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COVID-19: The neurorehabilitation perspective

Edited by
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COVID-19: The neurorehabilitation perspective

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Editorial: COVID-19: the neurorehabilitation perspective

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Editorial on the Research Topic
COVID-19: the neurorehabilitation perspective

COVID-19 and neuro-disabilities—A 2-fold consideration

On 11th March 2020, after a sharp increase in confirmed cases, the World Health Organization (WHO) announced the COVID-19 outbreak as a pandemic. Given the global public health threat, there was an urgent need for research and knowledge distribution on how best to manage patient care for those affected by the Coronavirus Disease 2019 (COVID-19).

Most people with COVID-19 have mild symptoms and recover, while 6.1% become critically ill (respiratory failure, septic shock, and/or multiple organ dysfunction/failure) (1) and might develop a "post-intensive care syndrome" (PICS) with motor, cognitive, and emotional disorders, necessitating intensive rehabilitation (2, 3). Indeed, multi-national observational studies indicated that neurological signs and symptoms can be observed in the majority of COVID-19 cases with a need for hospitalization (4). Equally important, even subjects with an initially mild course of COVID-19 reported symptoms that interfered with everyday life considerably over an extended period (5), i.e., for more than 4 weeks post-COVID-19 onset (called "Long COVID-19") or more than 12 weeks (called "post-COVID-19"), again frequently including neurological symptoms (6). More recently, the Global Burden of Disease Long COVID-19 Collaborators (7) analyzed data from a total of 1.2 million individuals who had symptomatic SARS-CoV-2 infection. In the modeled estimates, 6.2% [95% uncertainty interval (UI), 2.4–13.3%] of these individuals experienced at least one of the three Long COVID symptom clusters, 3.2% (95% UI, 0.6–10.0%) reported persistent fatigue with bodily pain or mood swings, 3.7% (95% UI, 0.9–9.6%) reported ongoing respiratory problems, and 2.2% (95% UI, 0.3–7.6%) reported cognitive problems.

Hence, priority research was and is necessary to elaborate rehabilitative needs, therapeutic options, and managed care for those affected by COVID-19 and developing neurological impairments, i.e., "Neuro-COVID."

Along these lines, research has to document the epidemiology and rehabilitation needs of COVID-19 cases and their clinical course. It should further address the effectiveness of neurorehabilitation treatment including the use of new technologies for home care purposes (e.g., the use of low-cost technologies such as smartphones or tablets for virtual medical examination, counseling, and tele-rehabilitation), as well as healthcare system questions (e.g., how to cope with rapidly increasing demands for services), and guidance (practice recommendations).

Furthermore, the effects of the mandated COVID-19 restrictions (social distancing) on people with neuro-disabilities (not caused by COVID-19) and their possibility to receive neurorehabilitation treatment have been major healthcare concerns in the field. Here again, research to elucidate such effects and to suggest means to overcome the detrimental effects of the mandated COVID-19 restrictions are of utmost importance since people with neuro-disabilities frequently have a long-term or ongoing need for therapy to support their physical, mental, and emotional wellbeing.

Accordingly, COVID-19-related practice recommendations have a 2-fold focus, one being rehabilitation to combat COVID-19 sequelae, and the second being rehabilitation during a pandemic and its restrictions imposed on those in need of rehabilitation (not caused by COVID-19) (8, 9).

To promote the rapid access to and exchange of COVID-19-related research relevant to neurorehabilitation, the World Federation for Neurorehabilitation (WFNR; wfnr.co.uk) initiated this Research Topic (RT) in collaboration with Frontiers. Overall, the RT attracted 25 articles with a broad scope of contents.

Neurorehabilitation services—The impact of the COVID-19 pandemic, steps to be taken, and chances for the future

Recognizing the need to reorganize hospital and outpatient rehabilitation activities, the document by Bartolo et al. describes the measures adopted by the rehabilitation structures that first faced the fight against COVID-19 to inform all those who consequently found themselves involved in this rampant battle.

