "DSA" model of big data prevention and control of public health emergencies. In order to make the results of model construction clearer and more comprehensive, the model is specifically explained as follows.

5.1. The data layer

This part mainly includes four aspects of data collection, processing, analysis, and visualization. The main task is to realize the value-added process of data–by carrying out a series of tasks on multi-source big data information closely related to the epidemic, fully extracting valuable information, opening up cross-border information integration channels, realizing the circulation

TABLE 2 Axial coding forms the main category.

Main category	Corresponding category
M_1 Subject classification	I_1 Government; I_{10} Medical institutions; I_{26} Enterprises; I_{12} Media; I_{24} Public
M_2 Subject information demand	I_{32} Global needs; I_{15} Clinical data; I_3 Healthcare resource; I_{17} Platform data set; I_{36} Information source; I_{19} Information authenticity; I_{34} Information timeliness; I_8 Risk perception; I_{22} Medical treatment
M_3 Multi-subject collaboration	I_{23} Data collaboration; I_{28} Goal coordination; I_{25} Decision collaboration
M_4 Data type	I_9 Epidemic big data; I_2 Health Care big data; I_{16} Government big data; I_{29} Internet big data
M_5 Data value-added	I_5 Data collection; I_{31} Data processing; I_7 Data analysis; I_{21} Visual display
M_6 Incubation period	I_{11} Epidemic monitoring; I_{27} Epidemic warning
M_7 Outbreak period	I_{13} Epidemic traceability; I_4 Path prediction; I_{30} Infected person tracing; I_6 Close contact screening; I_{14} Intelligent medical; I_{33} Drug R&D
M_8 Recovery period	I_{20} Helping to resume work; I_{35} Government interaction; I_{18} Program optimization

of information among multiple subjects and preparing for the effective control and prevention of the epidemic (31).

From the perspective of data sources, some data such as social media, drug sales, search engines, electricity consumption, etc. do not appear to contain too much information related to the epidemic, and cannot replace clinical data as the mainstream. However, if these structured and unstructured data are combined through correlation analysis and refined using tools, it will be found that they not only have advantages in terms of data availability, but also reflect a picture that is more referential and valuable than clinical data. Referring to the views on data types put forward by scholars such as Fang (32), Liu (33), Wu (34), and Costa (35), this paper divides the data sources involved in public health emergencies into the following categories. First, the epidemic big data, such as the type, scope, level, hazard, etc. of infectious diseases. Second, the medical and healthcare big data, mainly including clinical treatment, pharmaceutical research and development, personal electronic health records, etc. Third, the government's open and public big data, mainly including population migration, community, traffic, environment, etc. Fourth, the internet big data, generally coming from public platforms such as social media, in addition to some information provided by the active participation of users, web browsing records, travel data, transaction data, etc. These data generated by individuals when using mobile phones may also become "passive" collection sources.

Data is usually collected through a combination of big data technology and traditional manual methods. With the main method of big data such as docking API interface, web crawler, and direct network transmission, the data from multiple departments such as municipal, health, telecommunication, and transportation are unified into a regional epidemic prevention and control analysis platform to realize real-time data collection and access, enrich data samples and improve collection efficiency. It is supplemented by traditional manual collection, which effectively avoids the problem of data limitations caused by too many blind spots in the network, and minimizes the "pseudo-big data phenomenon" caused by the "observer effect" and its negative effects using rational thinking and judgment of human beings.

Data processing is the process of improving data quality using methods such as cleaning, filling in vacancy values, and standardization. The most intuitive change brought by the convergence of data from multiple sectors is the expansion of data capacity and diversification of structure, which brings serious challenges to the data processing work. Therefore, the data format must be unified to achieve the integration of heterogeneous epidemic data from multiple sources. Natural language processing, semantic association, and other technologies can be fully used to automatically check and verify logical errors, content fragmentation, duplicate reporting and other issues to ensure data availability.

Data analysis is the core of the whole big data processing process, mainly including epidemic information relevance analysis, subject sentiment tendency analysis, and epidemic evolution prediction, etc. It works by converting multi-source data into mathematical models according to industry logic for business requirements, so that the machine can automatically output the results according to the algorithm requirements to meet decision-making needs (36, 37). Accordingly, data modeling to support business decision-making is the essence of data analytics, which also determines that the way of thinking must be transformed from causal analysis to knowledge discovery, from logical reasoning to association rulemaking, and from empirical judgment to deep processing of model fitting.

The visual display is the final result based on a comprehensive grasp of epidemic big data information, the core of which is to enhance data interpretation capabilities and avoid misleading people. It is generally presented visually in the form of charts and graphs to strengthen the effect of information reporting to relevant decision-makers so that they can understand the real-time development of the epidemic situation in a clear, accurate, and timely manner. For example, the heat map is an intuitive presentation based on visualization technology, which integrates information on geographical location, population flow, and group behavior of public health emergencies. The heat map significantly reduces the cognitive threshold of complex data for decision-makers so that they can participate in epidemic prevention and control work to the greatest extent.

Through the above analysis of the value-added process of big data in the management of public health emergencies, it can be found that its essence is to "extend" the tools of human cognition and exploration of the unknown with the support of data and algorithms, and gradually change people's working methods while solving the epidemic prevention and control problems. The collection, processing, and analysis of information by big data is a

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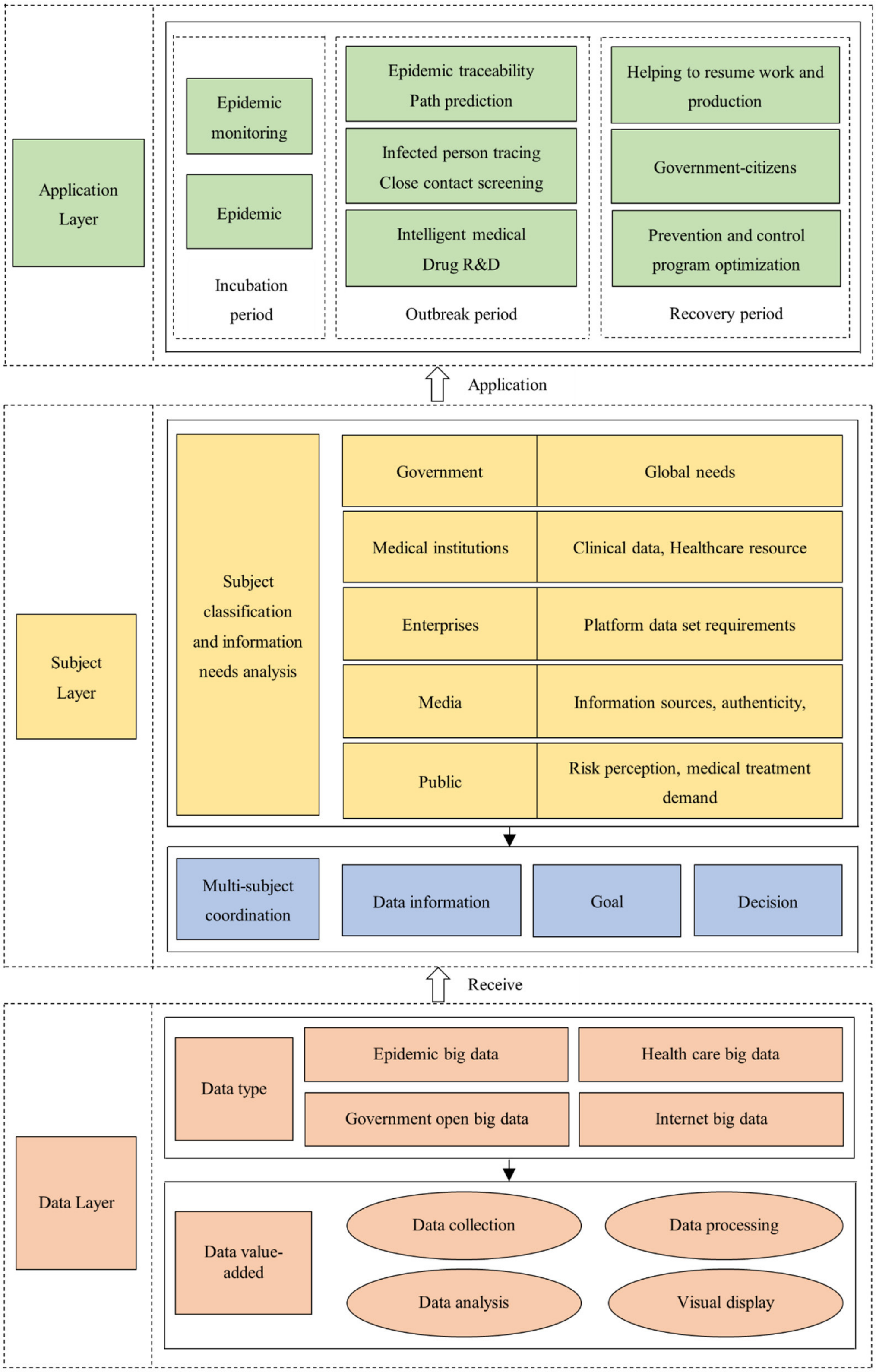

FIGURE 3
The "DSA" model of big data prevention and control of public health emergencies.

necessary path of technology development, and data will certainly play an important role as "blood" in the actual epidemic prevention and control applications. This means that to enjoy intelligent and informative services, people must transfer their information as a prerequisite. Therefore, the use of big data technology to help prevent and control epidemics while taking into account data security and personal privacy protection, so as to give full play to the real value and positive effects of big data technology, should become a key issue for research.

5.2. The subject layer

The main task of this part is to promote consensus among multiple subjects on collaborative management of epidemics based on the access to multi-source big data information by epidemic prevention and control subjects according to their needs, and realize all-round and seamless governance through communication, cooperation, and grid-based integration.

5.2.1. Subject classification and their needs analysis

Participants in epidemic management mainly include the government, medical institutions, enterprises, media, and the public. Participants' needs in the epidemic response process can both reflect the selection preferences of the public and drive the steady improvement of the epidemic prevention and control work. The government assumes the overall planning and coordination function in response to public health emergencies, and its main task is to effectively integrate the interests and resources of all parties and establish a cooperative and complementary relationship among all subjects, forming a compound governance model of risk-sharing and coexistence under government leadership. On the one hand, we need to enable accurate prevention of emergencies and send out monitoring and warning signals. On the other hand, it needs to respond quickly to effectively control the spread of the epidemic. In addition, it has the unshirkable responsibility for the effective allocation of resources and the recovery and reconstruction after the epidemic. Therefore, in epidemic prevention and control, the government's demand for data and information is global, and runs through the incubation, outbreak, and recovery periods of the epidemic.

Medical institutions, including hospitals, CDCs, medical research institutes, etc. are mainly responsible of the isolation and treatment of patients, virus origin-tracing, transmission cause analysis, and diagnosis plan selection, which are of great significance to epidemic early warning, situation assessment, and crisis decision-making. The needs of medical institutions for data and information include medical network resources, epidemic prevention observation data, patient clinical data, disease diagnosis case base, etc. For example, according to the data of suspected and confirmed cases in a certain area, the demand for medical supplies can be accurately grasped. Combined with the growth rate of confirmed patients and epidemiological regularity, the scale of the potentially infected population can be described to determine the emergency response level of the epidemic.

Enterprises including Alibaba, Sina, Baidu, etc., can obtain abundant Internet data based on huge user groups. For example, Baidu Maps can accurately grasp the migration status of population flow through personal positioning. Sina Weibo can timely send epidemic warning signals through the frequency of user searches and information interaction feedback. It can be seen that the demand of enterprises for data information is "a platform data set that can fully reflect public opinion and needs based on public behavior and motivation." Companies track and analyze the real-time data obtained from the platform, and then provide society with products and services that are more targeted, more practical, and more satisfying to the needs of the public.

Media are the mouthpiece of government departments. Their objective, accurate and timely reporting of epidemic information can effectively satisfy the public's extreme desire for information due to panic and blind obedience, and nip negative public opinion in the bud or reduce its negative impact. The media's demands for data and information are mainly manifested in the following aspects. First, is the need for information sources, as the "gatekeeper" for selective dissemination of events, the media has a strong guiding power over the immediate reaction of the public to receive information, and it is crucial for the media to grasp first-hand information on time. Second, the demand for information authenticity. Revealing the truth, reflecting the reality of the problem, and correctly guiding public opinion are the responsibilities of the media, which requires the media to have a precise command of events in terms of authenticity. Third, the demand for timeliness of the information. The delay of information disclosure or information disclosure without a considered order will make it difficult for the public to distinguish the authenticity of the information, making the situation worse.

The public is the smallest unit in response to public health emergencies, and also the "basic statistical population" of most of the epidemic big data information, such as communication data, consumer behavior data, traffic data, etc. The behaviors of each member of the public have a significant impact on epidemic prevention and control. The public's demand for data information mainly includes two aspects. Risk perception is most important the public needs to know information about the spread of the epidemic, patient treatment and severity, and then perceive the risk of public health emergencies to take appropriate preventive measures. The second is the demand for information on medical treatment and materials, including hospitals designated for medical treatment, online consultation, contactless drug purchase, etc.

5.2.2. Coordination and cooperation of multiple subjects

To effectively respond to COVID-19, China has established a joint prevention and control mechanism under the State Council, which is vertically classified into three levels of national, provincial, and local, and sets up a horizontal organization structure, including working groups for medical treatment, scientific research, epidemic prevention and control, logistics material support, and publicity. The work was both relatively independent and managed centrally to form an effective synergy force for epidemic prevention and control (38). The mechanism emphasizes three synergies between organizations:

1. Data and information synergy. The information sources and analysis of a single subject often have great limitations, so an information platform for public health emergencies should be built to share epidemic information and break the barrier of information sharing to the maximum.

2. Goal coordination. The division of professional functions of different subjects determines the difference in their goals, and the divergence of goals triggers behavioral conflicts and buck-passing. Therefore, goal consistency is the core element for multiple subjects participating in epidemic prevention and control.

3. Decision-making coordination (39). Decision-making coordination is a "consultative" decision-making process that requires coordination, communication, negotiation, and compromise among multiple organizations. In this way, arbitrary could be avoided, and problems of centralized power and conflicting functions could be alleviated.

5.3. The application layer

Big data must be combined with specific application scenarios to realize its full value (40). Based on various models of epidemic evolution at home and abroad, this paper divides the evolution of public health emergencies into three stages: the incubation period, the outbreak period, and the recovery period. The following analyzes the main application scenarios of big data in the three stages of epidemic development to fully demonstrate the specific role of big data.

5.3.1. The incubation period

This phase focuses on epidemic awareness, both monitoring and early warning–through the analysis of epidemic characteristics, information needs of multiple subjects targeted collection of various types of epidemic data, the use of multi-source information to do the corresponding monitoring of the global situation. When the monitoring results exceed the preset threshold, early warning signals shall be sent to relevant departments and the public in time, to realize "prevention first."

5.3.1.1. Epidemic surveillance based on internet big data

Internet big data refers to the traces left by individuals when using the Internet. Internet big data related to public health mainly includes information shared on social networking platforms, information recorded by search engines, and information reported by news media. The reason why these multiple sources of information can be used for epidemic risk monitoring is based on a common premise: not all patients will go to hospitals for checkups when infectious diseases are prevalent, and some of them will look up information through the Internet to seek help. Therefore, one may capture and track these data (e.g., keyword frequency statistics) to predict disease incidence. For example, foreign social platforms such as Twitter and Facebook, as well as domestic Weibo and WeChat can analyze the spatial clusters of health and disease-related content and use this "aggregated intelligence" to assist in epidemic monitoring; In 2009, the Google search engine successfully predicted the outbreak of influenza by analyzing the total search volume and frequency of keywords in a specific region, and its influenza information reports were released more than a week earlier than the Centers for Disease Control (CDC) in the United States (41). The Global Public Health Intelligence Network (GPHIN), established by the World Health Organization, links more than 3,000 news sources in nine languages around the world in an aggregator to identify public health threats in a timely manner through real-time translation and data processing (42).

5.3.1.2. Epidemic surveillance based on medical and health big data

The monitoring of epidemics by medical and health big data is mainly realized through citizen behavior and symptom monitoring, among which drug retail data and health electronic records data provide the main support for epidemic monitoring. Drug retail data (respiratory and intestinal drugs, antiviral drugs, cold drugs, etc.) can reflect the occurrence of diseases to a certain extent, and have significant advantages in terms of geographical location identification and early warning timeliness. It has been shown that sales of antiviral drugs are closely related to the total number of confirmed cases of influenza, and sales of thermometers and hand sanitizers are also significantly associated with influenza cases (43). Based on this, the UK has begun to use OTC sales records for monitoring the spatial and temporal patterns of influenza activity. The convergence of data on cases, clinical diagnoses, and treatment outcomes recorded in electronic health records can effectively help build epidemiological analysis models, detect abnormal aggregations of infectious diseases in time and space, and improve the sensitivity to new diseases and explosive epidemic situations.

5.3.1.3. Precise information pushing early warning based on big data technology

The early warning of public health emergencies is based on monitoring. When the monitoring results exceed the preset threshold, it is crucial to deliver the early warning information to the relevant emergency management departments and the public in time (44). Unlike ordinary emergencies, public health events have group differences in the immunity of the public to viruses due to the biological characteristics of viruses (e.g., the elderly, the weak, the sick, the disabled, the young, and women, etc.), which puts forward new requirements for the accuracy of information delivery. The information pushes warnings based on big data following the thinking of "let the information find the user" and has the characteristics of "target user accuracy," "user acquisition timeliness," "information and user demand consistency," etc. It relies on user identification, automatic recording, information retrieval, and other technologies to understand different users' immediate and potential needs, and realizes personalized information delivery through the Internet, social networking platforms, broadcasting, mobile communication, and other channels. For example, with the help of Internet social platforms such as Tencent and Sina, information containing early warning signals is broadcasted on a rolling basis in the user interface of specific regions to achieve zero error and full coverage of early warning.

5.3.2. The outbreak period

The focus of this phase is on epidemic response, collecting and analyzing epidemic-related information, and assessing the type, level, region, and possible hazards of the outbreak, while tracking the epidemic process and intervening in a timely manner to reduce negative impacts and losses.

5.3.2.1. Epidemic traceability and transmission path prediction based on big data

By deeply integrating medical data, Internet data, and open government data, big data technology can realize the interconnection between social reality and epidemic development, which helps trace the epidemic's source and predict the transmission path. Based on daily case statistics, statistical models can be built with the help of machine learning and correlation analysis technologies on medical admissions, regional distribution, regulatory isolation, etc. The models can not only retrace the trend of the spread of the epidemic to locate its source, but also provide an important scientific basis for predicting the spreading path of the epidemic. For example, the European CDC and the Umea University in Sweden used data such as Twitter, climate change, the estimated number of Aedes albopictus mosquitoes, and international air passenger traffic to build a big data model to successfully project the origin and spreading path of the 2017 Chikungunya virus outbreak in Europe (45). Xumao Zhao and other scholars from Lanzhou University successfully used big data to retrace the trend of virus spread at the early stage of the outbreak of COVID-19. They concluded that "the population exported from Wuhan is the main threat to the spread of COVID-19 in China" (46).

5.3.2.2. Infected person tracking and close contact screening based on big data

Accurate identification and timely isolation of infected persons and close contacts is a key link to contain the further spread of the epidemic. Traditionally, manual investigation (household interviews, questionnaires, etc.) is mainly used to accomplish this, which has shortcomings in terms of cost, efficiency and accuracy, and may miss the best time for epidemic prevention and control. The ubiquitous network and intelligent sensing technology based on big data can track population flow, individual relationship mapping, facility environment, etc. in real-time, and accurately locate infected persons and close contacts. Through the comprehensive application of temperature-sensing camera and public security face database, combined with the recognition of physical features by multi-modal algorithm, body temperature data collection can be completed within 2 m and matched with identity information quickly. Once a fever patient is found, an alarm signal will be issued automatically to realize the "carpet" investigation of suspected cases. In addition, with the help of telecommunications big data, migration big data, e-billing and other information, correlation analysis and social network distance measurement can provide users with "14 days to visit the place of inquiry" service, so as to quickly screen close contacts and take isolation and treatment measures. For example, the "green, yellow, and red" three-color health code, which is widely used during the prevention and control of COVID-19, is generated by using big data to quantify the three dimensions of time, space, and interpersonal relationships.

5.3.2.3. Intelligent medical and drug R&D based on big data

Currently, the most typical application in the field of intelligent medical applications empowered by big data is none other than medical image analysis (13, 47). The diagnosis of COVID-19 mainly relies on chest CT images and nucleic acid detection. However, the traditional manual reading mode is far from satisfying the consultation needs of many patients, which leads to misdiagnosis and omission and is also challenged by insufficient medical staff. The wide application of image recognition technology based on convolutional neural networks in the medical field has effectively solved this problem. The technology is based on big data deep learning algorithms, which automatically construct pattern recognition by repeatedly training the machine with medical images, greatly reducing the pressure on the medical staff. For example, the COVID-19 AI-assisted diagnosis system created by Alibaba Cloud Computing can handle a case in 20 s on average, which is 50 times faster than doctors. In drug research and development, the new drugs go through a series of processes such as drug screening, pharmacological analysis, and safety testing, which require extremely high economic and time costs, and the use of big data-based evaluation networks and Monte Carlo Tree Search algorithms (MCTS) (48) can effectively alleviate this problem by selecting the safest from tens of thousands of compounds as the best alternative for new drugs.

5.3.3. The recovery period

In the recovery stage, the epidemic is effectively controlled, and the affected areas and people's lives begin to recover orderly. The focus of this phase is to sort out, evaluate, and analyze the information on the whole process of the epidemic, propose recovery and reconstruction plans, and at the same time summarize the experience of epidemic prevention and control to provide theoretical guidance for future related work.

5.3.3.1. Big data helps enterprises to resume work and production

Big data can guide relevant departments to resume production and economic restart plans. On the one hand, through the construction of algorithmic models and data-sharing platforms, it can make forward-looking predictions on the trend of the epidemic and distribution of high-risk areas, and determine whether a series of emergency response measures for the epidemic can be lifted, so as to provide scientific support for relevant decision-making. For example, the big data platform of "Resumption of Work and Production Analysis" built by the Tianjin Municipal Tax Service has established a real-time data sharing mechanism with 18 departments, including the Municipal Government, the Municipal Finance Bureau, the Municipal Bureau Statistics, the Municipal Commission of Housing and Urban-Rural Development, and the Administration for Market Regulation, and has shared up to 6 million pieces of data, which provides strong support for the work according to local conditions (49). On the other hand, the full exploration and application of big data on electricity can assist the government in applying early intervention and dynamic management to the company that resumes work and production. Taking the average daily power consumption of enterprises during the outbreak of the epidemic as the basic data and the fluctuation of the average daily electricity consumption as the focus point (focusing on enterprises with electricity consumption growth rate above 100%), combined with the model calculation, the "big data portrait" of enterprises in the city can be constructed to realize the accurate control of the dynamics of enterprises' resumption of work and production.

5.3.3.2. Big data promotes government-public interaction and epidemic prevention and control program optimization

In the recovery phase of the epidemic, the public is easily misled by inaccurate statements, which may induce secondary and derivative hazards of the epidemic, so it is essential to strengthen the construction of public mental health. Big data can analyze the behavior of netizens and information dissemination rules, and carry out intelligent government-public interaction based on a full understanding of the real needs of the public, to deliver timely and accurate information about the disposal of the epidemic and follow-up plans to the public, and nip the negative public opinion caused by rumors in the cradle. In addition, the virtual simulation technology based on big data can digitally reproduce the whole picture of the development of the epidemic, help the relevant departments to make systematic summaries of the causes, losses, and lessons learned from the outbreak, and realize the optimization of the epidemic prevention and control plan and the update of the historical case knowledge base.

6. Discussion

The essence of the "DSA" model for big data prevention and control of public health emergencies is a comprehensive body integrating "data acquisition and analysis," "subject demand analysis and collaboration," and "phased application of big data" with the goal of realizing intelligent, collaborative, and efficient epidemic control. Undeniably, there may be some shortcomings in this study. First, this paper is limited to a theoretical discussion. Collecting real data from public health emergencies, verifying, and improving the model will be the main work in the next stage. Second, this study attempts to explore and construct the "DSA" model from the data-subject-application multiple perspectives. However, there are many factors affecting the management of public health emergencies, such as national policy guidance, regional differences in epidemic prevention and control, virus types and transmission capacity, etc., all of which point out the direction of efforts for future work. Third, the selection of data samples in the construction of the DSA model is based on the policy texts and academic studies issued in China, which inevitably brings the question of whether the model is universal and representative in the international arena. Therefore, how to use big data technology to help prevent and control epidemics while taking into account the basic conditions of most countries in the international community is also the focus of the next research.

In addition, future research will focus on preventing "data leakage and privacy violation," because the construction of the "DSA" model relies on big data technology, whether it is high precision mining, full sample collection, or high rule association and full data analysis, it cannot escape the fetters of "privacy protection" and "analysis bias." For example, while enterprises use big data technology to provide intelligent services for epidemic prevention and control, it also poses a huge challenge to the protection of personal privacy: by collecting and linking the data footprints left by people on the Internet into a complete information chain, it is possible to draw some conclusions related to personal privacy, which can be used by criminals to commit fraud and bring economic losses or mental distress to individuals. In order to effectively respond to the challenges facing personal information protection, China has successively introduced laws and regulations such as the *Decision on Strengthening the Protection of Network Information*, the *Cybersecurity Law of the People's Republic of China*, and the *Civil Code of the People's Republic of China*, which clearly stipulate the basic principles of personal information processing activities and significantly enhance the protection of personal information. For example, there is no problem with collecting personal information on the whereabouts of individuals by scanning the "health code" in the context of epidemic prevention and control, but if the information is used to obtain further information on personal consumption preferences, home addresses or even resold to others, it involves the excessive collection and illegal leakage. Therefore, although we expect the full use of big data to bring its value into play, we cannot rely on it entirely. We must keep a clear head and think rationally in the wave of big data, use it as an effective tool rather than the ultimate means, and continue to promote fundamental changes in the governance mode of public health emergencies by increasing the depth of data and information intervention.

7. Conclusions

Public health emergencies are usually complex and long-term. The traditional response and disposal mode has been difficult to meet the practical needs of the prevention and control of various new infectious diseases. There is an urgent need to introduce the emerging technology group represented by big data, to achieve significant innovation in the concept, thinking, and technology related to prevention and control. Compared with existing research, the strength of this study lies in the construction of a generic model of big data prevention and control based on a holistic perspective and applicable to different stages and spatial scales. Based on the collection of real-time data, the model processes and obtains accurate information on the risk of public health emergencies to assist government departments in prediction and early warning, emergency response and control, decision-making and implementation, and recovery and reconstruction activities, to achieve effective control of public health emergencies. From the perspective of structure, the model includes three parts: data information source, subject's demand for data, and data application, and has the characteristics of real-time, accuracy, and purposefulness.

This paper conducts an exploratory study on the construction of a big data prevention and control model for public health emergencies by using grounded theory, a qualitative research method, with literature, policies, and regulations as research samples, and makes a grounded analysis through three-level coding and saturation test. The main results are as follows:

(1) This paper constructs a "DSA" model for the prevention and control of public health emergencies from the data layer, subject layer, and application layer to comprehensively reflect the interaction of different elements in the epidemic, to assist the government in making appropriate decisions and policy adjustments, integrating prevention and control measures, and promoting rapid economic growth and recovery.

(2) The "data layer" module of the DSA model integrates the automated collection, standardized processing, intelligent analysis, and visualization of data from multiple sources to build a basic data warehouse, integrating cross-industry, cross-region, and cross-domain information of the epidemic into one systematic framework, which facilitates information collection, communication, and transmission channels and enhances the timeliness and integrity of public health information.

(3) The "subject layer" module of the DSA model provides a comprehensive analysis of the differences in information needs of multiple subjects such as government, medical institutions, enterprises, media, and the public during the epidemic outbreak. The government's demand for data and information is global. The needs of medical institutions include medical network resources, epidemic prevention observation data, patient clinical data, and disease diagnosis case base. The needs of enterprises are "a platform data set that can fully reflect public opinion and needs based on public behavior and motivation." The needs of the media include information sources, information authenticity, and information timeliness. The needs of the public include risk perception and medical treatment.

(4) The "application layer" module of the DSA model analyzes the application scenarios of big data technology in different stages of the "incubation period, outbreak period, and recovery period" of the epidemic development. In the incubation period, the main applications are epidemic monitoring and accurate information delivery. In the outbreak period, the main applications are epidemic tracing and transmission path prediction, infected person tracking and close contact screening, and intelligent medical and drug R&D. In the recovery period, the main applications are helping enterprises to resume work and production, promoting government-public interaction, and epidemic prevention and control plan optimization. These applications put macro policy initiatives into practice and contribute to the prevention and control of epidemics, effectively responding to the disconnection between current technological development and real demand.

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

Conceptualization and writing—original draft preparation: HW and HY. Methodology: LL. Data curation: HY and LL. Writing—review and editing: HW, HY, and LL. All authors have read and agreed to the published version of the manuscript.

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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.

Publisher's note

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Transformation of chronic disease management: Before and after the COVID-19 outbreak

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Adults with chronic diseases often experience a decline in their quality of life along with frequent exacerbations. These diseases can cause anxiety and impose a significant economic burden. Self-management is a crucial aspect of treatment outside of the hospital and can improve quality of life and reduce the financial burden resulting from unexpected hospitalizations. With the COVID-19 pandemic, telehealth has become a vital tool for both medical professionals and patients; many in-person appointments have been canceled due to the pandemic, leading to increased reliance on online resources. This article aimed to discuss various methods of chronic disease management, both traditional self-management and modern telehealth strategies, comparing before and after the COVID-19 outbreak and highlighting challenges that have emerged.

KEYWORDS

COVID-19, chronic disease management, mobile health, telemedicine, technology-based education

1. Introduction

Chronic diseases such as hypertension, diabetes, and chronic obstructive pulmonary disease are major causes of disability worldwide. Almost one in three adults suffer from at least one chronic condition, and research has suggested that 16–57% of adults in developed countries suffer from multiple chronic conditions (1). Disease management, such as persistent monitoring of vital signs, screening of biomarkers, and lifestyle modification can reduce premature mortality from chronic diseases (2). Chronic disease management often requires a patient-professional partnership, including self-management education, which traditionally provides only information and technical skills; however, current self-management education offers problem-solving skills that emphasize the enhancement of self-efficacy, improved health outcomes, and reduced costs for patients (3).

After the global outbreak of the COVID-19 pandemic, patients with chronic diseases had difficulty attending outpatient meetings and, in some cases, needed to postpone or cancel follow-ups. In response, outpatient visits and meetings for patients have mainly been moved to telehealth platforms due to personal preferences and potential contagion risk (4). The COVID-19 pandemic and the need for social distancing have further accelerated the rapid shift to technology-enabled patient education and healthcare interactions. Despite the convenience and reduced cost of healthcare in the pandemic era, whether the use of telemedicine can be a complete substitute for face-to-face meetings is still questionable (Figure 1).

2. The burden of chronic diseases

2.1. Patients

Individuals with chronic diseases face physical and psychological inconveniences due to persistent symptoms. Chronic diseases have a major impact on patients' health-related quality of life and are associated with decreased function, increased mortality risk, and higher costs of personal medical care (5, 6). For individuals with low socioeconomic status, chronic diseases can be perceived as an extra burden and distraction in addition to poverty, social isolation, and poor education (7). Patients with chronic diseases often exhibit psychological symptoms, such as anxiety and depression, which have adverse effects on their conditions (8). Furthermore, interruptions in care and other challenges related to the COVID-19 pandemic may lead to poorer mental health outcomes in patients with chronic diseases (9).

2.2. Society

Chronic diseases impose a tremendous burden on society and the economy. It is estimated that by 2030, the total cost of chronic diseases in the United States will cumulatively exceed 42 trillion USD, with an additional 794 billion USD per year of losses resulting from the loss of employee productivity (10). Chronic diseases are responsible for the death of approximately 41 million people each year, accounting for 74% of global deaths (11). Several studies have also indicated that mortality rates of potentially preventable diseases (including chronic diseases) are higher in low- and middle-income countries than in those with high income (12, 13).

3. Traditional disease-specific chronic disease self-management intervention

3.1. Diabetes mellitus

Diabetes is a chronic disease that requires intervention, self-management, education, and support for patients to improve their daily quality of life and outcomes (14). According to the American Association of Diabetes Education, diabetes self-care can be divided into seven categories: healthy eating, being active, health monitoring, taking medication, problem-solving, healthy coping, and reducing risks (15). A study in the US showed that medical costs are about 2.3 times higher for patients who are diagnosed compared to those who are not (16). A randomized controlled trial conducted by Eroglu et al. (17) designed to evaluate the effect of diabetes self-management education among patients with type II diabetes reported that after a 6-month follow-up with an educational program, individuals in the intervention group had more controlled diabetes and higher scores for self-efficacy. The diabetes community has been and remains heavily impacted by the COVID-19 pandemic; a meta-analysis in China found that 9.7% of COVID-19 patients with coexisting diabetes had triple the risk of developing severe disease (18).

3.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a prevailing threat in modern society, mostly causing chronic cough, dyspnea, and exhaustion. It is ranked as the third leading cause of death worldwide and caused 3.23 million deaths in 2019 (19). A systematic review by

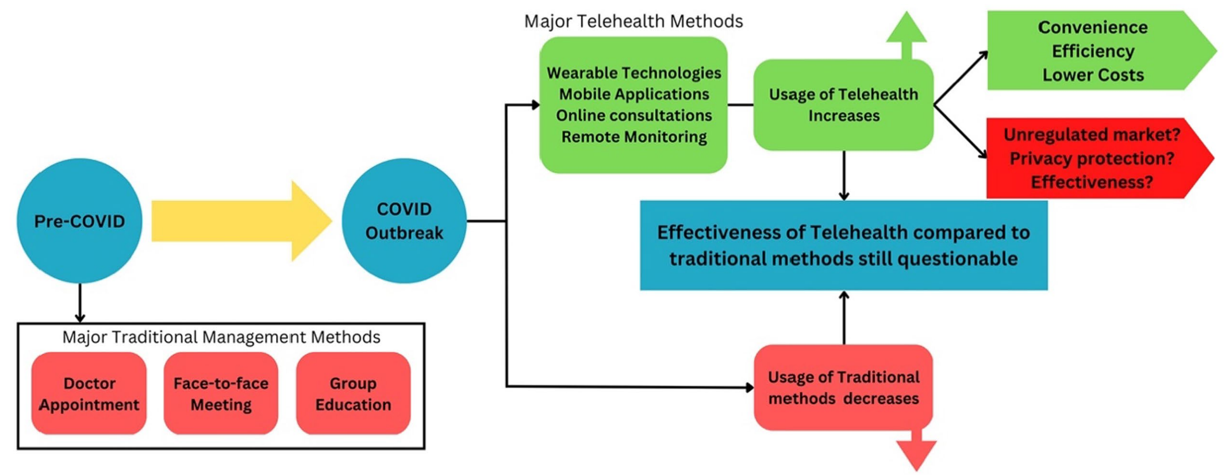

FIGURE 1
The shift of chronic disease management method after COVID-19 outbreak. Following the outbreak of COVID-19, there was a significant increase in the use of telehealth, which brought convenience and benefits to patients, but also raised several concerns, such as an unregulated market, privacy protection, and the effectiveness of telehealth. Simultaneously, the use of traditional chronic disease management methods has decreased significantly. Whether or not telehealth can truly replace traditional methods remains to be determined, in addition to the effectiveness of each approach.

Effing et al. summarized that COPD self-management programs can be categorized as either smoking cessation support, self-recognition and treatment of exacerbations, increased exercise, nutritional advice, or dyspnea management (20). For long-term impact and sustainability, education provided by professionals to patients, health care workers, and families is best to ensure enforcement and efficiency (21). Most education requires patients to attend face-to-face meetings and receive interventions. One beneficial therapeutic approach that can be used to assist in improving psychological and physical outcomes is cognitive-behavioral therapy (CBT), where patients work with therapists to exchange their thoughts and understanding of symptoms, mentality, and knowledge about the disease (20). Compared with usual care for COPD, intensive CBT has shown greater improvement in psychological and physical symptoms (22); however, cessation of non-pharmacological interventions, including rehabilitation, has become a dilemma for patients during the pandemic. Challenges that have emerged are whether or not the traditional algorithms of pharmacological management in COPD still work, as well as how pandemic-related limitations in non-pharmaceutical interventions can be overcome, as COVID-19 circulation increases healthcare utilization risk for these patients (23).

3.3. Cardiovascular diseases

Cardiovascular diseases (CVD) were the most common causes of death worldwide and led to almost 17.9 million deaths per year globally (24). The American Heart Association suggests that people undergo lifestyle changes to manage and prevent CVDs based on seven factors (Life's Simple 7): smoking status, physical activity, body weight, diet, blood glucose, cholesterol, and blood pressure (25). It is essential for potential and diagnosed CVD patients to receive self-management interventions, as the diseases could be present but remain asymptomatic for years. The most common self-management for CVD patients is introduced in segments of self-responsibility, health status recognition, diet, weight control, aerobic exercise, smoking cessation, alcohol consumption, and medication adherence (26). During the pandemic, diet management has faced problems in decreases in food security and nutrition provision, which are detrimental to vulnerable patients with CVD (27).

3.4. Cancer

Traditional cancer self-management programs are mainly derived from focus groups and adapted from other chronic disease management programs (28). Research on the use of self-management interventions in cancer care has grown tremendously over the past few decades, resulting in significant changes in symptom management assistance during treatment to address both physical symptoms and psychosocial distress (29). The PROSELF Pain Control Program (PSPC), a psychoeducational self-management program that aims to assist patients in managing cancer-related pain, promotes self-assessment of pain, appropriate use of analgesics, and self-dosing to prevent pain escalation, providing participants with improved management of pain and a lower pain intensity score (30).

Even though the specific vulnerability of cancer patients to COVID-19 has yet to be determined (31), cancer patients are still recommended to receive stronger protection and more intensive surveillance than the normal population (32).

4. Acceleration of telehealth development during the COVID-19 outbreak

4.1. Telehealth encouraged as face-to-face visits decrease

At the beginning of the pandemic, strict and inconsistent quarantine policies caused patients with chronic diseases to suffer from changed lifestyles and medical routines. A survey conducted in the United States indicated that more than half of patients with chronic conditions felt that their lifestyles and routines, including medical plans, had been altered significantly (33). In Belo Horizonte, a major city in Brazil, the hospitalization rate for patients with cardiovascular diseases decreased by 16.3% from March to December 2020 in contrast to expectations (34). Similarly, 17.7% of patients with chronic diseases who participated in a survey in Japan canceled their face-to-face visits and experienced a shortage of drugs in April and May of 2020 (35).

The enthusiasm for telehealth adoption from patients with chronic diseases has increased during the pandemic. Patients, especially older adults, are now willing to pay the same amount of money for online remote sessions as face-to-face sessions (36). McKinsey and Company conducted a study that indicated increased use of telemedicine in recent periods; telehealth usage rates jumped from 11% of United States consumer users in 2019 to 46% in May 2020. In April 2020, the movement from office visits and outpatient care to telehealth skyrocketed 78 times higher than that seen in February. Data also show that stabilization of telehealth utilization increased 38 times compared to before the pandemic (37). A cross-sectional study conducted at the Royal College of General Practitioners Research Surveillance Centre found that face-to-face consultations fell by 64.6% and home visits fell by 62.6%, with almost a two-fold increase in telephone/electronic usage compared to the same timeframe during the early pandemic stages (38).

The COVID-19 pandemic has shifted government and public focus towards the use of digital and mobile apps (mAPPs) due to surging case numbers and strict quarantine measures. The global usage of mAPPs for health monitoring, education, and COVID-19 detection has skyrocketed, especially in densely populated countries in East and Southeast Asia (39). Mobile applications have matured and become increasingly used in chronic disease management for patient education, monitoring, and interactions for the last few decades (40), potentially showing a positive trend in patient adherence to chronic disease management (41). mAPPs have also been proven to be effective tools for reducing hospital burden, obtaining reliable information, tracking symptoms, and improving mental health (42).

Apart from traditional video conferences and phone calls to communicate with providers, telemonitoring combined with plentiful modern technologies has attracted more attention than usual during the pandemic (43). Wearable technology that can monitor physical activity, blood pressure, and other information has gained traction, allowing real-time synchronous and asynchronous data and biodata to be delivered to healthcare providers to provide more personalized and precise decisions for patients with chronic diseases (44, 45).