New forms to organize neurorehabilitation with the use of technology such as a "digital and artificial intelligence platform" (DAIP) were introduced and used effectively to cope with new affordances for rehabilitation services during the COVID-19 pandemic, providing qualitative support for goal-setting for remote consultations and reducing the time for scheduling and registering sessions (Saverino et al.).

A telemedicine process flow representing a replacement for in-person treatment and thereby the provision of equitable access to the care of vulnerable people was proposed by Matamala-Gomez et al. It has been conceptualized as a comprehensive service including (1) tele-assistance with patient counseling and medical treatment, (2) tele-monitoring of patients' health conditions and any changes over time, as well as (3) tele-rehabilitation, i.e., interventions to assess and promote body functions, activities, and participation, consecutively.

Survey data on professionals, adult patients, and children's caregivers' perceptions and satisfaction with tele-rehabilitation during the COVID-19 lockdown were presented by Assenza et al. indicating that tele-rehabilitation can indeed be a useful practice.

While such endeavors might serve to foster opportunities for improved healthcare (beyond the COVID-19 pandemic), nevertheless regulations against the spread of coronavirus (COVID-19) have not infrequently interrupted non-essential rehabilitation services globally.

As shown by the survey conducted by Surya et al. neurorehabilitation services were severely affected across India during the COVID-19 pandemic. Tele-neurorehabilitation has emerged as a new service delivery model during the pandemic and online means of education as the primary source of continuing medical education during the pandemic. Indeed, the pandemic situation has been seen to provide an opportunity to optimize the technological innovations in health and scale up these innovations to meet the growing burden of neurological disability in Low- and Middle-Income Countries (LMICs; Srivastava et al.).

COVID-19 pandemic, specific clinical syndromes, and neurorehabilitation

Furthermore, in this Research Topic, specific recommendations were provided for specific clinical syndromes.

Neuro-COVID-19

With severe COVID-19 infection, complex and long-lasting physical, cognitive, and functional impairments have often been observed after COVID-19. As outlined by Pincherle et al. early—defined as during and immediately after intensive care unit (ICU discharge)—rehabilitative interventions are fundamental for reducing the neurological burden of a disease that already heavily affects lung function as a possible long-term consequence.

Liguori et al. analyze the critical issues of COVID-19 on neuromuscular disease (NMD) and propose a home-based rehabilitation program targeted for this population after mild to moderate SARS-CoV-2 infection.

Sozzi et al. appropriately point out the need for neuropsychologists' intervention in taking care of COVID-19 patients, considering that this pandemic, in its manifestation as Neuro-COVID, may result in cognitive and behavioral alterations. Accordingly, all structures in which COVID-19 patients are hospitalized should be provided with information on cognitive, affective, and behavioral alterations resulting from this pathology, and integrate such knowledge into their patient care. Indeed, the findings of an observational study with COVID-19 and Post COVID-19 subjects with a need for rehabilitation highlight the gravity of neuropsychological and psychological symptoms that can be induced by COVID-19 infection and the need for tailored rehabilitation, including cognitive training and psychological support (Pistarini et al.). The paper by Mantovani et al. offers a perspective on the

role of tele- and virtual rehabilitation to achieve adequate cognitive stimulation in the era of social distancing related to the COVID-19 pandemic.

Pandemic-related restrictions and neurorehabilitation in general

With spasticity, prolonged suspension can potentially accelerate the morphological alterations connected (e.g., myotendinous and joint contractures and pain) which could potentially cause a long-term negative impact on the patient's level of activity and participation, as well as a deterioration in their quality of life. Several factors must be taken into account to guarantee both patients' necessary care and indications for minimizing the further spread of the pandemic. For this purpose, an *ad-hoc* treatment protocol was summarized by Baricich et al..

For the UK, it was demonstrated that both referrals to speech and language (SLT) services and access to SLT by patients were substantially less during the acute COVID-19 period in the UK than in the same period in 2019 (Chadd et al.). In addition, several service changes were common, including adopting more flexible approaches to provision (such as tele-therapy) and being unable to provide services to some patients.

Individuals with physical disabilities such as children with cerebral palsy could no longer benefit from physical rehabilitation during the pandemic. Using either a synchronous or asynchronous format, in collaboration with a therapist via tele-rehabilitation, Demers et al. suggest that active video games and low-cost virtual reality are promising delivery modes for at-home rehabilitation in the context of a global pandemic.