4.2. Telehealth usage for specific diseases

To continuously monitor clinical conditions, a special garment with an integrated sound acquisition module which directly decreased the patient's role in operating the machine was implemented during the pandemic to capture thoracic sounds and monitor patients with COPD (46). To ensure the safety of sleep apnea patients and reduce the workload for medical workers in the COVID-19 era, a portable sleep apnea monitoring system that integrated with the mobile phones of doctors and patients' relatives were designed, and patients were satisfied with the convenience, accuracy, and lower cost of the system (47). When technology-based pulmonary rehabilitation education was delivered to patients with chronic respiratory disease, no significant differences in quality of life and exercise ability were found compared to those who received traditional pulmonary rehabilitation, indicating that telehealth could be a trustworthy replacement during the pandemic era (48).

For diabetes, technology such as remote continuous glucose monitoring helped healthcare workers remotely grasp glucose level data for diabetic patients in both inpatient and outpatient wards. It has been proven to help the management of glycemic index levels during pandemics (49, 50). Healthcare workers and companies also turned to technology at the start of the pandemic, and diabetes-related educational applications and digital support groups including online courses and discussions were set up to help with patient care (51).

Known as Tele-CR, the delivery of cardiac rehabilitation online to help with goal setting, delivering self-management advice, and counseling for CVD patients was recommended by healthcare workers during the pandemic (52). Along with wearable trackers and telehealth tools, CR exercises could be conducted and prescribed remotely, leading to potential resource and cost savings for the healthcare system (53). Telehealth enhances the monitoring, tracking, and communication of biometric information, allowing hypertensive patients to participate better in their care which reduces their stress. Services can be easily used to notify referring physicians of the onset of acute symptoms or sudden increases in blood pressure (54).

Studies have suggested that telemedicine in cancer patient care leveraged innovative responses during the COVID-19 pandemic that may provide durable solutions that allow patients to receive proper care in their homes (55). In an randomized controlled trial conducted by Maguire et al., Advanced Symptom Management System, a remote monitoring system, was shown to be a highly efficient tool for improving the quality of life of individuals undergoing chemotherapy for various cancers. ASyMS enables real-time 24/7 monitoring and management of chemotherapy toxicity by collecting patient data and transmitting it to clinicians for evaluation. It has been demonstrated to have a positive impact on symptom burden, anxiety, self-efficacy, and other critical outcomes in patients undergoing chemotherapy; additionally, it supports patients who remain at home to receive optimal care by providing a secure and reliable platform during health crises (56).

4.3. Telehealth and COVID-19

Long-COVID is a newly emerging phenomenon that refers to persistent physical and neuropsychiatric symptoms after COVID-19 infection that last over 12 weeks without a clear cause (57), causing a health burden of up to 30% across all age groups and can potentially impact the healthcare system and economy (58). A 10-week virtual rehabilitation program for Long-COVID patients, led by multidisciplinary team, conducted weekly one-hour video learning sessions and peer interaction on Long-COVID symptoms and education. Participants have highly regarded the program, especially the guidance on breathlessness and fatigue management (59). Furthermore, a project that incorporated standardizing patient assessments, ensuring individual rehabilitation plans, and reporting activity performance was conducted in Italy, showing improvement for Long-COVID patient and caregiver education and creation of a regional database for data collection (60). Additionally, the use of telehealth could effectively assess patients with Long-COVID, providing a convenient and reliable means of remote health assessment in the absence of established guidelines or diagnostic procedures. Advanced analysis implemented in telehealth could detect disorders and facilitate further diagnostic evaluation, thereby also reducing the stress associated with Long-COVID (61).

Inadequate telehealth training among healthcare workers is another concern (62). Especially in the current phase of COVID-19 when quarantine and lockdown are no longer recommended, it is necessary to increase the number of trained and educated telehealth workers and provide them with rigorous training (63). Moreover, Covid-19 will not be the first or the last major infectious disease or natural disaster. A recent study suggests several ways to improve the utilization of telehealth during similar situations in the present or future, including training healthcare professionals, introducing accreditation and funding services, redesigning care models, and integrating telehealth into routine clinical work (64). Determining a path for utilizing telehealth after the pandemic can motivate and guide researchers, medical and government personnel to make advanced contributions on the telehealth area (65). A study proposed that telehealth should be widely and permanently implemented to achieve significant public health benefits such as reducing workload for physicians and alleviating patient flow during the current pandemic and in the future (66). However, given that both COVID-19 infection and its post-acute syndrome are relatively new phenomena, additional research and optimization of their relationship with telehealth are necessary.

4.4. Emerging problems

As telehealth is still in its youngest stage, patient satisfaction depends on the modality and functionality of delivery; however, current conclusions surrounding telehealth platform efficiency and effectiveness are uncertain (67). The effectiveness of telehealth in individuals with complicated and mixed chronic disease conditions remains unclear, thus self-management and clinical decision-making are not recommended as the main components of telehealth for patients with complex chronic conditions (68). Even though telehealth could maintain the doctor-patient relationship during the pandemic, patients still suggested that a combination of telehealth and offline face-to-face meetings would be preferable in the future (69).

Notably, telehealth platforms pose ethical and legal issues than traditional management, surrounding the liability of professionals, quality of care, and protection of personal data (70). Even in developed countries, policies and regulations associated with telehealth privacy are underregulated. The Health Insurance Portability and Accountability Act, a United States federal law enacted almost two decades ago that protects patients' health privacy, has barely been updated since it came into law (71). Furthermore, the quality of mobile applications with diagnosing and rating functions has been found to be spotty, functionally inaccurate, and inefficient. Frequent updates and adjustments to the mAPP from the operator could pose a further barrier for government regulators to supervise the mAPP update in a timely manner (72). In addition to regulations on privacy and safety, informed consent is another essential component of telehealth; patients not only have to understand their rights and have them fulfilled, but providers must also understand the purpose of their actions, acquire consent from consumers, and ensure that patients understand every instruction (73). Access to telemedicine also poses challenges to users. A recent study indicated that females and families with relatively lower household incomes tended to participate less in telemedicine for CVD during the COVID-19 pandemic (74). Another less-active group was older adults, the majority of whom could not use video visits and other telemedicine methods due to lower levels of education, living alone, and low electronic literacy (75). Seniors' experiences with telehealth are still evolving, and innovative technologies that address their needs must be explored to increase telehealth usage and acceptance (76).

With the existing unsolved barriers in this fast-developing field, ethical and legal issues still require more standardization and regulation to guarantee patients' rights and quality of care. Groups that are often overlooked should also be a focus of attention for healthcare workers and telehealth companies.

5. Discussion

This review discussed and analyzed modern chronic disease management strategies before and after the COVID-19 pandemic. The shift from traditional in-person care to technology-based telehealth management has been obvious, as an increasing number of patients have opted for telehealth over traditional clinical visits. It is expected that if more novel communication channels between patients and doctors can be developed, communication will become smoother, easier, and more efficient. Cutting-edge technology and telehealth have resulted in improved patient adherence to programs and convenience for users, but despite its demonstrated benefits, uncertainties regarding the quality of privacy protection and safety remain. The overall impact of telehealth during the pandemic has yet to be determined, and patients and healthcare workers must collaborate to find the best solutions for disease management. This article intends to contribute to the advancement and evolution of chronic disease management methods. While the pandemic is expected to end at some point, the accomplishments made in the field of telehealth during this period must not be neglected and should be built upon to further refine chronic disease management approaches.

Author contributions

SY: conceptualization, writing, revision, and approval of the final version. JJ and YL: revision and approval of the final version. RW: revision and writing. LB, QJ, and BZ: revision and methodology. All authors have contributed to the manuscript and approved the submitted version.

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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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Digital literacy level and associated factors among health professionals in a referral and teaching hospital: An implication for future digital health systems implementation

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Background: In Ethiopia and other developing countries, electronic medical record systems and other health information technology are being introduced. However, a small proportion of low-income countries have successfully implemented national health information systems. One cause for this can be the lack of digital literacy among medical practitioners. As a result, this study aimed to assess health professionals' digital literacy level and associated factors in Northwest Ethiopia.

Method: A quantitative cross-sectional study was employed among 423 health professionals working in a teaching and referral hospital in Northwest Ethiopia. We modified and applied the European commission's framework for digital competency to assess the level of digital literacy among health professionals. We used stratified random sampling with proportional allocation to the size of the departments in the hospital to select study participants. Data were collected using a semi-structured, self-administered, and pretested questionnaire. Descriptive and binary logistic regression analysis techniques were used to describe respondents' digital literacy level and identify its associated factor, respectively. The odds ratio with 95% CI and value of p were used to assess the strength of the association and statistical significance, respectively.

Results: Out of 411 participants, 51.8% (95% CI, 46.9–56.6%) of health professionals had adequate digital literacy. Holding a master's degree (Adjusted OR=2.13, 95% CI: 1.18–3.85), access to digital technology (AOR=1.89, 95% CI: 1.12–3.17), having training in digital technology (AOR=1.65, 95% CI: 1.05–2.59), and having a positive attitude towards digital health technology (AOR=1.64, 95% CI: 1.02–2.68) were found to be significant factors associated with health professionals digital literacy level of health professionals.

Conclusion: Low level of digital literacy among health professionals was observed, with nearly half (48.2%) of them having poor digital literacy levels. Access to digital technology, training on digital technology, and attitude toward digital health technology were significant factors associated with digital literacy. It is suggested to increase computer accessibility, provide a training program on digital health technology, and promote a positive attitude toward this technology to improve the deployment of health information systems.

KEYWORDS

digital literacy, health professionals, associated factors, Northwest Ethiopia, referral and teaching hospital, digital health systems

Background

Digital technology has a tremendous effect on improving the quality of health services in both developed and developing nations by enhancing the accessibility of health information and creating an efficient service provision (1). In high-income countries, digital health solutions are gradually being implemented in healthcare settings (2). However, only 35% of lower-middle-income nations and 15% of low-income countries have implemented national electronic health record systems in hospitals (3, 4). Most health facilities rely on paper-based systems, leading to inaccuracies in data management practice, which impacts the quality of healthcare delivery (5, 6).

Evidence suggests that healthcare information systems can enhance the quality of healthcare delivery and are expected to be implemented in all healthcare services (7). Therefore, using and operating information technology is a requirement for healthcare workers. Digital health technology refers to the collection, sharing, and analysis of health information using digital information, data, and communication technologies to enhance patient health and healthcare provision (8, 9). Examples include computers, tablets, smartphones, digital medical equipment, smartwatches, and other digital technology. The term digital literacy refers to "the ability to use technology to participate in and contribute to modern social, cultural, political, and economic life" (10). For the successful transformation of healthcare delivery, digital literacy is a prerequisite (11). Technologically savvy health workers can better manage their patients (12). Excellent digital literacy can lead to increased readiness for electronic health record systems (13). In turn, this might improve healthcare systems' efficiency and long-term viability.

Ethiopia has several eHealth project initiatives underway, and most of the nation's previously implemented health information systems faced sustainability challenges (14, 15). The main reason for low adoption or sustainability issues for EHR systems is a lack of pre-implementation efforts, such as a lack of digital literacy among health professionals (16–18). As a result, identifying areas and requirements before implementation could assist in determining the areas of focus that must be addressed throughout implementation.

Various studies are being conducted worldwide to evaluate healthcare professionals' knowledge, perception, and willingness in using digital health tools (19, 20). Evidence also supports medical professionals' adoption of digital health technologies for clinical services in response to the COVID 19 pandemic (21, 22). Previous studies in similar situations demonstrate that a lack of digital literacy among health practitioners is a significant factor in digital health system failure (5, 18, 23). Healthcare practitioners in low-income nations such as Ethiopia should have at least a basic knowledge of digital technology to implement e-health systems successfully (16). According to studies, healthcare workers' digital skill gaps must be bridged for technology to be transferred to the point where health service quality can be maintained (5, 24).

Currently, the University of Gondar, in collaboration with the Ethiopian Ministry of Health (FMOH) and Digital Health Activities (DHA) agreed to customize and implement an Electronic Medical Record (EMR) at the University of Gondar Specialized and Comprehensive Hospital. The hospital serves as the sole referral center in Northwest Ethiopia, with a range of speciality healthcare services and a teaching and research center. Despite the range of services that it provides, its information system is not yet computerized. As a result of the adoption of e-health initiatives, the University of Gondar specialized hospital has been chosen as the pilot study for the EMR deployment. As far as we know, there are limited evidences available regarding the level of digital competency among healthcare professionals working in hospital settings. Hence, before starting a costly implementation, it is essential to assess the level of digital literacy of health professionals working at the implementation site. Therefore, this study aimed to evaluate the level of digital literacy and identify its associated factors among health workers at the University of Gondar Specialized and Comprehensive Hospital. Understanding the digital literacy of health workers could help take appropriate measures to successfully implement an EMR system at the hospital.

Methods

Study design and setting

An institutional-based cross-sectional study was conducted among health professionals at the University of Gondar specialized and comprehensive hospital from June 2 to June 25, 2022. The University of Gondar Specialized Hospital is located in the historic town of Gondar, northwest Ethiopia. Gondar is approximately 168 kilometres from Bahir Dar and 772 kilometres from Addis Abeba, the country's capital. Nearly seven million people are served by the University of Gondar Comprehensive Specialized Hospital, one of the

Abbreviations: E-health, Electronic health; EMR, Electronic medical record; FMOH, Federal ministry of health; DHA, Digital health analysis; CBMP, Capacity building and mentorship project; DUP, Data use partnership; AOR, Adjusted odds ratio; COR, Crude odds ratio; CI, Confidence interval; SPSS, Statistical Package for Social Science.

largest referral and teaching hospitals in the Amhara region (25). It employed 1,520 healthcare professionals across more than 20 departments to treat an average of 1,000 patients daily.

Study sample and eligibility criteria

All health professionals working at the University of Gondar Specialized and Comprehensive Hospital were included in this study. However, health professionals with less than six months of experience, those who will not be present in hospitals for various reasons, and those on yearly leave during the data collection period were excluded from the study.

Sample size determination and sampling procedure

The sample size was calculated using the single population proportion formula $n=\frac{(Z\propto/2)^2 P(1-P)}{d^2}$ using the following assumptions (26). Since there is a study in Ethiopia addressing the digital literacy of health professionals working in primary health centers ($p = 50\%$) (5), based on the assumptions of a 95% CI ($z\ \alpha/2 = 1.96$), a 5% degree of precision (d), the final sample size becomes 384. A total of 423 healthcare professionals were included in the study after accounting for the 10% non-respondent rate. Each department served as a stratum in our department-based stratified random sampling design. A list of health professionals was used as the sampling frame. The level of digital literacy and related parameters were evaluated by proportionally allocating the sample to each department based on the number of healthcare providers. Participants in each department were then selected using a computer-generated simple random sampling technique.

Study variables

The dependent variable in this study was the digital literacy level of the healthcare practitioners, while the independent variables were socio-demographic characteristics (sex, Age, Profession, Educational level, Work experience), technological variables (Access to digital technology, Internet access, Training on digital technology), organizational variables (Staff motivation and workloads), and attitudes towards the use of digital health technology.

Measuring instruments

Digital literacy: Twenty-one item questions were adapted from the European Commission's digital competency framework and used to assess health workers' digital literacy (27). The digital literacy level is measured using a 5-point scale (Very Good, Good, Acceptable, Poor, and Very Poor) and separated into five primary components (Information processing, content creation, Communication, Safety, and Problem-solving). Since the data is not normally distributed, a median of the 21 questions about health professionals' digital literacy level was calculated, and those who scored higher than the median were classified as having adequate digital literacy. In contrast, those who scored lower were classified as having inadequate digital literacy (5).

Attitude towards digital health technology: sixteen questions adapted from The Digital Health Scale were used to measure the health professionals' attitude toward using digital health technology (28). The attitude toward digital health technology was measured using a 5-point scale (Strongly Agree, Agree, Neutral, Disagree, and Strongly Disagree). The item scores for each composite variable were added and divided by the number of items to create a composite variable ranging from scores 1 to 5 for the data analysis (29–31). As a result, the above three of final scores (strongly Agree, and Agree) were labelled as "Favorable attitude'. In contrast, final scores of three or less (strongly disagree, disagree, and neutral) were categorized as "Unfavorable attitude' (31, 32).

Data collection tool and quality control

The questionnaires used in this study were developed after a review of related literature (5, 27, 28). A self-administered and pretested questionnaire was developed in English to collect the required data. The questionnaires assess the level of digital literacy among health professionals and their attitudes toward digital health technology, socio-demographic variables, technological attributes, and organizational characteristics. The data collection process involved two supervisors and twelve data collectors. Supervisors and data collectors received three days of training to minimize ambiguity. A pretest was conducted outside the study area, in Gondar town health centers, with 10% of the study population. The pretest results were used to evaluate the data collection instrument's validity and reliability. Cronbach's alpha scores were used to assess the data collection instrument's internal consistency. As a result, the Cronbach alphas for digital literacy level (0.97) and attitude toward digital technology use (0.91) were found to be within the acceptable range.

Data processing and analysis

The Epi Data version 4.6 software packages were used for data entry, and the Statistical Package for Social Sciences (SPSS) version 25 was used for analysis. Descriptive statistics were computed to describe socio-demographic variables and health professionals' digital literacy levels. Bivariable and multivariable binary logistic regression analyses were used to identify the relationship between the dependent and independent variables. Variables with a value of p less than 0.2 in the bivariable regression analysis were considered potential candidates for the multivariable regression analysis to assess their adjusted impacts on the dependent variables. An odds ratio with a 95 percent confidence level and *p*-value was calculated to determine the association's strength and statistical significance. The cut-off value for all significantly associated variables was $p < 0.05$.

Ethics approval and consent to participate

Ethical clearance and approval letters were obtained from the Institutional Review Board (IRB) of the University of Gondar with reference number (**Rfe. VP/RTT/05/571/2022**). After explaining the study's objective, each health professional signed a written consent form. The University of Gondar's specialized hospital also obtained a letter of support. Confidentiality and privacy were ensured during data collection by keeping participants anonymous.

Results

Socio-demographic characteristics

This study enrolled 411 health professionals, and the response rate was 97.1%. The participants' average age was 30.3 years, with a standard deviation of +4.8 years, and a minimum and maximum age of 21 and 60, respectively. Of all participants, 240 (58.1%) were men, and 161 (39.2%) of the respondents identified as nurses. The majority of 336 (81.8%) health professionals had a degree or below in education, and 222 (54.0%) were married at the time. Regarding employment history, participants had an average of 6 years of experience (Table 1).

Technological and organizational factors

Most health professionals, 298 (72.5%), have access to digital devices like computers, tablets, smartphones, digital medical devices, smart watches, etc. Of all respondents, around 350 (85.1%) have access to a smartphone. A desktop computer, a laptop computer, and smartwatches are accessible to 154 (37%), 187 (45%), and 42 (10.2%) health professionals, respectively. However, only 51 (12.4%) health workers had access to one of the digital medical devices, such as an electronic (digital) vision chart, wearables, an auto-refractor, a scan biometer, glucose monitors and heart-rate monitors. Accessible digital medical equipment included glucose monitors, heart-rate monitors, wearables, an auto-refractor, a scan biometer, and an electronic (digital) vision chart. Nearly half, 221 (53.8%) of the respondents had access to one of the aforementioned digital technologies at work, and 332 (80.8%) of them had access to an internet connection (Table 2).

Regarding organizational characteristics, health professionals claimed that they visit an average of 19 and more patients daily. From the total of 231 (56.2%) respondents, the staff is also driven to use digital technology for patient care. Furthermore, 215 (52.3%) health professionals have received training in digital technology.

Attitude towards digital health technology

Of the total respondents in this study, 307 (74.7%) with (95% CI:70.4–78.9%) had a favourable attitude towards using digital health technology to provide patient care.

Table 3 shows that 194 (47.2%) health professionals agreed that booking an appointment on a computer or smartphone was more

TABLE 1 Socio-demographic characteristics of respondents.

Socio-demographic variables	Category	Frequency	Percentage
Sex	Male	240	58.4%
	Female	171	41.6%
Age	30.3 ± 4.89		
Profession	Physician	89	21.7%
	Nurse	161	39.2%
	Pharmacy	18	4.4%
	Midwifery	51	12.4%
	Laboratory	32	7.8%
	Psychiatry	7	1.7%
	Public health	21	5.1%
	Physiotherapy	7	1.7%
	Optometry	9	2.2%
	Anesthesia	8	1.9%
	Radiology Assistant	8	1.9%
Marital status	Single	183	44.5%
	Married	222	54.0%
	Divorced	4	1.0%
	Widowed	2	0.5%
Educational level	Degree and Below	337	82.0%
	MSc and Above	74	18.0%
Work experience	6.78 ± 6.5		

TABLE 2 Technological and ororganizational-relatedariables.

Variables	Category	Frequency	Percentage
Access to digital technology	No	113	27.5%
	Yes	298	72.5%
Which digital devices do you have access to?*	Desktop computer	154	37.5%
	Laptop computer	187	45.5%
	Smartphones	350	85.1%
	Digital medical devices**	51	12.4%
	Smartwatch	42	10.2%
Accessible digital technology in the workplace	No	190	46.2%
	Yes	221	53.8%
Internet access	No	79	19.2%
	Yes	332	80.8%
Where do you get access to the Internet?*	Private Wi-Fi and Mobile data	305	74.2%
	Internet cafe	88	21.4%
	Workplace	232	56.4%
Training in digital technology	No	196	47.7%
	Yes	215	52.3%
Motivation	No	180	43.8%
	Yes	231	56.2%
Number of Patients served per day	19.60 + 10.4		

*Multiple options possible, ** Glucose monitors, heart-rate monitors, wearables, an auto-refractor, a scan biometer, and an electronic (digital) vision chart.

TABLE 3 Attitude towards digital health technology.

Attitude variables	SD (%)	D (%)	N (%)	A (%)	SA (%)
Making an appointment on a computer or smartphone would be more convenient for me.	27 (6.6)	59 (14.4)	46 (11.2)	194 (47.2)	85 (20.7)
I think using technology has improved healthcare	34 (8.3)	41 (10.0)	31 (7.5)	185 (45.0)	120 (29.2)
I really understand how to use health technology	22 (5.4)	74 (18.0)	80 (19.5)	178 (43.3)	57 (13.9)
Video and telephone appointments with my patients are as good as meeting them in person	38 (9.2)	84 (20.4)	80 (19.5)	157 (38.2)	52 (12.7)
Health technologies are easy to use	35 (8.5)	87 (21.2)	77 (18.7)	166 (40.4)	46 (11.2)
Patients and hospitals rely too much on technology	76 (18.5)	99 (24.1)	93 (22.6)	116 (28.2)	27 (6.6)
Technology could never replace real health professionals	44 (10.7)	91 (22.1)	83 (20.2)	131 (31.9)	62 (15.1)
I would like to see more use of technology in healthcare	29 (7.1)	61 (14.8)	62 (15.1)	170 (41.4)	89 (21.7)
Health technology is less likely to break down, and my work will not be affected	36 (8.8)	95 (23.1)	86 (20.9)	151 (36.7)	43 (10.5)
Health technology reduces human error	46 (11.2)	51 (12.4)	69 (16.8)	185 (45.0)	60 (14.6)
The thought of using an online appointment system makes me relaxed	48 (11.7)	50 (12.2)	72 (17.5)	177 (43.1)	64 (15.6)
The thought of new developments in health technology is exciting	16 (3.9)	69 (16.8)	71 (17.3)	196 (47.7)	59 (14.4)
I often use health technology	27 (6.6)	73 (17.8)	73 (17.8)	176 (42.8)	62 (15.1)
Health technology is good for everyone	17 (4.1)	42 (10.2)	58 (14.1)	209 (50.9)	85 (20.7)
I'm confident that technology will keep the medical records private	18 (4.4)	49 (11.9)	58 (14.1)	207 (50.4)	79 (19.2)
I enjoy using health technology	14 (3.4)	24 (5.8)	62 (15.1)	221 (53.8)	90 (21.9)

SD, Strongly Disagree; D, Disagree; N, Neutral; A, Agree; SA, Strongly Agree.

practical. A total of 185 (45.0%) respondents said using technology had improved healthcare. Around 44% of health professionals responded that they understand how to use digital health technology. Surprisingly, 157 (38.2) respondents asserted that video and telephone appointments with patients are just as effective as in-person meetings. Nearly half of the responders (209) (50.9%) believed that health technology benefits everyone. Similarly, 207 (50.4%) of participants expressed confidence in the confidentiality of medical records due to technology. Additionally, 170 (41.4) respondents were enthusiastic about the increased usage of technology in healthcare.

Health professionals' digital literacy level

Overall, 213 (51.8%) (95% CI, 46.9–56.6%) health professionals have adequate digital literacy levels (Figure 1). As shown in Table 4, the combination of five digital literacy components, information and data literacy, collaboration and communication literacy, literacy in creating digital content, safety, and problem-solving, was used to assess the respondents' overall levels of digital literacy. Of the total, 233 (56.7%) had adequate information and data literacy. Regarding collaboration and communication, more than half of the health professionals, 223 (54.3%), possessed adequate literacy. Of the total respondents, 220 (53.5%) had adequate literacy in digital content creation. Additionally, 206 (50.1%) and 249 (60.6%) exhibited adequate literacy levels in safety and problem-solving, respectively.

Factors associated with health professionals' digital literacy level

The factors affecting the level of digital literacy among health professionals were examined using bivariable and multivariable logistic regression analysis. In the bivariate analysis, sex, age, educational status, monthly income, work experience, access to digital technology, internet access, training on digital technology, organizational motivation, attitude towards digital technology, and patient served per day were taken into consideration as candidates for the multivariable logistic regression analysis.

According to the multivariable logistic regression analysis results, respondents with master's degrees were 2.13 times more likely to have good digital literacy than those with degrees and below educational levels (AOR = 2.13, 95% CI: 1.18–3.85). Health professionals with access to digital technology were 1.89 times more likely to have adequate digital literacy than those without (AOR = 1.89, 95% CI: 1.12–3.17). The current study also found that healthcare professionals who had received training in digital technology were 1.65 times more likely to have adequate digital literacy than their counterparts (AOR = 1.65, 95% CI: 1.05–2.59). Additionally, Health professionals with a favourable attitude toward digital health technology were 1.64 times more likely to have adequate digital literacy than those with unfavourable attitudes (AOR = 1.64, 95% CI: 1.02–2.68) Table 5.

Discussion

The results of this study revealed that 51.8% of health professionals have adequate digital literacy levels. This finding is consistent with studies in Ethiopia (5) and other studies conducted in Indonesia (7). However, our finding is lower compared to those of research studies which are conducted in Australia (33), Vietnam (34), and India (6). The discrepancy could result from variations in internet usage and ICT facilities among countries compared to Ethiopia. Evidence suggests that Ethiopia lags behind Africa's average internet penetration rate (39%) (35).

The other explanation for this discrepancy could be that only roughly two-thirds (72%) of the study's participants had access to digital technology, which is much fewer than in other wealthy nations like Australia (33) and may result in lower levels of digital literacy among health professionals in Ethiopia. In most affluent countries, digital health system implementation has been effective due to high computer literacy (33, 36). However, in underdeveloped countries, there is a low level of digital literacy among health workers, resulting in the stoppage of many e-health projects (37, 38). As a result, given the growing usage of technology in healthcare, it is critical that healthcare professionals are digitally literate (39, 40).

Respondents with master's degrees were 2.13 times more likely to have adequate digital literacy than those with a degree and below educational levels. This finding is in line with previous research studies indicating that health professionals with higher education levels were more likely to have adequate digital literacy (5). This might be because health professionals with higher education levels were more likely to use digital technology for their education, such as research and data gathering tools, which were more frequently employed by master's-level and more educated health professionals.

The current study also found that healthcare professionals receiving training in digital technology were 1.65 times more likely to have adequate digital literacy than their counterparts. The findings align with earlier studies conducted among nurses in Indonesia (7) and health professionals in Austral (33). This finding implies that general training on digital health technology and the specific eHealth software application that will be implemented may significantly impact how well the healthcare system adopts technology.

Health professionals with access to digital technology were 1.89 times more likely to be highly digitally literate than those without. This finding is in line with other research showing that medical personnel with access to digital devices, including computers, laptops, smartphones, and digital medical equipment, have a high level of

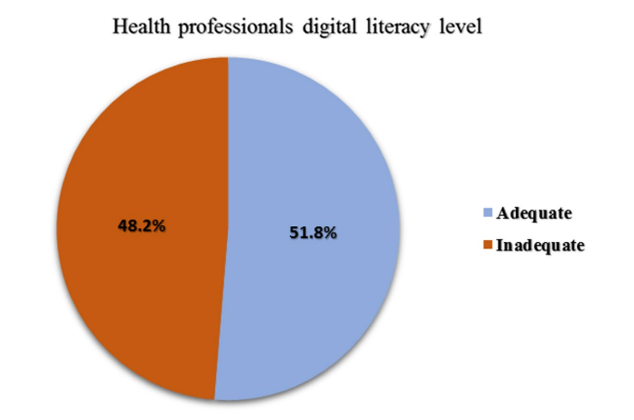

FIGURE 1
Health professionals' digital literacy level.

TABLE 4 Components of health professionals' digital literacy.

Digital literacy subscales	Median (±SD)	Poor	Good
Information and data literacy	10.00 ± 3.45	178 (43.3%)	233 (56.7%)
Communication and Collaboration	20.00 ± 6.48	188 (45.7%)	223 (54.3%)
Digital content creation	12.00 ± 4.33	191 (46.5%)	220 (53.5%)
Safety	14.00 ± 4.64	205 (49.9%)	206 (50.1%)
Problem-solving	12.00 ± 4.54	162 (39.4%)	249 (60.6%)

TABLE 5 Factors associated with health professionals' digital literacy level.

Variables		Digital literacy		COR (95% CI)	AOR (95% CI)
		Good (%)	Poor (%)		
Sex	Male	134 (32.6)	106 (25.8)	1.47 (0.99–2.18)	1.27 (0.82–1.96)
	Female	79 (19.2)	92 (22.4)	1	1
Age	30.3 ± 4.89			1.01 (0.97–1.05)	1.02 (0.97–1.08)
Education level	Master's Degree and above	53 (12.9)	21 (5.1)	2.79 (1.61–4.83)	2.13 (1.18–3.85)*
	Degree and Below	160 (38.9)	177 (43.1)	1	1
Working experience	6.78 + 6.5			0.97 (0.94–1.01)	0.95 (0.91–1.01)
Access to digital technology	Yes	174 (42.3)	124 (30.2)	2.66 (1.69–4.18)	1.89 (1.12–3.17)*
	No	39 (9.5)	74 (18.0)	1	1
Internet access	Yes	184 (44.8)	148 (36.0)	2.14 (1.29–3.55)	1.28 (0.70–2.33)
	No	29 (7.1)	50 (12.2)	1	1
Training on digital technology	Yes	129 (31.4)	86 (20.9)	2.00 (1.35–2.96)	1.65 (1.05–2.59)*
	No	84 (20.4)	112 (27.3)	1	1
Staffs motivation	Yes	131 (31.9)	100 (24.3)	1.56 (1.05–2.31)	1.04 (0.66–1.64)
	No	82 (20.0)	98 (23.8)	1	1
Patients served per day	19.60 ± 10.4			1.01 (1.00–1.02)	1.01 (0.99–1.02)
Attitude	Good	169 (41.1)	138 (33.6)	1.67 (1.06–2.61)	1.64 (1.02–2.68)*
	Poor	44 (10.7)	60 (14.6)	1	1

*Significant at value of $p < 0.05$.

digital literacy (41–44). This indicates that the Ethiopian ministry of health should increase the accessibility of digital health technology in the hospital setting to increase digital literacy among health professionals and successfully implement clinical health information systems.

Furthermore, this study found a significant association between the level of digital literacy and attitudes toward digital health technology. Health workers with a favourable attitude toward digital health technology were 1.64 times more likely to have good digital literacy than those with unfavourable attitudes. This conclusion is supported by earlier research showing that a positive attitude toward digital technology is associated with a greater likelihood of digital competence (33). This suggested that initiatives were required to alter health professionals' attitudes toward digital health technology. This is because adopting a new mindset significantly contributes to efficiently integrating health information technologies into the healthcare system (45).

Implication for policy and practice

This study has an implication for future digital health systems implementations. A possible way to raise the success rate of eHealth project implementations in Ethiopia is to increase computer accessibility, offer a training programme on digital health technology, and encourage a favourable attitude toward this technology. The study serves as a basis for the continuous implementation and customization of the electronic medical record at the University of Gondar Specialized and Comprehensive Hospital. Determining the level of digital literacy among the medical professionals working at the implementation location was the major objective to increase implementation success.

Conclusion and recommendation

This study aimed to determine the digital literacy level of health professionals and the associated factors that have implications for future digital health systems implementation. The results of this study help us better understand the level of digital literacy among health professionals at the specialized hospital where an EMR system will be implemented. The results of this study demonstrated that health professionals have a relatively low level of digital literacy. It is suggested to increase computer accessibility, provide a training program on digital health technology, and promote a positive attitude toward this technology to improve the deployment of health information systems.

Limitations and future works

The limitation of this study is that the data was collected through self-report, which could be prone to social desirability bias, so participants may have overestimated their responses. However, we tried to reduce this bias by making the questions as fair, neutral, and unthreatening as possible. Future work is required to determine the current status of adopting digital health tools by health professionals in Ethiopia. This will provide reliable data to assess interventions intended to increase the efficiency of various eHealth initiatives in Ethiopia.

Data availability statement

The data presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical clearance and approval letters were obtained from the Institutional Review Board (IRB) of the University of Gondar with refernace number (Rfe. VP/RTT/05/571/2022). After explaining the study's objective, each health professional signed a written consent form. The University of Gondar's specialized hospital also obtained a letter of support. Confidentiality and privacy were ensured during data collection by keeping participants anonymous. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TY and MT made significant contributions to the conceptualization, design, data collection supervision, data analysis, interpretation, and writing of the publication. BT, AMa, HK, FN, EZ, AMe, GS, RG, HG, AS, and ST contributed equally to the data collection, analysis, interpretation, and manuscript review. All authors contributed to the article and approved the submitted version.

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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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Digital dashboards visualizing public health data: a systematic review

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Introduction: Public health is not only threatened by diseases, pandemics, or epidemics. It is also challenged by deficits in the communication of health information. The current COVID-19 pandemic demonstrates that impressively. One way to deliver scientific data such as epidemiological findings and forecasts on disease spread are dashboards. Considering the current relevance of dashboards for public risk and crisis communication, this systematic review examines the state of research on dashboards in the context of public health risks and diseases.

Method: Nine electronic databases where searched for peer-reviewed journal articles and conference proceedings. Included articles (n = 65) were screened and assessed by three independent reviewers. Through a methodological informed differentiation between descriptive studies and user studies, the review also assessed the quality of included user studies (n = 18) by use of the Mixed Methods Appraisal Tool (MMAT).

Results: 65 articles were assessed in regards to the public health issues addressed by the respective dashboards, as well as the data sources, functions and information visualizations employed by the different dashboards. Furthermore, the literature review sheds light on public health challenges and objectives and analyzes the extent to which user needs play a role in the development and evaluation of a dashboard. Overall, the literature review shows that studies that do not only describe the construction of a specific dashboard, but also evaluate its content in terms of different risk communication models or constructs (e.g., risk perception or health literacy) are comparatively rare. Furthermore, while some of the studies evaluate usability and corresponding metrics from the perspective of potential users, many of the studies are limited to a purely functionalistic evaluation of the dashboard by the respective development teams.

Conclusion: The results suggest that applied research on public health intervention tools like dashboards would gain in complexity through a theory-based integration of user-specific risk information needs.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=200178, identifier: CRD42020200178.

KEYWORDS

visualization, risk information, health literacy, information needs, representations, dashboard

1. Introduction: monitoring public health

The current COVID-19 pandemic poses immense challenges for nation-states and civil society alike. Not only does the current situation severely restrict public and private life, but also affects governmental agencies which are constantly confronted with dynamic decision-making si[illegible]s. Both private individuals and decision-makers are carefully observing developments and using different types of media and formats to make sense of the current crisis as well as finding appropriate ways to communicate data and messages (1). Quality media such as public service broadcasting in Germany use figures from universities or from national and international health organizations such as the Robert Koch-Institute (RKI) or the World Health Organization (WHO) in their reporting. The findings and forecasts on the spread of the virus are increasingly presented in so-called dashboards (2) i.e., through a specific type of visualization "of a consolidated set of data for a certain purpose" (3), using a combination of numerical, temporal, geographical, and diagrammatic forms of presentation.

These dashboards capture the extent of the outbreak by visualizing cases, hospitalizations, deaths, vaccination rates etc. and allow to track the outbreak from a regional up to a global scope. They can be used to gain a quick overview, allow specific analysis and facilitate decision-making. Thereby, surveillance activities provide an instrument to prevent diseases, reduce morbidity and mortality, and promote health—objectives that define public health (4).

Worldwide, the globalization and the dissolution of national boundaries for diseases, disease spread, pollution, or environmental catastrophes foster the emergence of public health surveillance infrastructures (5) including a wide range of mobile health tools (6). With the expanding digitization, data-driven developments become more important for the assessment and surveillance of public health issues (7, 8). In the context of infectious disease surveillance, for example, dashboards are often the focus of scientific interest as a tool for visualizing epidemic data (9, 10). The focus of these studies is on increasing the efficiency of surveillance systems by identifying potential gaps—ranging from technical improvements over data quality to modeling these data. Additionally, the COVID-19 pandemic has shown, that not only epidemiologists, statisticians or data modelers are interested in near real-time COVID-19 data (11), but also the general public seeks for information about the spread of the virus (12, 13).

Therefore, the evaluation of an online communication format such as a dashboard is important with regard to many different aspects. Through a meta literature review, we were able to crystallize a not necessarily exhaustive but nonetheless comprehensive list of four different aspects that are important to consider in dashboard research. Major aspects mentioned in the literature here were (a) how public health data is visualized (14, 15), (b) the modes of communication used (16), (c) how the visualized data can be understood, is read and filled with meaning by various subpopulations (17, 18), and (d) how effective different (communication) formats are (16, 17, 19). At the same time, the large amount of data that can be provided via dashboards, as well as their scientific nature, pose various challenges to users—whether in understanding, processing or contextualizing the information (13, 20). Accordingly, there is a need for research on the needs of users.

Until 2020 and to the best of our knowledge, no systematic review on public health dashboards existed. Only two other reviews have appeared in this context by now (June 2022). A literature review provides insights into the technological advances of dashboards (21). One dashboard review sheds light on design modes of U.S. COVID-19 State Government Public Dashboards (15).

Therefore and from a communication science perspective, we investigate scientific studies on dashboards as a form of diagrammatic images in science communication covering public health issues—from non-communicable diseases (e.g., diabetes), communicable diseases (e.g., Ebola) and natural disasters (e.g., floods) to addictive disorders and related health risks such as drug abuse (22) or obesity (23). These behavioral risk factors have a public health impact as they can cause non-communicable diseases. We are particularly interested in whether empirical analysis will provide indications for a more effective visualization of scientific data, e.g., by drawing on cognitive and affective factors to process visual information. Thus, this systematic review aims to assess the state of research on dashboards, that are utilized in a public health context and provide information on divergent public health phenomena such as risks, pandemics, infections or health crises, with a focus on the methods of gathering and presenting public health information as well as the methodological approaches used to develop or evaluate the dashboards.

2. Methods

Our systematic literature review followed the steps, comprehensively described by Xiao and Watson (24): (1) formulating the research problem, (2) developing and validating the review protocol, (3) searching the literature, (4) screening for inclusion, (5) assessing quality, (6) extracting data, (7) analyzing and synthesizing data, and (8) reporting the findings.

2.1. Formulating the research problem

Research on the effective visualization of scientific data through dashboards from a communication science perspective is scarce. This literature review is therefore devoted to two distinctive objectives, which in turn are structured by a total of three research questions (RQs). First, it aims to offer an overview of different dashboards described in the scientific literature as relevant to the field of public health, thereby encompassing elements of a scoping review (RQ 1 & RQ 2). Second, it pursues to gain insights into the needs and demands of different user groups while engaging with a public health dashboard (RQ 3). Answers to the last research question are expected to be gained exclusively from those studies that have conducted a user study, assessing their specific needs and demands. Thus, the review needs to further differentiate between user studies and mere descriptive studies (see Section 2.5). In that sense, the derived research questions have been defined as follows:

- RQ 1: Which dashboards that are thematically related to the field of public health have been examined in the scientific, peer-reviewed literature and what is known about them? In particular:
    - RQ 1.1: Which areas relevant to public health—such as diseases, risks or crises—are covered by these dashboards?
    - RQ 1.2: From which sources do these dashboards retrieve their data?
    - RQ 1.3: What information (data or indicators) is visualized through these dashboards?