Another concern of pandemic-related restrictions is that people with neuro-disabilities have fewer opportunities for physical activities and training (aside from healthcare), being an essential part of their continuous efforts for wellbeing. The survey by Nightingale et al. investigated associations between physical activity and health-related quality of life outcomes in individuals with a neurological condition during government-mandated COVID-19 restrictions. The authors documented increased depression and fatigue, and a decrease in vitality with less leisure-time physical activity, highlighting the importance of and need to safely promote leisure-time physical activity during the COVID-19 pandemic in this at-risk population to help support health-related quality of life.

Conclusions

The articles on the Research Topic "COVID-19—The Neurorehabilitation Perspective" collectively provide insights into the effects of COVID-19 on the nervous system, and hence, neurological manifestations called Neuro-COVID and rehabilitation needs to be addressed. In addition, the research demonstrates how—on a global level—mandatory restrictions during the pandemic affected rehabilitation services and, hence, the many people with neuro-disabilities in need of prolonged or ongoing treatment or other activities to promote and maintain their physical, mental, and emotional wellbeing. Finally, suggestions on how to promote telemedicine in neurorehabilitation, solutions being used, and user satisfaction all indicate technological options that might serve to generate a more widespread benefit of services well beyond the pandemic.

Author contributions

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Urgent Measures for the Containment of the Coronavirus (Covid-19) Epidemic in the Neurorehabilitation/Rehabilitation Departments in the Phase of Maximum Expansion of the Epidemic

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COVID-19 has rapidly become a pandemic emergency, distressing health systems in each affected country. COVID-19 determines the need for healthcare in a large number of people in an extremely short time and, like a tsunami wave, overruns emergency, infectious diseases, and pneumology departments as well as intensive care units, choking healthcare services. Rehabilitation services are also affected by this epidemic which forces radical changes both in the organization and in the operating methods. In the absence of reference literature on this issue, this report aims to provide a background documentation to support physicians and healthcare personnel involved in neurorehabilitation and rehabilitation care.

Keywords: COVID-19, rehabilitation, neurorehabilitation, epidemic, infection, health care, organization

INTRODUCTION

The spread of coronavirus disease 2019 (COVID-19—COrona VIrus Disease 2019) has become unstoppable and in the last few weeks has reached the epidemiological criteria to be declared a pandemic by the World Health Organization, having widely exceeded 400,000 (updated to March 25 2020 Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering at Johns Hopkins University) infected people in the world in over 100 countries (1, 2).

In Italy, in February 2020 the emergence of the COVID-19 epidemic first in Lombardy, and then in the other regions, determined the need to implement containment measures for a phenomenon that in a few days has put a strain on the healthcare system, clogging many emergency, infectious diseases and pneumology departments, as well as intensive care units, with obvious dramatic relapses in the health system's ability to offer adequate assistance to patients with different pathologies (3).

Ever since the coronavirus emergency began in China (4), in the current unavailability of an effective etiological therapy, governments have reacted with the standard measures usually adopted in the event of epidemics, represented by quarantine, and by travel and mobility restrictions

for the populations involved in outbreak areas. However, unlike in the past, this is a public health emergency that is developing in a globalized and interconnected world like never before. The infectious disease is developing and spreading in an economic and socio-cultural context characterized by populations that tend to aggregate in highly urbanized and overcrowded contexts and by extreme ease of movement, including intercontinental travel (5, 6). The way in which the COVID-19 epidemic is spreading must also be considered, it has rightly been compared to a real "tsunami" wave (7). In fact, the epidemic is expressed by the tremendous number of infections in an extremely short period of time, thus affecting large portions of the population, which leads to the concentration of a disproportionate number of requests for assistance compared to the emergency response capacity of the health systems.

The epidemic growth that is happening in other European (Spain, France, Germany, etc.) and non-European countries, shows that the challenge is similar for everyone. Nonetheless, the absence of a common pandemic plan in Italy and Europe, with Regions and individual countries that are still adopting different methods of managing the epidemic, runs the concrete risk of dissolving the effectiveness of the stringent measures implemented in different areas or countries. This can also be observed in China, where, in the face of an internal growth of new cases equal to zero over the past few days, new infections have been recorded due to the presence of the so-called "re-entry cases." It must also be taken into account that the epidemic spread will occur with peaks at different times and areas, within and between the various countries, so the overall consequences will be related to the effectiveness of the different health systems.

Numerous mathematical models for predicting the progress of the epidemic are being proposed in Italy and in the world in an attempt to provide useful tools to decision makers (8). However, beyond the absolute numbers of the infections, the increase in new cases in recent weeks, at least in the most affected Italian regions (Lombardy, Emilia-Romagna, Veneto) and European Countries (Spain and France) seems to show a very similar growth curve, only delayed for a few days compared to each other. However, it is also likely that due to the lack of available, prompt, and reliably diagnostic procedures, the officially identified cases only represent the tip of the iceberg, with a spread of unidentified mild/asymptomatic cases well above the estimates.

The currently still limited number of cases, albeit growing, in the central-southern regions, should teach us not to repeat the error of a *wait-and-see* attitude, but should rather induce us to learn from this "temporal advantage," promptly implementing all the social distancing measures essential to reduce the circulation of the virus.

One of the most worrying aspects of the COVID-19 epidemic is linked to the involvement of frail and vulnerable people, in particular the elderly, subjects who suffer from multiple comorbidities or chronic diseases and people with disabilities. For this reason, it is essential to address and focus on prevention, health interventions and care in chronically ill patients staying in health care facilities, as well as patients suffering recent functional limitation requiring rehabilitation (or admitted to rehabilitation facilities).

In fact, in an extremely short time compared to the spread of the epidemic, Rehabilitation Facilities need to enact prompt remodellling of the health organization both in the internal structure and in the strategy and approach of care delivery, which presents unique peculiarities within healthcare organizations (9, 10).

Furthermore, in some areas due to the lack of beds, rehabilitation facilities are now being occupied with other patients, with consequent difficulty in hospitalizing patients, for example, discharged from stroke units.

Therefore, in the need to reorganize hospital and outpatient rehabilitation activities (11, 12), this document describes the measures adopted by the rehabilitation structures that first faced the fight against COVID-19, hoping for a rapid spread to all those who find themselves involved in this rampant battle.

REMODELING OF NEUROREHABILITATION/REHABILITATION ACTIVITIES DURING COVID-19 EMERGENCY

The following indications are suggested in order to make the reorganization of rehabilitation activities homogeneous, whether they are carried out in hospitalization or outpatient settings or at home, with the main aim of limiting patient flows within the facilities and maintaining staff safety. For some structures, these indications must take into account territorial and network needs, as well as the possible increase in hospital admission in order to favor discharge from acute care facilities.

"SYSTEM" INTERVENTIONS

The definition of dedicated territorial and local pathways for patients from acute care facilities, separating noCOVID or negative COVID patients from suspected positive or positive Covid cases.

"STRUCTURAL" INDICATIONS

1. Admissions to hospital wards must be limited to only those that are essential, and in any case supervised by personnel equipped with personal protective equipment. All other accesses must be closed.
2. Posting of notices with behavioral rules at the entrances to and within all the departments [see (13)]
3. Posting of hand hygiene recommendations near hand-sanitizing gel dispensers [see (13)]
4. Staff of external companies are required to comply rigorously and systematically with standard precautions in addition to those provided by air, by droplets, and by contact, as indicated in the behavioral rules.
5. Preparation of extraordinary plans for daily cleaning and sanitization of the rooms.