  - RQ 1.4: Which graphical representations are used to visualize the data or indicators in these dashboards?
  - RQ 1.5: Which functions do these dashboards offer besides the pure visualization of information?

- RQ 2: Which challenges and objectives are addressed in the sampled articles (a) in regards to the consolidation of public health and (b) in regards to the use of dashboards in that specific context?

  - RQ 2.1a: Which public health challenges do the sampled articles address?
  - RQ 2.1b: What public health objectives are they pursuing?
  - RQ 2.2a: What specific technological or administrative challenges are associated with the use of dashboards in public health?
  - RQ 2.2b: What are the specific technological or administrative objectives associated with the use of dashboards in public health?

- RQ 3: Which information needs can be identified in the assessed user studies regarding the engagement with public health dashboards?

2.2. Developing and validating the review protocol

Before the systematic search was carried out, we conducted a cursory review and pre-review mapping of relevant articles on the use of dashboards in public health settings. These articles were identified through quick-scan searches in various databases such as Scopus or Google Scholar. A loose combination of search words (such as "public health dashboard", "evaluation", or "perception") was used in order to obtain an overview of the body of literature on dashboard research and to identify possible keywords for the definition of viable search strings.

2.3. Searching the literature—identifying relevant articles

After formulating the research questions, validating, and publishing our research protocol on PROSPERO (CRD42020200178), two different search strings were conceptualized in order to retrieve relevant articles. Using Boolean operators "AND", "OR", "NOT", the first search string combined different user-centered (e.g., "literacy" or "knowledge") as well as visualization-centered (e.g., "graph" or "multimodal") keywords with the search term "dashboard" and different areas of public health (e.g., "epidemiology"). The focus on these categories is intended to limit the broad field of dashboard research to those articles that specifically relate to the field of public health and potentially address the question of user preferences and design considerations. Due to the increasing and striking relevance of dashboards in the context of the current COVID-19 pandemic [for a critical discussion see Everts (25)], we further defined an additional search string, covering a spectrum of recently published articles on COVID-19-relevant dashboards.

To conduct the review, multi-disciplinary databases such as Scopus, Web of Science, technical-oriented databases like IEEE Xplore and ACM Digital Library and databases from different disciplinary fields such as communication sciences (Communication Abstracts, Communication & Mass Media Complete) or psychology (PsycArticles, PsycInfo) were selected. We included Open Gray as an additional database to identify further relevant papers. Through this range of databases, it is assumed that a wide range of literature on public health dashboards is covered, as, for example, Scopus also includes records from the MEDLINE and EMBASE databases.

2.4. Screening for inclusion

Before running both search strings in the mentioned academic databases, several inclusion and exclusion criteria were defined in order to evaluate identified papers for further consideration in the literature review (eligibility assessment). These criteria are presented in Appendix A. Figure 1 illustrates the complete search process.

After retrieving a total of 1,836 papers by running both search strings in the aforementioned nine academic databases (see Section 2.3), an automated duplicate removal, supplemented by a subsequent hand search for duplicates, reduced our sample to a total of 1,191 papers.

These remaining 1,191 papers went through different selection stages. To test for interrater reliability two researchers randomly selected 100 papers from our sample and assessed their titles for further selection based on the previously defined inclusion and exclusion criteria (see Appendix A). Belur et al. (26) report several methods for calculating interrater reliability, including Cohen's κ, where a score of 1 indicates perfect agreement and a score of 0 equates agreement totally due to chance. By comparing individual ratings, we finally calculated a Cohen's κ of 0.78—implying, according to Landis and Koch (27), substantial agreement.

Our review applies a titles-first then abstracts screening strategy, which was already recommended by Mateen et al. (28) based on an empirical comparison of different screening methods, as a titles-first strategy guarantees an "accurate, less time-consuming process that does not compromise the quality of the final review". In accordance with a previously defined code book, supplementing our defined inclusion and exclusion criteria (see Appendix A), all 1,191 identified papers were assessed for eligibility based on their titles. This procedure left us with 296 remaining papers of which all titles and abstracts were read and assessed for eligibility in accordance with the above mentioned inclusion and exclusion criteria. Critical or unclear cases were deferred for further review by all researchers involved. Finally, discrepancies or disagreements concerning the eligibility assessment were solved by discussion and consensus-based decision-making. The review of the remaining abstracts left us with a total of 86 papers. However, nine more papers

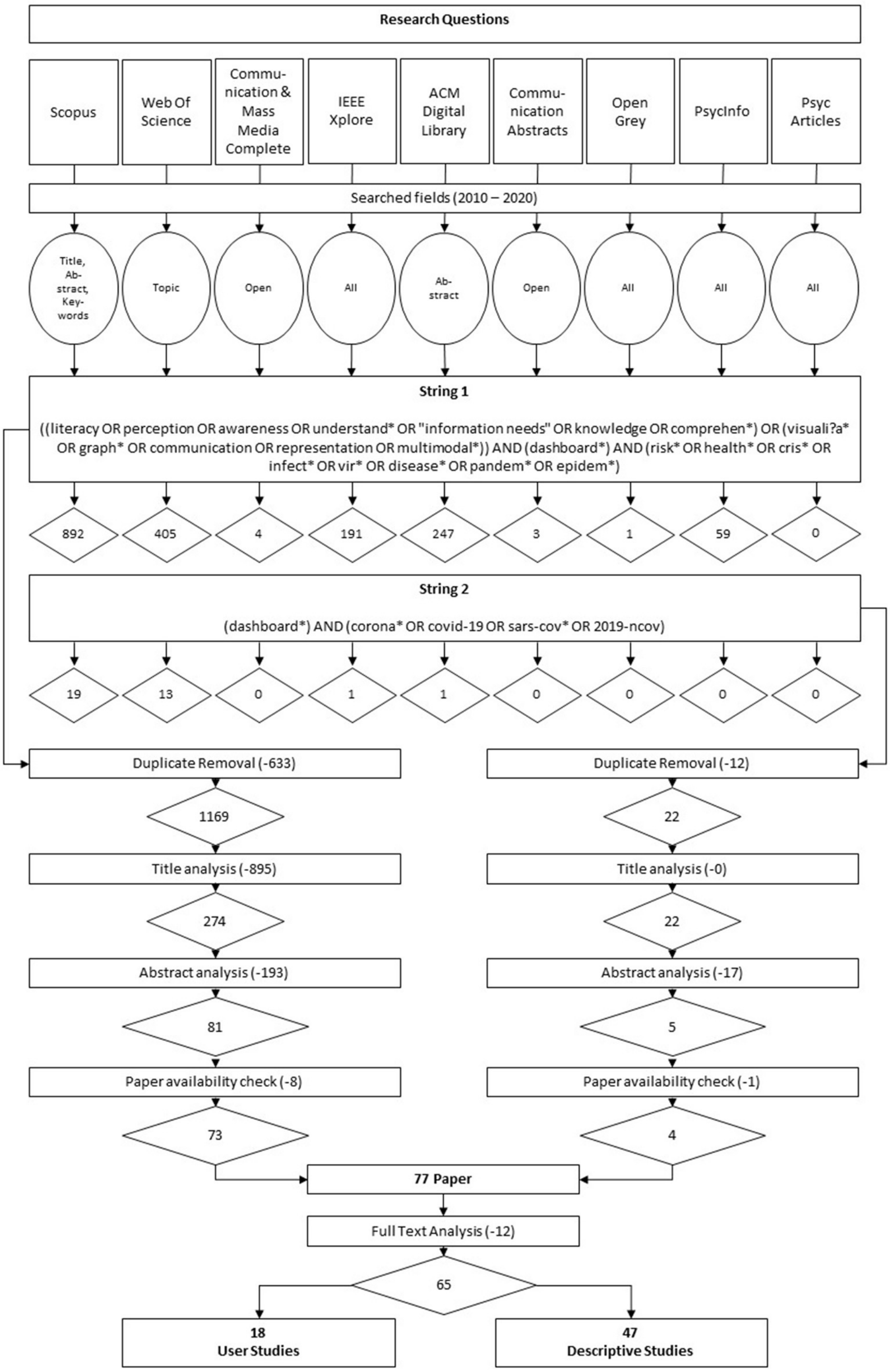

FIGURE 1
Research questions and visualization of the literature search process including search strings and number of retrieved and assessed publication.

had to be further excluded from the study either because they were not available or could not be acquired. After a thorough reading of identified and potentially relevant full-text articles as well as a consequent reapplication of the defined inclusion and exclusion criteria, we finally selected 65 articles for our final literature review.

2.5. Assessing quality

In order to adequately assess the quality of identified studies, we developed a scheme to differentiate the selected 65 articles according to their empirical focus (see Figures 2, 3). Studies that had executed a user study (n = 18), meaning an empirical assessment of a focal dashboard through different user groups, were considered for further quality assessment by means of the Mixed Methods Appraisal Tool (MMAT) which was specifically developed for critically appraising the quality of different study designs in systematic mixed studies reviews (29).

The MMAT provides the possibility of assigning ratings in order to record the quality of the included studies by using descriptors such as (*) or (%). The final quality rating is determined by the summarized total number of "yes" items assigned to the respective study category (e.g., qualitative studies). For mixed-methods studies, the developers of the MMAT state that "the overall quality of a combination cannot exceed the quality of its weakest component" (30). Since there are 15 criteria to rate for mixed-methods studies (including the five items for the first applied method as well as five items for the second method employed in the respective articles), the overall score for these types of studies is based on the lowest score of all considered study components.

The remaining 47 articles focused either on the development of dashboards and their respective testing through various IT-related measures or on the pure description of a respective dashboard system and were classified as descriptive studies. They were considered relevant for answering the defined research questions as well and thus incorporated in the next step.

2.6. Extracting, analyzing, and synthesizing data

After performing a comprehensive quality assessment, all 65 articles were finally coded with MAXQDA according to the research questions, defined above. Both inductive and deductive coding was used. Three researchers were involved in the inter-coder process to achieve coding consistency (31, 32). Disagreements were debated until consent was reached. After the first tests for consistency, all papers were coded by two researchers. Whenever discrepancies arose, a third researcher was consulted. Every time a new code was added to the coding system, all papers that had already been coded were revised again. After initial coding and fine-tuning of respective coding categories, further fine coding was carried out, which formed the basis for the results reported below.

3. Results: answering the research questions

3.1. Public health dashboards in the scientific literature providing information on public health issues (RQ 1)

3.1.1. Public health issues covered by dashboards (RQ 1.1)

In total 65 papers were included in our literature review. They cover topics from infectious diseases like Dengue (33), Ebola (34), or COVID-19 (35) (n = 21), crises caused by emergencies and disasters, such as floods [e.g., (36)] (n = 6) or other health hazards such as those caused by pollution (e.g., 37) (n = 4) (see Appendix B for raw data, Figure 4 on dashboard topics).

3.1.2. Data sources used by dashboards (RQ 1.2)

Data displayed on the dashboards is derived from different sources like (a) governmental institutions (37) (n = 14), (b) health organizations like the World Health Organization and health care facilities (38) (n = 25) (c) national or local Research Organizations like the National Center for Health Statistics (39) (n = 6), (d) cities or communities (40) (n = 11), (e) news and journals (41) (n = 8), and (f) social media such as Twitter (42) (n = 8). Also, eleven papers report that (g) the users of the dashboard can be a source of information (43). Often dashboards derive their information from more than one source (see Appendix C). For example, Zheng et al. (44) created a dashboard to exchange critical information for the private and public sector in case of a crisis situation. The information is gathered from County Emergency Offices, company reports and messages as well as the news. Also, users can add further reports. Another dashboard tracking COVID-19 cases collects and displays data from a medical community online platform as well as Twitter and online news (35).

3.1.3. Information (data or indicators) visualized through dashboards (RQ 1.3)

As stated above, the papers analyzed describe dashboards that deal with the visualization of data on, for example, diseases, crises and risks. Key indicators mentioned in different studies are (see Appendix D):

1. The number of reported cases (e.g., of a disease) or rates (e.g., death rates) (n = 15).
2. Health data including patient attributes (e.g., weight) and type of disease (e.g., HIV) (n = 43).
3. Social and environmental factors (e.g., education) (n = 7).
4. Environmental data (e.g., air pollution, temperature) (n = 15).
5. Demographics (e.g., age, gender) (n = 14).
6. Time (e.g., time of an event, variation in time) (n = 14).
7. Location (e.g., region or country) (n = 38).

3.1.4. Graphical representations used to visualize data or indicators in dashboards (RQ 1.4)

The visualization of data is one of the main goals of the dashboards. To do so, the dashboards mainly feature maps (see Figure 5), charts and tables. Forty dashboards reporting incidences of health hazards or the magnitude of a crisis caused e.g., by natural disasters, use maps to visualize the spread or effected areas (45). These are often further enhanced by symbols (38) (n = 5), icons (46) (n = 6) or pop-ups (47) (n = 11) that become visible when the users hover over the map.

Charts and graphs are used in different formats such as bar charts (48) (n = 24), pie charts (33) (n = 16), or line graphs (49) (n = 6; see Figure 6). All types of charts and graphs facilitate date visualization in general but it is not further explained how the

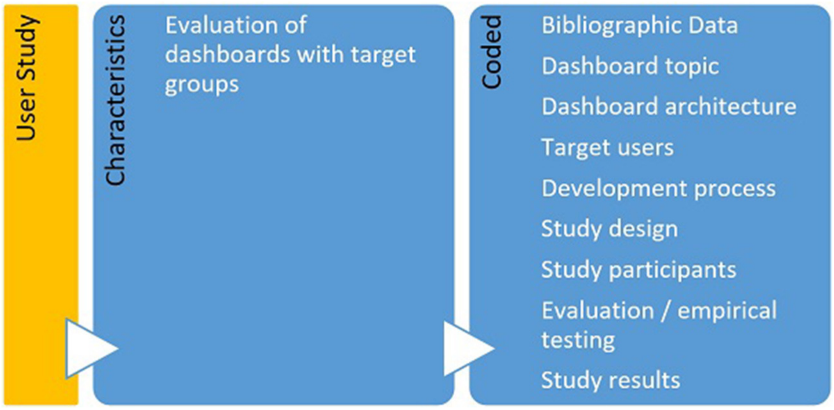

FIGURE 2
Characteristics and associated codes for user studies.

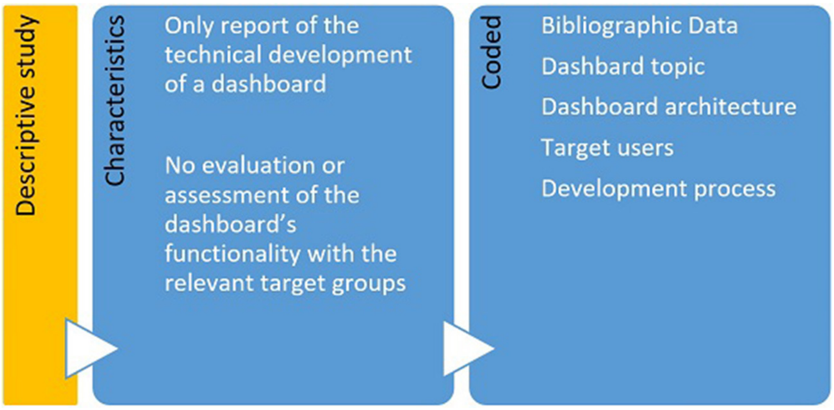

FIGURE 3
Characteristics and associated codes for descriptive studies.

developers of the dashboards decided which type of chart or graph they were going to use. Tables are used to display rankings, precise numbers and scores and to list different data on one aspect (50) ($n = 21$).

Besides the mentioned, common visualizations, four dashboards incorporate timelines aiming at a more holistic understanding of the situation and analyze events over a period of time (41, 51). Concannon et al. (47), for example, uses tree maps as they are preferred by the users of the dashboard and allow for more precise display of labels. Word clouds are primarily used to visualize social media data such as keywords from Twitter posts to give a quick overview of main topics or locations (52) ($n = 3$). Several papers describe the use of distinct sub-sections of the page like sidebars (37) or tabs (53) ($n = 9$) which facilitate the navigation.

Nineteen papers describe the use of color to further enhance understanding. Some of them explicitly use the traffic light colors—green, amber and red—to take advantage of the popular associations regarding these colors (54). In some areas—as described by Bernard et al. (55) for the medical sector—it is beneficial to use color codes that are prominent in a certain work environment (e.g., black for "death of disease") (see Appendix E).

3.1.5. Functions that dashboards offer besides the pure visualization of information (RQ 1.5)

Dashboards are not only used for the visualization of data but offer further functions, features and components depending on the situation or task at hand. These include, for example, the possibility to look at data representing longer time scales (56) ($n = 13$) or to conduct predictive analysis (57) ($n = 4$). The possibility of data customization is described in almost half of the papers considered in the review. This includes the possibility of (a) selecting and filtering datasets (58) ($n = 27$), (b) searching for datasets of variables (38) ($n = 8$), and (c) sorting or grouping data (59) ($n = 4$).

In addition, ten papers describe dashboards that offer direct export e.g., of data files, screenshots (50) or reports (60). These downloads can be used for in-depth analysis, as illustrative material in meetings, or they can be uploaded into other tools for further use

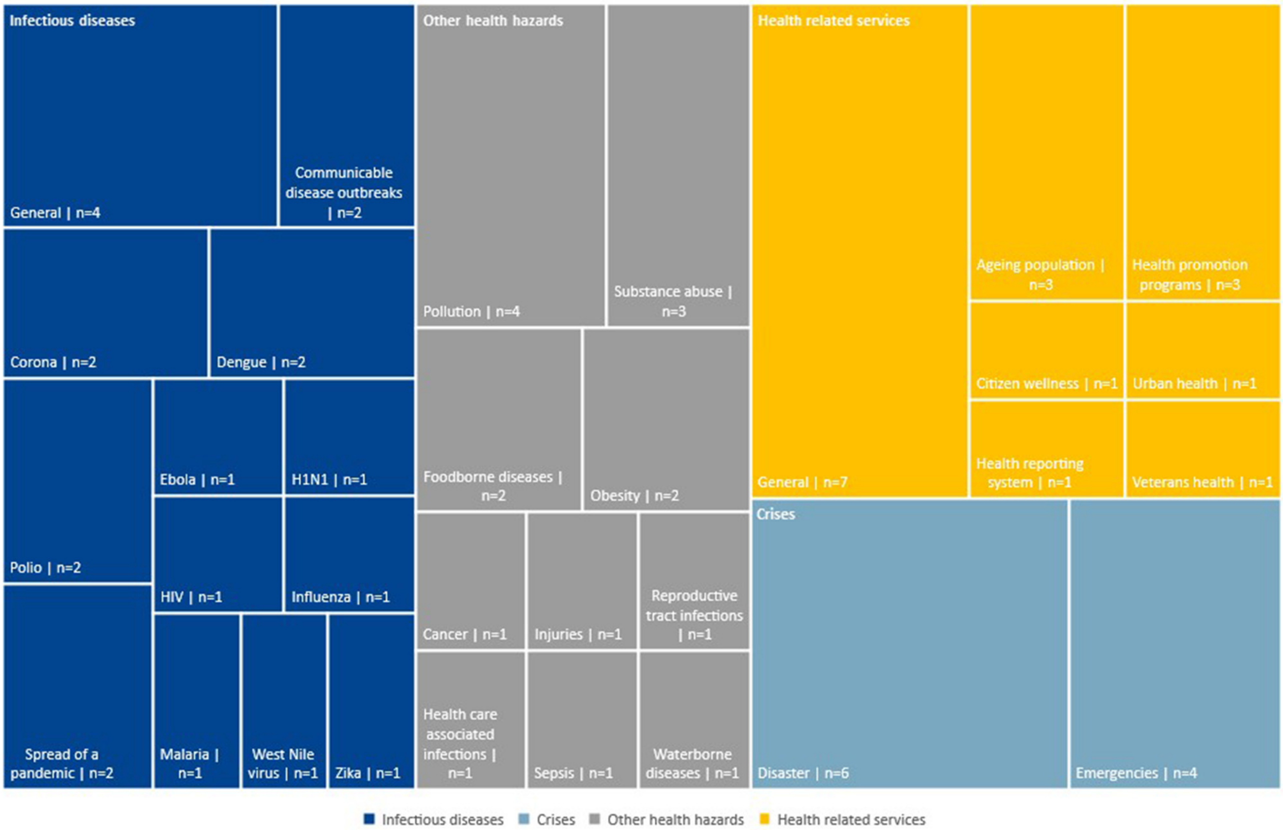

FIGURE 4
Subcategories of the four main dashboard topics.