6. Preparation of plans for extraordinary sanitization and cleaning in cases of access or identification of a "suspected case."
7. Reorganization of work shifts (medical and non-medical staff) with reduction of activities in order to reduce contact and movements. Where possible, encourage staff to work from home (e.g.,: administrative activities, social worker, etc.). Obligation for everyone to report any symptoms that have arisen recently; in this case, respect home isolation.
8. Strengthening of patient and caregiver support networks, also through information technologies.
9. Emphasis on the role of remote assistance and/or tele-rehabilitation in particular as remote home monitoring for patients who are unable to access rehabilitation hospitals or must be discharged in advance as well as for consulting activities in hospitals or in case of consultation for out-patients
10. For all, monitoring of body temperature <37.5°C—(if higher, do not allow access and indicate home isolation)
11. Even in the absence of fever, it is necessary to subject people to careful triage by explicitly asking for their place of origin and detecting potential contacts.

INDICATIONS FOR THE ACTIVITIES OF NEUROREHABILITATION/REHABILITATION UNITS

1. Suspension of caregiver visits to hospitalized patients (underwear, clothes, and necessities will be delivered to hospital staff at the entrance of the building, thus avoiding the need to enter). Exceptional cases must be authorized by clinicians according to the rules of the health management; access in derogation will be managed by the staff in order to avoid any contact and for a limited time.
2. Rehabilitation units will have to keep the doors closed in order to control and direct the flow (if possible all the entrances should be recorded, indicating the time). for all health personnel and visitors with permission, monitoring of body temperature <37.5°C (if higher, do not allow access and give indication of home isolation)
3. For discharges (see rules for access in derogation and compliance with point 2)
4. Suspension of all meeting activities, replaced by the use of telephone or email contact.
5. Clinical interviews with family members by phone or email only.
6. Remodeling of rehabilitation programs, identifying the most relevant goals, among the short-term achievable ones
7. Suspension of all rehabilitation activities that require internal flow (movement between floors or to reach gyms)
8. Carrying out of rehabilitation activities in the patients' room where possible; in the case of gym activities, strictly keep the distance of at least 2 m between the patients.
9. Reduction of the rehabilitation team's activities (keep only those which are strictly necessary, which will be carried out by the clinician together with the coordinator, after collecting updates from the other staff)
10. Education and empowerment of all healthcare professionals involved in rehabilitation team, by means of specific targeted training (e.g., about the correct use of PPE)
11. For all healthcare professionals, it is recommended to "enhance hand hygiene by following the WHO instructions, before and after each patient and whenever the hands move from the patient to another surface" (14)
12. Remember that "Masks with greater protection (FFP2, FFP3) are indicated only in suspicious or full-blown cases, therefore it is suggested not to abuse these devices, so as not to reduce their availability for cases of real need"
13. In the management of suspicious cases (cases with not deferrable treatment) (15), remember.
    a) patient with respiratory symptoms (no COVID19): the patient is recommended to wear the surgical mask; keep a distance of at least 1 m or wear a surgical mask;
    b) patients suspected or affected by Covid-19: the use of FFP2 or FFP3 mask, protective gown, gloves, eye protection (goggles or face shield) is recommended;
    c) patients suspected or affected by Covid-19 during the execution of procedures capable of generating aerosols: the use of FFP3 mask, protective gown, gloves, eye protection (goggles or face shield) is recommended
14. Even in the absence of fever, people must be subjected to careful triage by explicitly asking where they came from and detecting potential contacts.

NOTE: Remember that it is possible to carry out "*... respiratory physiotherapy in hospitalization and re-education settings in recent outcomes of surgery, in trauma with fractures and the immediately post-acute phase of cardiac and neurological disabling pathologies (heart attack, stroke, etc.) (with appropriate personal protective equipment due to the impossibility of maintaining a distance of <1.5 meters)...*," for this specific area, please refer to the joint document of the Association of Rehabilitators of Respiratory Insufficiency and the Italian Association of Physiotherapists (AIR and AIFI, Indications for respiratory system physiotherapy in patients with COVID-19 infection) (update of 16/03/2020) (16).

INDICATIONS FOR PATIENTS SUFFERING FROM RECENT ONSET OF NEUROLOGICAL DISORDERS REQUIRING REHABILITATION

1. Neuro-rehabilitation/neurological Units located in multi-disciplinary Hospitals can admit patients with sub- acute neurological impairments due to severe acquired brain lesions or stroke coming from an acute unit of the same hospital (Intensive care Units, neuro-surgery, neurology), if they are not affected or suspected by Covid-19.
2. Patients suspected or affected by Covid-19 with neurological impairments requiring rehabilitation and according to clinical conditions (hemodynamic parameters, breathing

capacity, consciousness) should be treated in the room (*with appropriate personal protective equipment due to the impossibility of maintaining a distance of <1.5 m*)
3. Patients with neurological disorders requiring rehabilitation and coming from acute units outside Hospitals should be admitted if throat and nasal swab resulted negative and after proper time assessment (14 day) without fever and cough suggestive of Covid-19 infection.
4. Neurorehabilitation/rehabilitation Unit located outside general and multi-disciplinary Hospitals should only admit patients with sub-acute neurological disorders negative for Covid-19 infections in order to facilitate prompt availability of intensive care unit.

INDICATIONS FOR OUTPATIENT AND HOME REHABILITATION ACTIVITIES

1. Suspension of all outpatient and/or Day-hospital rehabilitation activities and/or with access from the outside (only activities that cannot be postponed according to clinical judgment are maintained, subject to communication, and approval by the Health Department)
2. Suspension of all activities including those of a freelance type (re-scheduling of visits and activities)
3. Suspension of all home rehabilitation activities except those that cannot be postponed according to clinical judgment.

CONCLUSIONS

The greatest difficulty in applying these indications in the field of neurorehabilitation/rehabilitation is related to the need to find the right balance between the provision of services useful to the patient (in case of not deferrable treatment) and the reduction of the risk of spreading the virus. In this phase of maximum spreading speed, priority must be given to reducing the risk of spreading the infection.

The carrying out of rehabilitation activities in hospital stays, and in services in general, can only be continued in compliance with the needs of the patients and the protection of the health of all staff, as activities require close contact with the patient, or with the production of aerosols and secretions as for respiratory rehabilitation interventions (Joint document AIFI - Commission of Physiotherapists Register, 2020) (17). Finally, please note that the WHO protocols indicate minimum standards for the protection of health workers and each Ministry of Health, based on its own risk assessment, can raise the levels of protection of its personnel.

It must be reiterated that given the specificity of Rehabilitation/Rehabilitative interventions, which necessarily have to take into account the territorial contexts, the above indications must be adapted to the specific realities, while adhering as closely as possible to the recommendations.

In fact, it seems useful to reiterate that the indications and measures to be taken are valid for all and should be applied in all countries and in the different areas as simultaneously as possible, because a non-uniform alignment would also lead to the risk of an inevitable misalignment in the desirable economic restart, with heavy long-term relapses.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MB conceived the study. MB, DI, CL, GS, SP, and MZ also on behalf of the Authors listed in the **Appendix** reviewed and discussed the study and approved the last version of the paper.

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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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OPINION
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Spasticity Treatment During COVID-19 Pandemic: Clinical Recommendations

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Keywords: pandemic (COVID-19), COVID-19, intrathecal baclofen, Botulinum Toxin, rehabilitation, spasticity, Coronavirus

INTRODUCTION

Spasticity is a symptom that describes involuntary muscle hyperactivity in the presence of central paresis due to several neurological conditions (1). It can consist of various clinical forms, and it has been reported (2, 3) that spasticity showed a prevalence of 28–38% in patients with stroke, 41–66% in patients with multiple sclerosis, 13% in patients with traumatic brain injury, and up to 80% of children with cerebral palsy.

Spasticity can affect quality of life, impair function and heighten economic burden (4, 5), and it could be associated with several complications, including contractures, pain, fall risk, pressure ulcers, and infections (6). In addition, caregivers of patients affected by spasticity are more likely to experience anxiety and depression (7).

Spasticity management aims to reduce its negative impact on patients and carers and to prevent irreversible soft-tissue changes and tendon contractures by maintaining muscle length and normalizing limb positioning (8, 9).