(61). For participatory dashboards that rely on data from sources such as the public or medical staff (62), the possibility to directly add data to the dashboard is an important function. Data entry is provided through web-based report files (63), customized online forms, via posts or SMS and some dashboards provide direct data upload (64). To further enhance user experience, data can be copied and edited (65) ($n = 22$). Eight papers note that an alarm function is particularly useful for dashboards on crisis management, which allows users to receive messages about alarming situations or noteworthy developments via SMS or email (66). Seven dashboards make use of apps to display alerts or to report data (64).

To facilitate cooperation and communication between dashboard users, dashboards can offer the possibility to communicate within the dashboard (67) via discussion forums, messaging and comments (68) ($n = 10$).

Over one third of the described dashboards offer possibility to customize the visualization of the dashboard ($n = 24$). Especially zooming in or out of maps and drilling down to a specific region, for example, enables the user to explore the data in detail (47) ($n = 12$). Moreover, modifying templates, charts and other visual elements enhances user experience (59) ($n = 3$) (see Appendix F).

3.2. Using dashboards in public health: challenges and objectives (RQ 2)

In terms of RQ 2, dashboard objectives offered answers to public health challenges. First, we will sketch these public health objectives and challenges. Second, the objectives and challenges of public health dashboards described in the study sample will be outlined (see Appendix G).

3.2.1. Public health challenges addressed (RQ 2.1a)

3.2.1.1. Challenge: data collection for developing and implementing interventions

The first challenge addresses the identification of health threats by adequate surveillance/monitoring systems. These health threats can be classified into three categories. In some of the articles examined, the disease is explicitly associated with certain risks or vice versa, leading to counting in several categories (see Appendix H):

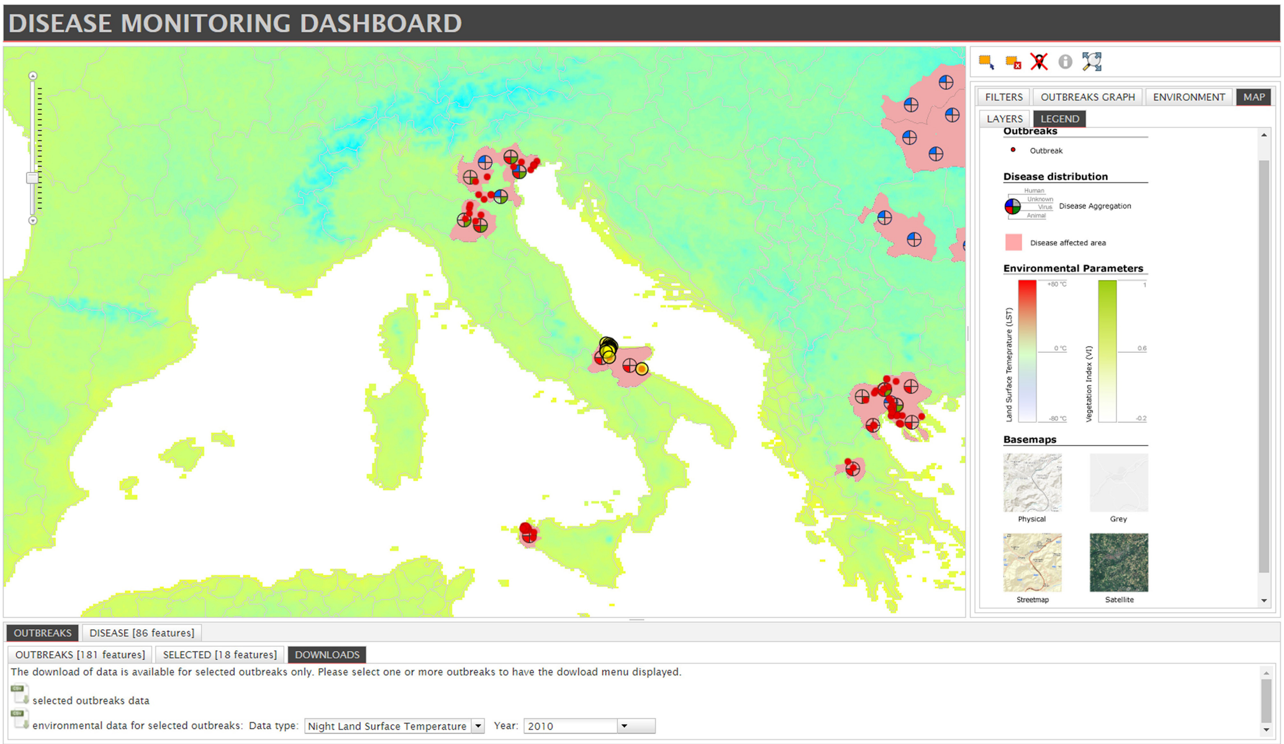

FIGURE 5
Example for a map with symbols, taken from "Disease Monitoring Dashboard" by Lara Savini et al. is licensed under CC BY 4.0 (38).

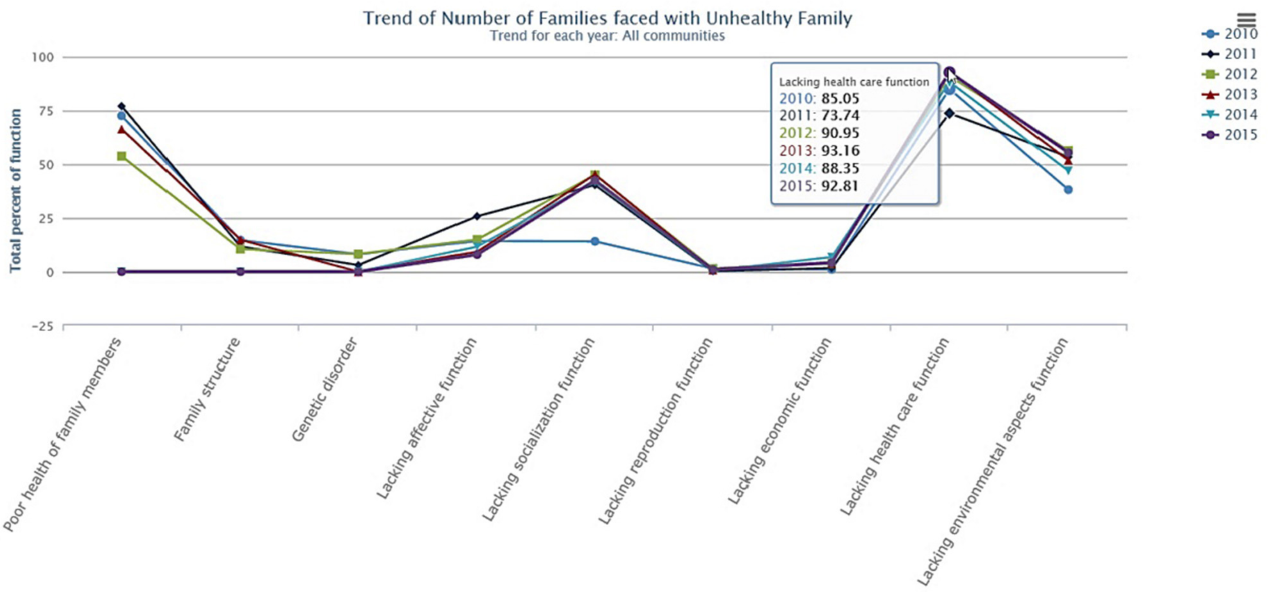

FIGURE 6
Example for a line graph, taken from "Trend of Number of Families faced with Unhealthy Family" by Puangrat Jinpon et al. is licensed under CC BY-NC-ND 4.0 (49).

a) Risks such as obesity (69), environmental pollution (70), food contamination (64), or injuries (51) ($n = 18$);

b) Communicable/infectious diseases like Dengue Fever (33) or reproductive tract infections (62) ($n = 29$) as well as non-communicable diseases like cancer (55) or dementia (71) ($n = 10$);

c) Emergencies such as natural catastrophes (72) or human-made disasters (73) ($n = 17$).

All three kinds of health threats are a global issue beyond political borders due to rising cross-border mobility, poverty or climate change. This requires an alignment of data: So far, missing or not transferable data makes it difficult to identify new diseases (58), to track and explore these diseases (74) as well as to develop strategies eliminating causes for illnesses or death (54).

3.2.1.2. Challenge: communication management and the use of information and communication technology

Related to the first challenge is the question of how to manage the vast amount of produced and collected information in public health. All articles included in the sample deal in one way or another with time, effort and cost as a key challenge in dealing with the high volume of data and its digitisation. Articles critically addressed an insufficient use of health-related ICT solutions in (1) monitoring social disparities leading to higher mortality and morbidity rates (62), (2) enabling access to health care as a marginalized community (64), or (3) dealing adequately with mis- and disinformation (52, 75).

Furthermore, a lack of training for health workers was stated—leading to an improper use of digital tools (75). These shortages result in (a) a poor management of scarce resources (72), (b) missing target group specific evidence-based communication strategies including the tracking of health issues as an objective (52) and (c) inefficient decision-making (76) leading to high economic and social costs.

3.2.2. Public health objectives pursued (RQ 2.1b)

Four main public health objectives could be identified to tackle these challenges. (A) Threatening situations shall be controlled, for example, through surveillance or risk prevention (77) ($n = 40$). (B) Information management has to be improved ($n = 26$) by for instance enhancing knowledge (75) or addressing target groups (78). C) Quality of life has to be enhanced ($n = 17$) by improving health care and services, e.g., through health promotion (39) or risk reduction (79). D) And in response to threatening situations, public health policies resp. measures have to be adjusted ($n = 16$): Policy programs focusing on health promotion, for example, need to be sustainable and long-term, community protection initiatives need to be supported, and digital tools for efficient decision-making need to be implemented as well as their access guaranteed (42).

3.2.3. Specific technological or administrative challenges related to the use of public health dashboards (RQ 2.2a)

Besides the distinctive objectives of public health dashboards, the reviewed literature also helps to extract various challenges (see Appendix G) that might be of relevance while constructing, using or deploying dashboards in a public health context. The identified dashboard challenges refer to (a) the visualization and processing of the data ($n = 46$), (b) the development of the dashboard ($n = 7$) and (c) the use of the dashboard ($n = 9$).

3.2.3.1. Challenges regarding the visualization and processing of data

First and foremost, the identified literature focused on different challenges associated with the visualization as well as the complexity, integration, quality and analysis of data. Zhu et al. (53), for example, underline the challenge that data visualizations need to be adaptable to different usage patterns as well as scenarios, while Zheng et al. (80) accentuate the need of accurate, visual information summarization for an appropriate understanding of e.g., crises or outbreak events. This last aspect already points to another challenge, associated with the development and use of public health dashboards: the complexity of visualized data. Husain et al. (59) note that the complexity and heterogeneity of (big) data may ultimately constrain the use of established methods, tools and services. In this context, challenges regarding the construction of dashboards may especially involve the need to tackle possible information overload (76), associated with e.g., data redundancy or the amount of information, received by a respective dashboard system (44). Corresponding with this finding, another issue described in the reviewed literature is the integration and transfer of data from diverse and heterogeneous sources. Data collected through different systems such as spreadsheets, via email or non-interoperable systems could cause serious problems in regards to its integration in a coherent dashboard system (65). Lack of standards or unstructured data formats, often coming from different sources (76), may ultimately inhibit holistic data understanding and interpretation (59). In addition, the reviewed articles highlighted that there are challenges in designing dashboards in terms of data quality, especially in the context of public health. In this context, Vila et al. (40) note diverse challenges such as data accuracy (66) and consistency as well as ensuring and fulfilling the legally required regulations on data protection. Lastly, the literature also frequently discussed challenges regarding the analysis of data. Rees et al. (37) accentuate that the type of surveillance method employed by involved response units (for example in infectious diseases control) can lead to an under- or overestimation in observed prevalence. Recently, and especially concerning dashboards that integrate data from diverse social media platforms, misinformation has been noted as a major problem, compromising data analysis (52). In line with this, the time needed to analyze visualized data may also pose a major challenge in dashboard design (68).

3.2.3.2. Challenges regarding the development of the system or dashboard

Further challenges discussed in the reviewed literature were concerned with the development of the system incorporating a dashboard or the dashboard itself. A concern that was selectively addressed in the identified literature has been the cost effectiveness in regards to a specific dashboard and its system architecture (81). Moreover, the use and design of dashboards in a public health context also faces legal challenges in particular, as pointed out by Vila et al. (40). As already mentioned, the design of dashboards and the use and visualization of specific data needs to be aligned with and fulfill respective government regulations and laws.

3.2.3.3. Challenges regarding the use of dashboards

Other major challenges that have occasionally been discussed in the reviewed articles relate to the actual use of a dashboard. In this context, the articles particularly highlight challenges with regard to the use of a corresponding dashboard by specific user groups. Key aspects in this context were that the dashboard itself is "user-friendly" (44), implying the need to design dashboards that are easy to understand, appealing and intuitive. Appropriately designed systems should take the information-seeking behavior of respective user groups and their respective health literacy skills into account (82), as these aspects may ultimately affect the utilization of a dashboard and the interpretation of its visualized and aggregated data sets. Furthermore, and with special regard to participatory dashboards, the design of a dashboard system needs to be concerned with securing the pro-active participation of focal user groups (68).

3.2.4. Specific technological or administrative goals related to the use of public health dashboards (RQ 2.2b)

Besides underlining the challenges associated with the development or use of public health dashboards, the reviewed literature also helps to identify objectives that are specifically linked to the use of dashboards in a public health context (see Appendix G). Overall, the objectives that are discussed in the literature can be grouped into four main categories, underlining the aims that are hoped to be achieved by implementing or using a dashboard: (a) improving surveillance and monitoring (n = 49), (b) improving (crises) management procedures as well as inter-agency coordination (n = 22), (c) providing (public) access to information (n = 18) and, finally, (d) enabling participation (n = 8).

3.2.4.1. Improve surveillance and monitoring of public health risks or crises

The literature reviewed primarily highlights the function of dashboards to improve the monitoring and surveillance of, for example, infectious disease outbreaks. Benson et al. (83) note that dashboards might support involved response units in situational awareness and collaborative decision-making. In this context, the cross-verification (68) and early warning (34) of outbreak or other adverse events as well as the possibility to trace back and rapidly detect respective crises situations (74), were repeatedly underlined as objectives of data visualization as well as aggregation via dashboards. However, the discussed dashboards are not just limited to the immediate surveillance of crises events, but also aim at the prediction of outbreaks and other adverse events, as was noted for the dashboard, focused on in Jamil et al. (77). More so, dashboards aim to present relevant information and thus reduce time spent searching for information (44).

3.2.4.2. Improve (crises) management procedures and inter-agency coordination

The above mentioned factors associated with the improvement of surveillance and monitoring ultimately correspond to another, frequently discussed objective of public health dashboards: the improvement of (crises) management procedures. In this context, public health dashboards support decision-making under high time pressure and thus reduce the time needed for effectively mitigating the effects of outbreak events (63). In addition, they improve inter-agency coordination or cross border surveillance (58) by combining and aggregating data from agencies with different mandates (37). Furthermore, dashboards may as well facilitate information sharing between different actors.

3.2.4.3. Provide (public) access to information

The legitimation of political-administrative decision-making by means of data visualization through public health dashboards played a marginal role in the reviewed literature and, even more so, was not mentioned as a particular objective of information provision. Nevertheless, the relevance of public access to certain information was discussed in a fraction of evaluated articles—both for non-professionals and citizens as well for special user groups, such as public health experts and professionals (64). Associated with this, Thomas and Narayan (62), for example, discussed the relevance of dashboards for supporting the health of citizens by increasing access to health related information and allowing to understand crises situations across space and time (37).

3.2.4.4. Enable participation

In addition to the mere access to or the reception of relevant information, reviewed articles have occasionally also noted the active involvement and inclusion of user groups in order to support the surveillance and management of infectious disease outbreaks or public health in general. Tegtmeyer et al. (74), for example, cite the general participation of users as a distinctive objective of their focal dashboard. Moreover, Rees et al. (37) explicitly note the involvement of users in reporting—in this case: of suspect animals—as an objective of their dashboard.

3.3. Information needs when engaging with public health dashboards (RQ 3)

The findings presented in the following are based exclusively on the assessment of the eighteen identified user studies. We refrain here from quantifying aspects and thus from stating item numbers in relation to the various information needs. This particular caution is mainly due to the fact that relevant terms such as "ease-of-use" or "usability" were often not operationalised consistently or at all in the evaluated articles. This in turn has made it difficult to compare the results of the different articles in a meaningful way. At the same time, however, specific article numbers are not given here, as a small n could imply that a certain aspect was not as relevant as others were, although this often does not have to correspond to its actual relevance, but can also be related to the focus of the studies and the overemphasis on other aspects.

Although the information needs of specific user groups may vary due to the diversity of dashboards (see Appendix I), a number of studies have identified similar core criteria.

The ease of use was one aspect frequently mentioned in the studies. The user must be able to use the dashboard intuitively. Some applications require technical understanding or a certain literacy as well as skills and qualifications of the users, which influences their acceptance of the dashboard and its implementation into the workflow (47). As described by Hamoy et al. (75), it is beneficial to train the staff or users of the dashboard, e.g., through workshops. The provision of a hotline can be another way to improve acceptance and ease of use (75). Furthermore, the technical devices should allow for easy handling of the application. Usability is otherwise limited (e.g., small screen for displaying complex tables).

Besides the qualifications of the users, the compatibility of the dashboard with the work environment of the user is crucial for its successful implementation. Several papers describe the demand that dashboards have to be compatible with the users' workflow. This implies that its use (a) does not entail more work but facilitates specific work steps like data collection, updates or analysis while also (b) saving time (42, 75). The latter often includes the need to work with real-time data. Thus, saving time refers to both, finishing a task in less time but also saving time in the provision of data. The application should allow the quick update of data (61). There are also additional delays when data needs to be validated or verified. Dashboards that can be accessed independent of time and place are particularly convenient (84).

Rural areas are a particular challenge with regard to the collection of data, as the infrastructure is not always in place and developers have to plan with fewer employees, lack of electricity, poor internet reception, and inadequate availability of technology (75). In this case, the question of how users can access and enter the data is a particular challenge.

Several aspects can enhance the engagement with a dashboard and facilitate the usage. For example, several papers state that users wish for interactive features such as notifications. These can be used to inform the user about news on the dashboard or can pop-up whenever a task, such as a data upload, is completed. Besides notifications, the possibility of networking is mentioned to be a helpful and often requested feature of a dashboard (61, 85). Depending on the requirements, networking can include a messaging tool, the possibility to share data or a way to comment on or reply to other users' posts or other forms of input (85).

As described above, a multitude of visual elements is used in the dashboards. However, the use of different elements and colors is rarely evaluated in detail. More often, studies describe the overall success of the dashboard. It can be noted that the use of colors seems to facilitate understanding and is mostly intuitively understood [e.g., red for danger or severity, see Bernard et al. (55)].

3.4. Mixed Methods Appraisal Tool

Of the eighteen studies that were explicitly considered as user studies (and thus considered in the critical appraisal stage via MMAT), eight articles exclusively applied qualitative methods, while seven articles were decidedly quantitatively oriented in their study approach (see Appendix J). Three articles employed a mixed methods approach by combination of qualitative and quantitative methods. Our sample included neither randomized controlled trials nor non-randomized studies. Surveys were the method most often used in the quantitative studies. However, the insufficient description of the sample and target groups in some articles sometimes did not allow for an accurate assessment of the representativeness of the survey sample for the target population.

Moreover, in most cases, a final assessment concerning the risk of nonresponse bias as well as the appropriateness of the studies' statistical approaches was confounded by the lack of necessary data or information in the respective papers. In regards to the qualitative studies, interviews, were the most frequently used method. However, in some cases, authors simply stated, that they had received "input" from an unspecified group, which made it difficult to clearly evaluate the methods being used in these studies. Other methods used were focus groups as well as participant observations.

All in all, the quality appraisal of included studies by means of the MMAT yielded an average overall rating score of 40%, indicating a rather moderate average methodological quality of the eighteen studies considered in the quality appraisal step of our literature review.

However, significant differences in overall quality can be observed between the different types of studies. With regard to the qualitative oriented studies considered in this step of our literature review, a quality range of 20 to 100% can be noticed, whereby the average score for qualitative studies was 55%, suggesting a score higher than the overall average score. Assessing the quantitative studies as well as studies with a mixed-methods design, we see a considerably lower mean value with regard to the respective study quality (qualitative studies: 29%; mixed-methods studies: 27%). However, these final assessments should be approached with caution, since we had to select "Can't tell" at least once in each study, except for two qualitative oriented studies. As was discussed above, this indicates that critical or relevant data, required for a final assessment on a certain item, is often missing. This deficit, however, points to a general problem of methodological reporting in empirical studies, which is why a comprehensive and accurate appraisal of included studies is often more difficult than anticipated.

4. Discussion

Assuring public health in a world that is confronted with ever changing challenges due to globalization, climate change and various other developments demands for adapted technologies. The results of this literature review show that dashboards cover a wide range of public health issues—from foodborne diseases to environmental hazards (see Appendix B), and provide data for different target groups such as medical experts, researchers, or specifically concerned communities. Dashboards have become an important tool for communicating health risks through the visualization of data—offering options such as (near) real-time monitoring or retrieving data from a variety of sources ranging from health authorities on different levels, healthcare organizations to research organizations and the media. The dashboards addressed public health objectives in at least one of the four dimensions: Controlling threatening situations, improving information management, enhancing quality of life and adjusting public health policies and measures (see Appendix H).

This review examined 65 papers that allowed conclusions to be drawn about the objectives and challenges of public health communication via dashboards. In total 18 of them also provided user research and information on the user needs. Most of the papers emphasized that dashboards enable users to add, enter, copy or merge data followed by data export opportunities and data analysis. Involving users and enabling their (continuous) participation thus not only forms an objective of information provision via dashboards themselves, but also aims at supporting and improving the surveillance and management procedures, thereby improving public health surveillance. Linked to this is the argument that detection, prediction and the management of outbreaks will become easier. Dashboards provide a timely and accurate overview of the situation and automatically notify the user of alerts. We can conclude that the overall aim is thus to raise the situational awareness of health professionals, politicians and citizens in general.

Secondly, communication (management) processes can be improved through data reporting and sharing as well as specific data visualizations such as maps or graphs. Here our systematic review sheds light on the specific challenges faced by dashboard developers. These range from the integration and transmission of data from different and heterogeneous sources, to the alignment of data with legal requirements, data accuracy, as well as appropriate and comparable surveillance methods (see Appendix G). Interestingly, dashboards that work with social media data are particularly challenged when it comes to misinformation. As for the role of misinformation in crises (51), this is a research gap that definitely needs to be addressed.

Design is a challenge and essential: Maps showing disease or risk distribution and diagrams in all their variations play the most important role—often combined with questions of color use. Graphics, animations, or audio-visual means such as social media streams or videos were less frequently reported. Although a variety of visual elements are used in the dashboards, a detailed evaluation of these elements is missing, especially an evaluation of the interdependencies of different modes such as layouts or color. This is consistent with research gaps identified by Berg et al. (16). The compositionality of these individual modes can produce a different meaning compared to analyzing the modes separately (86). In addition, and given that somewhat more than a third of the articles included in the review describe how users can customize the visualization of the data, a related research question for future studies would have to be: How do dashboard users interpret the visualized data and make an overall coherence between the interacting modes? This also refers to the long-held recognition that users, as recipients, need to be seen as active participants who contribute content (87), draw their conclusions from the data on risks and take protective measures if necessary, or may misjudge risks, for example due to a lack of health literacy.

Another finding of this review also concerns the role of users in improving access to information through dashboards. Those studies considering the specific challenges and objectives from a technological, administrative, as well as a user perspective made evident how dashboards increase access to health related information and enable an understanding of critical public health issues (37, 62). Important for understanding the data, however, is health literacy, which is very rarely addressed in the sample studied. This also corresponds to existing research gaps identified so far and demands for future socio-technical research (13, 88).

One aim of this literature review was to identify information needs of dashboard users (see Appendix I). However, most studies are limited to describing the process of technical construction and design of a particular dashboard ($n = 47$). A comparatively small number of publications deal explicitly with the reception of dashboards by users ($n = 18$). Furthermore, some of these studies are limited to a purely functional evaluation of the dashboard by the respective development teams without applying user-centered design approaches. Identifying information needs by using risk communication models such as the Health Belief Model or the Extended Risk Assessment Model is the exception (58, 62). Relevant constructs such as risk perception, perceived severity and self-efficacy as well as existing concepts such as health literacy, numerical literacy and data visualization literacy (88) are not sufficiently taken into account to provide insights for data visualization and thus increase the comprehensibility of the data. Thus, the sample did not provide sufficient information on whether the dashboards meet the requirements of the respective users. This is consistent with the findings of reviews looking at public health dashboards (11, 89) revealing a relevant research gap, which should be taken into account for future projects. Accordingly, it can be concluded that a user-driven development strategy, theory- and evidence-informed, is key to developing a user-friendly design by capturing key information through a user-friendly interface design, for example by collecting data on perceived ease of use and perceived usefulness.

Precisely because public and scientific institutions also want to reach the public via an open data policy with the dashboard they created in connection with the COVID-19 pandemic (35), these gaps need to be explored. One way to do this is to use known communication models on information behavior to survey information needs and to take the corresponding results into account when designing the user interface.

4.1. Limitations

One limitation of the analysis of the papers was the inconsistent differentiation of the term "dashboard". While some papers only refer to dashboards as the visual representation of data (63), others describe entire systems that include various functions, as dashboards (73). We applied the understanding of the term that was expressed in the respective papers to our analysis.

As already described, the papers report little on their methodological approach. Accordingly, the educational effect for other researchers is limited. Even more than a shortcoming of the respective authors, we see a possible reason in the restrictive publication requirements of some journals, which make a detailed description of the methods difficult or even impossible.

Although a systematic approach in retrieving articles on public health dashboards was followed, we cannot guarantee that all eligible studies offering answers to the research questions were found. Firstly, we limited the number of years (2010–2020) and databases. Since we limited the field to dashboard solutions that are scientifically covered, the overview (Appendix B) does not provide information on all existing public health dashboards. Secondly, we had to differentiate between a user study and a descriptive one including brief communications articles as well as developer studies—excluding studies that only focus on predictive models instead of developing a real dashboard. There may be studies in which the difference between modeling and developing is very small. Thirdly, we conducted a review that explicitly aimed at papers from various scientific disciplines. The article followed specific rules of writing and structuring articles resulting in challenges to compare data, reporting, etc. Finally, we reviewed data reported in included studies. We did not request any further data by contacting the first authors.

5. Conclusion: implications for dashboard research

The aim of our systematic review was firstly to identify the public health challenges and objectives that were displayed by dashboards between 2010 and 2020. Analyzing the visualization of data and included functions, we aimed to outline solutions that dashboards offer as a specific digital health technology. Secondly, the review aimed to evaluate the empirical studies that focused on the needs of the users by applying the MMAT. Although dashboards have come to play an important role in data-based visualization of public health issues, particularly due to their use during the COVID-19 pandemic, the number of publications explicitly addressing user reception of dashboards is small. As a specific form of data visualization, dashboards are of particular importance—especially, when detecting and monitoring risks and crises and their effects on public health.

The dashboards studied reflect the challenges identified in the field of public health in relation to technological progress. They enable faster data collection, sharing and analysis of data. However, one identified research gap seems to be very important with regard to the usefulness of this risk and crisis communication tool. If the needs of users in the context of health information behavior are not sufficiently empirically investigated, the benefits of dashboards for risk reduction or risk behavior change will remain without evidence. This point goes hand in hand with the need to examine the information behavior of specific target groups based on existing and valid theoretical models and to think about multimodality in meaning-making.

Applied research would benefit (a) from including risk communication models and constructs such as scientific literacy as well as different disciplinary perspectives (e.g., IT, communication studies, psychology) and (b) from a more inclusive approach that involves potential target users throughout the construction and design process. For this, a pre-design consideration of risk information needs that potential target groups might have is essential.

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/s.

Author contributions

AS: conceptualization (main idea and theory), project administration, methodology (design and operationalization), data collection, data analysis, writing—original draft, and writing—review and editing. FB: methodology (design and operationalization), data collection, data analysis, writing—original draft, and writing—review and editing. JG: data analysis, writing—original draft, and writing—review and editing. G-FB: conceptualization (main idea and theory) and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.999958/full#supplementary-material

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Detecting user experience issues from mHealth apps that support stroke caregiver needs: an analysis of user reviews

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Background: Existing research has demonstrated the potential of mHealth apps in improving the caregiving outcomes of stroke. Since most of the apps were published in commercially available app stores without explaining their design and evaluation processes, it is necessary to identify the user experience issues to promote long-term adherence and usage.

Objective: The purpose of this study was to utilize published user reviews of commercially available apps to determine the user experience issues to guide future app development in stroke caregiving.

Methods: User reviews were extracted from the previously identified 46 apps that support stroke caregiving needs using a python-scraper. The reviews were pre-processed and filtered using python scripts to consider English reviews that described issues faced by the user. The final corpus was categorized based on TF-IDF vectorization and k-means clustering technique, and the issues extracted from the various topics were classified based on the seven dimensions of user experience to highlight factors that may affect the usage of the app.

Results: A total of 117,364 were extracted from the two app stores. After filtration, 13,368 reviews were included and classified based on the user experience dimensions. Findings highlight critical issues that affect the usability, usefulness, desirability, findability, accessibility, credibility, and value of the app that contribute to decreased satisfaction and increased frustration.

Conclusion: The study identified several user experience issues due to the inability of the app developers to understand the needs of the user. Further, the study describes the inclusion of a participatory design approach to promote an improved understanding of user needs; therefore, limiting any issues and ensuring continued use.

KEYWORDS

mHealth, APP, stroke, caregiver, user experience, needs, design

1. Introduction

Stroke caregiving is often associated with persistent psychological distress leading to depression, decreased life satisfaction, and reduced quality of life (1). The impact of stroke caregiving is due to the sudden onset of the disease that requires the caregiver to adjust to a new role with little to no preparation (2) resulting in the caregiver feeling disconnected, isolated, and distant from the recovery process (3).

Technological interventions such as telemedicine, mHealth and so on have in the past highlighted numerous benefits in the healthcare environment to enable caregivers to easily access valuable resources and participate in a variety of activities using their devices (4). These interventions allow the caregiver to ask questions or manage the survivors' needs at any given place or time (5). Hence, ensuring they feel prepared to manage the disease throughout the disease trajectory (6). In addition to ensuring that the caregiver feels prepared (7, 8), technology in stroke caregiving has the potential to reduce caregiver burden (6, 9), improve caregiver health status (6, 9–12), ensure better healthcare utilization (13), and enhance caregiver self-efficacy and esteem (9, 11, 14).

For over a decade, the number of people using mobile or other portable devices has increased exponentially (15) as a means to communicate with one another and access information at any place or time (16). In 2020, it was estimated that more than 85% of Americans own a smartphone, which is expected to rise in the coming few years (17). Consequently, there has been a significant rise in the development of mobile health apps (18) to address critical healthcare delivery issues through education/awareness, improved risk factor control, efficient screening procedures, and sustainable health system cost reductions (19). The benefits of mHealth apps in healthcare are promising, with research highlighting enhanced support for families caring for their loved ones, improved symptom management, and decreased hospital visits for the survivor (20).

Despite the potential benefits of mHealth applications, the overall adherence of these technologies is relatively low, with most end-users withdrawing from the application within 2 weeks of download (21). For many years, there have been many techniques to measure factors that may contribute to the lack of adherence, including; usability, efficiency, effectiveness, learnability, usefulness etc. In recent times, user experience have been considered by several authors as a recognized standard (22) due to its ability to achieve user satisfaction by focusing on hedonic and pragmatic goals (23).

This study, therefore, aims toward analyzing and evaluating the user reviews of apps that support stroke caregivers healthcare needs (24) based on seven user experience dimensions (25). The results of this analysis can potentially help mobile app developer's researchers to understand the factors that affect long-term adherence and usage in stroke caregiving technology.

Abbreviations: mHealth, Mobile health; NLTK, Natural language toolkit; LDA, Latent dirichlet allocation; CSV, Comma separated values; App, Application; TF-IDF, Term frequency-inverse document frequency.

2. Methods

2.1. App identification

A search strategy was developed based on a previous study (26) to identify apps related to stroke and caregiver. An electronic search was conducted between December 2022 and January 2023 of two app stores (i.e., Google Play Store and Apple App Store) and one commercial mobile repository (i.e., 42 matters). The search involved individual and Boolean searches of stroke and caregiver related MeSH terms identified through PubMed to ensure comprehensiveness.

Apps identified through the search were extracted and stored in a Microsoft Excel spreadsheet, where duplicates within the same platform (such as Android and iOS respectively) were identified and removed. Further, the apps available for different platforms were combined to a single row within the spreadsheet to prevent duplication. The apps were initially screened based on their published meta-data using a well-defined selection criterion (Table 1). After screening, the description of potentially relevant apps was independently reviewed by two authors to determine eligibility.

2.2. Review extraction and pre-processing

The user reviews and ratings from included apps were extracted from the app store pages (i.e., Google Play Store and Apple App store) using a Python-based scraper script and stored in a CSV file.

Prior to analyzing the dataset, the data in the CSV file were pre-processed using multiple python-based toolkits to ensure the system can understand the data. The pre-processing technique utilized in this study includes:

- Dataset cleaning and Unicode normalization: It is crucial to have clean and high-quality datasets for any data processing application. The process of dataset cleaning involves splitting text into individual words and handling punctuations and cases. This process was performed using Python NLTK (or Natural Language Toolkit) script making it ready for machine learning and deep learning algorithms. Further, all characters that do not meet the UTF-8 character list were filtered using a Python-based script. For example, the script filtered Unicode characters such as "ầ" or "ễ" and replaced them with "a" and "e," respectively.

TABLE 1 Inclusion and exclusion criteria used in the identification of Apps.

Criteria	Description
Inclusion	• Published in English language • Can be used in stroke care • Consists of a description of the app • Ability to address the needs of a stroke caregiver, i.e., information, involvement, self-care and support (24)
Exclusion	• Not available in English language • Not accessible on the app store website • Was not reviewed by the user through comments and ratings • Was designed for other chronic conditions • Was designed for clinicians and/or other healthcare professionals

- Stop word removal: Stop words are a list of the most commonly used words that do not have solid semantic properties but are required in a language for communicating information. These words include "the," "a," "in," "and," "this" and so on (27). The stop words were removed using a stored list present in the Python NLTK to decrease the size of the dataset while reducing the time to train the system and improve the performance during classification.
- Lemmatization: Lemmatization is the process of different grouping words together with a similar meaning to be analyzed as a single item. For example, the term good or better have the same meaning but are represented differently. A Python NLTK script was implemented along with the WordNet Word repository to identify words in the dataset with similar meaning using operations such as tokenizing, classification, stemming, tagging, parsing, and semantic reasoning to ensure greater accuracy.

2.3. Review filtration

Positive reviews were excluded from this study as the primary goal was to identify user experience issues present in the app. To determine all the positive, neutral, and negative reviews, sentiment analysis was conducted. Sentiment analysis is a type of text classification that relies on natural language processing, data mining, machine learning, information retrieval, and other processes to indicate the sentiments user expresses (i.e., positive, neutral, or negative) toward a product or feature (28). To perform a sentiment analysis on the dataset, the output of pre-processed reviews was categorized to determine users' positive, neutral, and negative opinions using a VADER sentiment library in Python.

The VADER library includes a lexicon and rule-based sentiment analysis tool to score text based on its level of positivity and negativity. The tool incorporates numerous lexicon features related to common sentiment expressions, including Western-style emoticons, sentiment-related acronyms, initialisms, and commonly used slang to determine sentimental values. Further, the tool converts feature candidates into sentiment expressions using a wisdom-of-the-crowd (or WotC) approach (29). The outcomes of the sentiment analysis process would be a sum of all compound score values between the ranges of −1 to +1, where the positive sentiment would be greater than or equal to +0.05, and the negative sentiment would be less than or equal to −0.05. All other compound score values would be denoted as neutral sentiments. The negative and neutral reviews were extracted and stored in a CSV file to analyze user experience issues.

2.4. Review analysis

The analysis of the negative and neutral reviews involved two stages to identify the user experience issues of stroke caregiving apps. In the first stage, the negative and neutral reviews were classified in python-language based on a TF-IDF vectorization and k-means clustering technique. The Term Frequency-Inverse Document Frequency (TF-IDF) technique is a process that converts the review into usable vector. It generally involves two concepts, (i) term frequency where the number of occurrences of a specific keyword is identified within the corpus represented in the form of a matrix whose rows include the number of reviews and columns represents the distinct terms in the corpus, and (ii) document frequency in which the number of reviews containing a specific keyword is determined. The inverse document frequency, however, determines the weight of a keyword to determine the occurrence of the keyword within the corpus. The TF-IDF score is expected to increase proportionally when the count of a specific keyword increases within the corpus, and can be calculated based on the product of *tf* and *idf* as given below (30):

$$tfidf(t,d,D) = tf(t,d) \times idf(t,D)$$

where *t* denotes the terms; *d* denotes each document; D denotes the collection of documents.

Term Frequency (tf):

$$tf(t,d) = \frac{Number\ of\ times\ the\ keyword\ t\ appears\ in\ a\ review}{Total\ number\ of\ keywords\ in\ the\ corpus, d}$$

Inverse Document Frequency (idf):

$$idf(t,D) = \log_e \frac{Total\ number\ of\ reviews\ in\ a\ corpus, D}{Number\ of\ reviews\ with\ keyword\ t\ in\ it}$$

The vectorized representation of the reviews is classified based on *k*-means clustering approach. *k*-means is an unsupervised learning algorithm that classifies the reviews into a certain number of clusters. The main idea is to define *k*-centroids for each cluster, and represent the vectorized data to the nearest centroid. The algorithm calculates the average position of the points based on the respective centroid and updates the position to determine the group to which each review belongs (31). The clusters are finalized when all points are at a minimum distance from their respective centroid, which are exported in the form of a CSV file.

During the second stage, two reviewers independently identified key issues within the apps based on the clusters represented within the CSV file. These issues were independently classified by the same two reviewers using NVivo 12 following the seven dimensions of user experience design, i.e., usable, useful, desirable, findable, accessible, credible, and valuable as shown in Table 2. Any discrepencies in the identification and classification of issues were discussed by all authors until a general consensus was achieved.

3. Results

The initial search yielded a total of 4,649 apps from various app stores (i.e., Google Play Store and Apple App Store) and app repository (42 matters). After removing duplicates, a total of 3,652 apps were screed based on their titles and meta-data. The descriptions of 171 apps were reviewed, of which 46 were included in this study. Figure 1 represents the app identification process used in the study.

A majority of the apps were developed by organizations ($n = 39$) generally located in the United States ($n = 32$). In addition, only two apps were developed by organizations funded by the government in Australia, and one app was developed by a healthcare professional in the United States as shown in Figure 2. The included apps were

TABLE 2 User experience dimensions as described by Morville (25).

Dimension	Definition
Usable	The system is easy to use and understand to achieve a desired goal effectively, efficiently and satisfactorily
Useful	The system needs to be useful and address the needs and wants of the user
Desirable	The visual esthetics of the system needs to be attractive and easy to translate
Findable	The functions of the systems needs to be findable and easy to navigate
Accessible	The system needs to be designed in such a way that users with disabilities can have the same user experience as others
Credible	The developer or company providing the system needs to be trustworthy
Valuable	The system needs to solve problems and deliver a return on investment

developed between 2009 and 2022 as illustrated in Figure 3 in both Android ($n = 40$) and iOS ($n = 41$) platforms. The features of these apps aimed at supporting a myriad of health needs, which can be classified into four critical needs especially in stroke caregiving, i.e., information ($n = 15$), involvement in care ($n = 32$), self-care ($n = 4$), and support ($n = 23$). Overall, the apps have a positive user rating with an average of 4.2 on a scale of 1–5, where 1 is the lowest rating and 5 is the highest rating. Supplementary Table S1 in the Supplementary material consists of the characteristics of apps included in this study.

3.1. Filtration of user reviews

The app meta-data extracted account for a total of 422,647 user reviews from the 46 apps included in the study. Out of 422,647 user reviews available, the python-based scraper extracted only 117,364 due to the limitations of both app stores (i.e., Google Play Store and Apple App Store), which formed the initial dataset for this study. The dataset

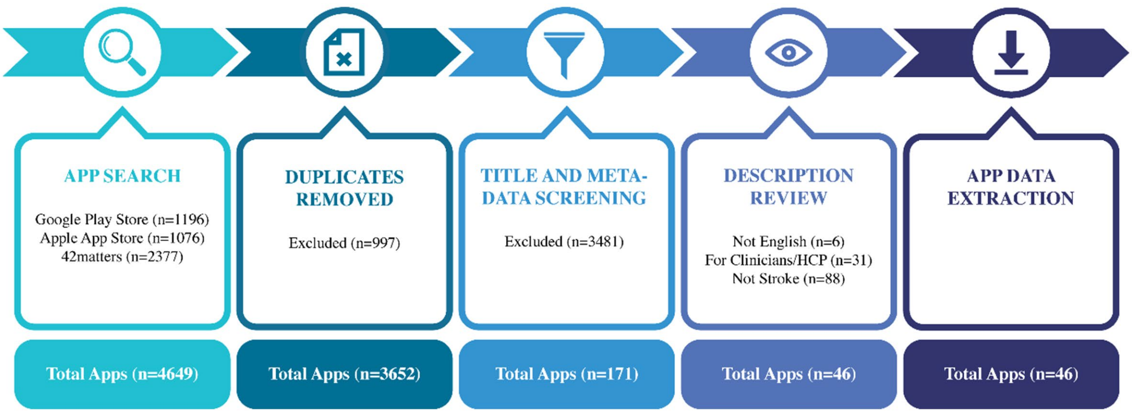

FIGURE 1
App identification process.

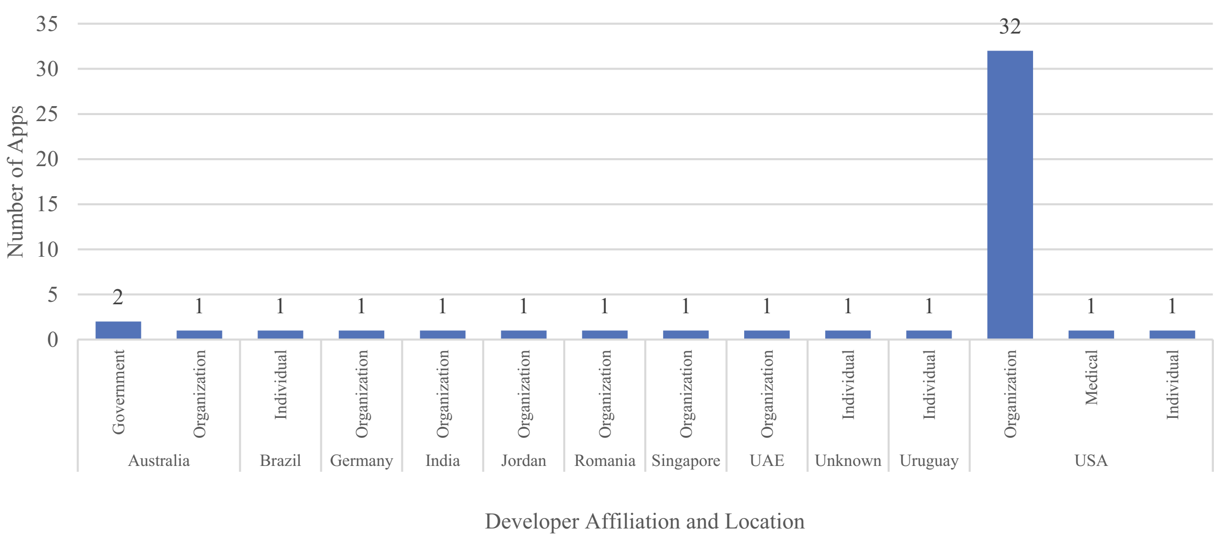

FIGURE 2
Distribution of Apps based on the developer affiliation and location.

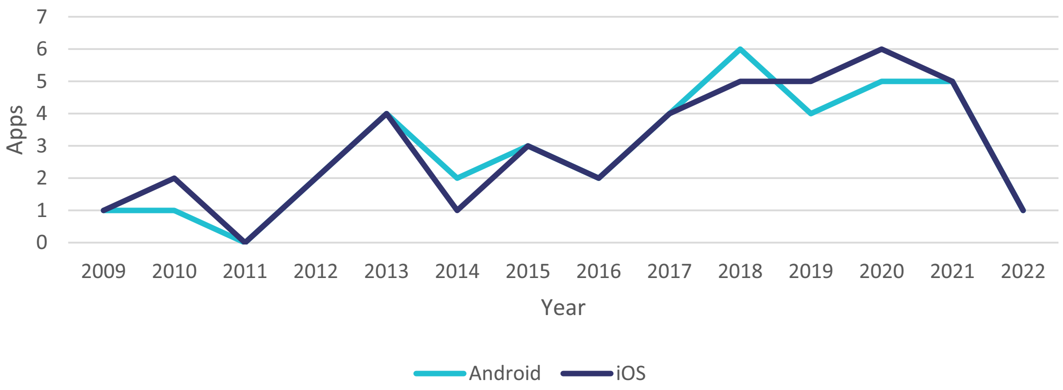

FIGURE 3
Distribution of Apps based on the publish year and platform.

was categorized based on user sentiments into positive (85,352/117,364), neutral (31,174/117,364), and negative (838/117,364) user reviews as illustrated in Figure 4. Positive reviews (85,352/117,364) and reviews not published in English (388/117,364) were excluded from the study forming a corpus of 31,624 user reviews that were classified based on the user experience dimensions described in Table 2.

3.2. Characteristics of user reviews

The corpus of 31,624 user reviews represents the user experience issues of 38 out of 46 apps as described in the Supplementary Table S1 in the Supplementary material. These user reviews consists of 11,360 unique users and 18,256 users with deleted accounts. Out of the 11,360 unique users, 9,385 users have only posted a single review, 1,910 users have posted two reviews, 46 users have posted three reviews, 17 users have posted four reviews, one user had posted five reviews, and one user had posted six reviews. These user reviews were posted in one or more apps.

Reviews posted by users with deleted accounts were excluded to ensure the findings are more trustworthy. Hence, 13,368 users reviews formed the final corpus that was analyzed in this study.

3.3. Analysis of the user reviews

Twenty-six clusters were identified based on the TF-IDF vectorization and *k*-means clustering technique as illustrated in Supplementary Table S2 in the Supplementary material. Each topic represents several issues within the app as shown in Figure 5 that were classified based on the dimensions in Table 2 to determine factors that affect overall user experience.

3.3.1. Dimension #1: usable

The first dimension, usability, consisted of four critical issues (unusable, compatibility, account issue, and feature issue) as described in several app reviews. The first issue described by the user was that the app was unusable due to constant crashes or freezing. In some cases, the app would also be slow to use or did not work which contributed to frustration. The second issue is with regard to compatibility, which is the inability of the app to work of a myriad of mobile devices irrespective of the platform. The third issue is related to the user account, where users described being unable to login or change password. In most cases, the users would receive an error, which is unclear and leads to confusion. The users, who were able to access their accounts, felt that the login process was complex and needed to be simplified, with one suggestion being the inclusion of a fingerprint login feature to reduce the number of steps. The fourth issue that is related to the app features was the most discussed that affected the overall user experience. Topics such as issues with (i) the reminder providing alerts at right times or being audible, (ii) missing notifications/alerts, (iii) location/GPS issues, (iv) internet or server connection issues, (v) customization of features such as alert volume and tunes, (vi) unresponsive buttons and scroll, (vii) effectiveness of the app in managing medication refills, and (viii) data upload were discussed by users within the app reviews. Users described the need for developers to fix these issues to improve their experience. Moreover, users described that the app widget, scheduling, and interface was difficult to use and outdated, with suggestions to include tutorials or help options to assist the user.

3.3.2. Dimension #2: useful

The second dimension, usefulness, was affected by three issues. The first issue is with the eligibility of the app. One user review described that the app was only available to adults, which resulted in it being uninstalled. Another issue narrated by the user includes the inability of the app to address all the needs of the user such as a complete medication list or missing features. Missing features reported in the reviews include ability to customize notifications, ability to log notes, features to edit and manage medications, ability to search and filter data, ability to import, export and print data, and ability to synchronize with other calendars or devices. The final issue faced by the user using an app to engage assistance from a formal caregiver was the lack of reply they would get to their message.

3.3.3. Dimension #3: desirable

The third dimension, desirability, consists of four issues related to the interface of the app. The critical issue that affects desirability is the inclusion of several advertisements (or ads) within the app. Users felt frustrated and annoyed with the number of ads they had to view to use the functionality of the app. Other issues included the lack of clarity and intuitiveness in the app interface making it difficult to

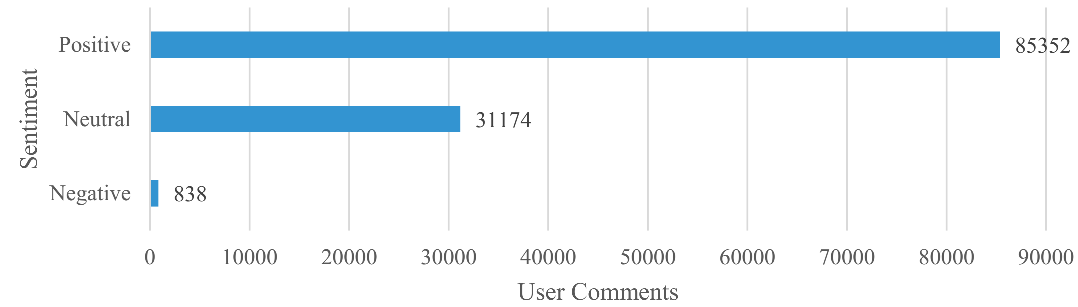

FIGURE 4
Distribution of App comments based on its individual sentiments.

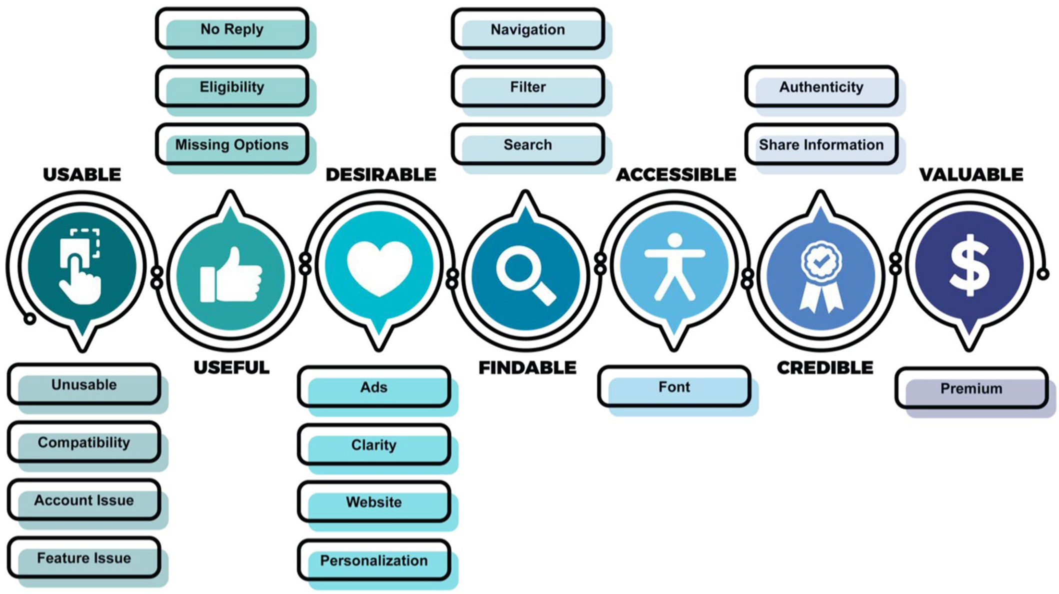

FIGURE 5
User experience issues.

understand, and the lack of personalization within the app to customize the app interface. For example, an app review described the inclusion of a dark mode feature. In addition, users reported issues with the website interface when accessing the app through other devices.

3.3.4. Dimension #4: findable

The fourth dimension, findable, consists of three issues with regard to the search, filter, and navigation of the app. Users described not being able to search or filter through their medication list making it difficult to perform their activities. The app reviews suggested including proper search options to find the required data. In addition, users found the navigation of the app extremely hard and confusing, with users suggesting the enhancement of menus to improve ease of use.

3.3.5. Dimension #5: accessible

The fifth dimension, accessibility, consists of one main issue, which is the font. Users reported having issues with the font size and color within the app that affected their ability to engage with the content provided.

3.3.6. Dimension #6: credible

The sixth dimension, credibility, consists of two main issues that leads to users uninstalling the app from their mobile devices. The first issue is authenticity of the app as users felt they were being scammed into paying for the features within the app. Moreover, users that contacted customer care services for assistance did not receive a reply, which increased their fears. Another issue faced was the reluctance of users in sharing their personal information with the app due to suspicions related to data privacy and security.

3.3.7. Dimension #7: valuable

The seventh dimension, valuable, consists of one critical issue that is the reluctance of users to pay from premium version. This is because users were looking for cheaper options and/or did not feel the app was worth upgrading to unlock the premium features, which resulted in the app being uninstalled by the user. One suggestion uncovered from the app reviews describes the possibility of including more options within the free version to make the user rethink their decision to uninstall the app.

4. Discussion

4.1. Principal findings

The purpose of this study was to identify the user experience issues faced by users of apps that can assist with the needs of stroke caregiving. The study included 46 apps on Android and iOS platforms, with over 422,647 user comments and a high average user rating (i.e., 4.2) on a scale of 1–5. On extraction of user comments, however, only 117,364 user comments were extracted due to app store restrictions with similar issues faced in the study by Maalej and Nabil (32). After filtration, 31,624 neutral and negative user comments in 39 apps were classified based on the seven dimensions of user experience to determine potential issues.

Understanding factors such as user experience is critical as it creates a positive relationship between the product, the user, and the organization (33) while also ensuring the system's long-term success (21, 34). This relationship was evident in this study, where several users reported the need to withdraw from the app due to issues with the app user experience. However, these issues could be expected as most apps were published by non-educational/medical organizations with limited evaluations.

Beyond the user experience issues, several users described the app's inability to support their needs, which contributed to their dissatisfaction with the app. Moreover, Torous, Andersson, Bertagnoli, Christensen, Cuijpers, Firth, Haim, Hsin, Hollis, Lewis, Mohr, Pratap, Roux, Sherrill, and Arean (21) suggests that the inability to align the app functionalities with the preferences and goals of the intended users may lead to a lack of adherence that may eventually influence the app usability. For example, one user mentioned that the paid app prices are incredibly high, especially for people assisting those with special needs that would require lifestyle adjustment and unavoidable financial responsibilities, which may affect their ability to engage with the app. Another user mentioned the need to include other useful aspects such as medication information, photo and notes in a medication management app to allow better support.

The design of any commercially available mHealth app ultimately depends upon the uptake and success of the app, which is found to be linked with the need to design the system based on user preferences and goals. Moreover, the app needs to function in a way to promote improved user experience. Hence, developers need to consider an approach that can understand the needs, engage the end-user and priorities the requirements to ensure effective outcomes. User-centered design is one such approach.

The user-centered design had been endorsed by the World Health Organization (WHO) as an effective approach to ensure improved outcomes in terms of usability and functionality (35). This approach provides the better inclusion of target end-users during the design and development of the app based on a clear understanding of the processes involved in the planning of care and recovery (36). Furthermore, if methods such as participatory design are implemented, it can create meaningful, actionable, and feasible strategies (37).

Participatory design has been used to align the concerns of users with health technologies (37). This is because the traditional design approaches fail to engage users in the design process, which eventually compromises the commercial opportunity and interactional experience of the users (38). Kushniruk and Nøhr (39) reported benefits of user involvement, particularly in participatory design, including (i) improving system quality as a result of more accurate understanding of user needs and preferences, (ii) greater likelihood of inclusion of features that are required by the user, (iii) higher levels of user acceptance as the system was developed based on user input, (iv) improved understanding of the usage issues, training needs, and user engagement, and (v) higher level of participation in the user decision making processes. Hence, making it an ideal approach in the design of mHealth technologies, especially in stroke caregiving.

Despite the numerous user experience issues, it is essential to note the high level of satisfaction among the user of the extracted app, with an average rating of 4.2 on a scale from 1 to 5 (26). Some users have discussed the presence of fake reviews in their user comments. For example, one user mentioned "many five star ratings" without any "meaningful" comments. In contrast, another user discussed the feeling that most fake positive reviews were posted by the developer for an "obviously subpar product." The suspicion for fake reviews can be further supported with a large number of reviews posted from deleted accounts as seen in this study and the rise in the illegal market for fake reviews to help app developers improve their rankings and ratings (40). These fake reviews have not only misled many customers into making poor decisions but also affect the users' trust in online reviews (41) as seen in several published user comments.

4.2. Strengths and limitations

This study has several notable strengths. The primary being the novelty. To the best of our knowledge, the analysis of user feedback in apps that support the needs of stroke caregivers has not been addressed. As a result, addressing a key gap in the literature. It also provides a voice to a large sample of users, highlighting their needs and expectations from the app. This feedback can be used to establish support for user inclusion in the design and development processes of the app. Moreover, it can provide future developers with the necessary guidelines in app design. In addition to providing a novelty and providing a voice to app users, the study is comprehensive. It gives a precise classification of user experience issues based on the seven dimensions of user experience design with high interrater reliability for each dimension.

Despite the strengths, the study includes a few limitations. First, the comments extracted were less than 28% than those published due to app store limitations. Another downside is the sensitivity of sentiment analysis used in this study. While sentiment analysis has been successfully applied to numerous different applications to understand user opinion, a few neutral or negative reviews may have been falsely classified as positive, which would have resulted in its exclusion from this study. The inclusion of more comments may have painted a different picture of the user experience issues and may have uncovered other problems within the app. Furthermore, the findings of this research only provides a high-level view of possible issues that the topic encapsulates, which may be different if a thematic analysis of reviews were considered.

5. Conclusion

The study explores the user experiences issues of apps that support the needs of stroke caregivers in their daily activities and considerations for future app development. The implication is to inform the development of apps by considering users using user-centered design approaches such as participatory design. Most apps have demonstrated a lack of understanding of user needs that contribute to user experience issues. Therefore, resulting in the lack of adherence and affecting user satisfaction. Hence, the collaboration with necessary stakeholders could contribute to the design of an app that is meaningful, actionable and feasible to the user preferences and goals.

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

EL, MA, and JG designed and conceptualized the study. EL coordinated the classification process between the two coders and analyzed the data under the supervision of MA. Further, EL drafted the manuscript based on the findings, which were reviewed, modified, and approved by MA, AF, LR, PL, SI, FK, and JG involved in the study. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1027667/full#supplementary-material

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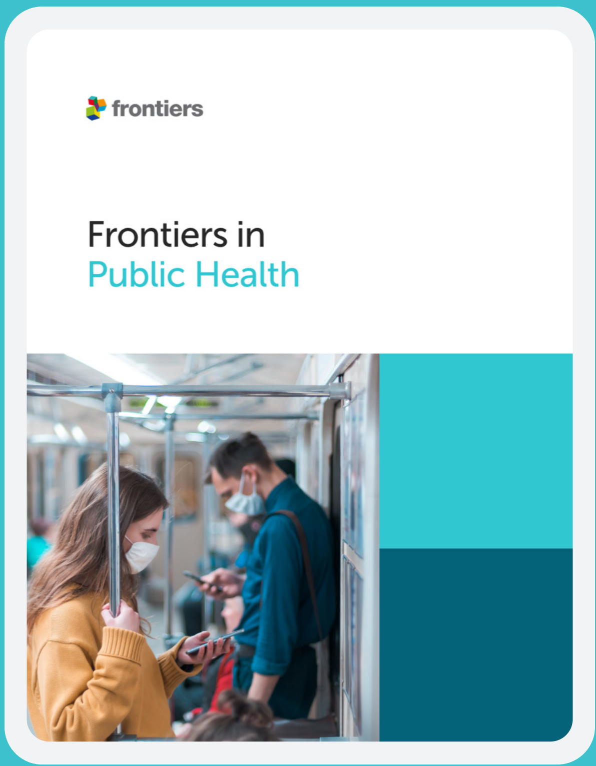

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