Identifying and treating clinically relevant spasticity is key to decreasing patients' impairments (10, 11). Interventions must be tailored to meet the problems faced by the person and their goals, including focal (e.g., chemodenervation with Botulinum Toxin, chemical neurolysis) and general treatments (e.g., oral antispasticity drugs, cannabinoids, intrathecal baclofen) (10, 11). Besides, a multidisciplinary team including doctors, physiotherapists, occupational therapists and nurses, is required: in fact, other physical modalities can optimize the effect of pharmacologic treatment (e.g., stretching, splinting, postural management, exercise, electrical stimulation, casting, splinting, extracorporeal shock waves, body vibration) (10, 12).

Noteworthy, it should be pointed out that patients affected by spasticity require periodic access to the health care facilities.

In particular, Intrathecal baclofen infusion (ITB) systems, proposed in case of severe generalized spasticity, imply a close follow-up for safety purposes; notably, ITB pump refill is a programmed procedure that requires regularity in its execution, and that cannot be postponed due to the risk of withdrawal symptoms (13).

Again, Botulinum toxin Type A (BoNT-A), the gold standard for focal spasticity treatment, requires a regular administration (every 3–6 months) in order to maintain the clinical effect (14); moreover, BoNT-A must be proposed by a multidisciplinary team, since optimal treatment involves physical therapy in conjunction with intermittent pharmacological treatment (14, 15).

It is well-known that when spasticity worsens, patients may experience a variety of symptoms (10). In particular, prolonged suspension can potentially accelerate the morphological alterations

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connected with spasticity (e.g., myotendinous and joint contractures, pain) which could potentially cause a long-term negative impact on the patients' level of activity and participation, as well as to a deterioration in their quality of life (8, 9).

The recent reorganization of non-urgent clinical activities, connected to the emergency generated by the COVID-19 pandemic, has also significantly involved the treatment of patients with spasticity.

As per institutional indications, most of these activities have been suspended or postponed (16, 17).

This situation, necessary in consideration of the pandemic, has nevertheless exposed patients suffering from spasticity to the risks connected to the interruption of the treatment as described above.

Based on these considerations, it seems reasonable to continue planning the spasticity treatment, carefully monitoring those that cannot be delayed.

However, several factors must be taken into account to guarantee both patients' necessary care and indications for minimizing a further spread of the pandemic.

For this purpose, an *ad-hoc* treatment protocol is summarized in the next section.

CLINICAL RECOMMENDATIONS

Some of these aspects are part of the general indications for patients' access to healthcare facilities (18). Still, some specific elements must consider the patients' characteristics (19) and the specific settings where the treatments are carried out (16, 17).

Inpatient Facilities

In this case, spasticity treatment is part of the rehabilitation program of the patient hospitalized for this purpose.

The hospital organization must consider the general indications for the containment of the infection (18, 20); therefore, all the appropriate procedures must be put in place to avoid exposing the patient to the risk of contracting COVID-19 (21), and in particular:

- adequate clinical monitoring of patients to identify clinical signs of potential COVID-19 onset (18)
- adequate use of personal protective equipment (PPE) about the procedures and clinical characteristics of the patients (18, 22, 23)
- monitoring of the health status of involved staff (18)
- training of staff and patients on compliance with hygiene rules (18)
- availability and easy retrieval of suitable indications (e.g., explanatory material distributed in hospital areas) and material (e.g., hand sanitizing gel) (18)
- blocking (or severe limitation) of access to visitors (18).

Outpatient Facilities

In this case, since the patient's access to the hospital or outpatient facility takes place from the outside, it is necessary to consider a series of procedures to ensure the safety of the patient and operators (24).

In particular, several aspects must be considered (**Figure 1**).

Patient Selection

- in consideration of current government indications (25), it remains a rule of good clinical practice to limit access to only patients for whom the treatment cannot be postponed (e.g., repetition of treatment with BoNT-A for significant reduction of autonomy consequent to the recovery of spasticity; ITB refill or follow up) (26)
- the use of telephone screening tools that allow remote pre-assessment is recommended to coordinate patient access to facilities: this is to facilitate the assessment of the patient's clinical needs and to monitor any presence of suggestive symptoms of COVID-19 or to identify any contact with other affected subjects; for this purpose, video call tools, where available, can also be supportive for an initial, albeit limited, clinical evaluation (17, 24).
- Alternatively, in this perspective, progressive implementation of suitable tools (video call programs, the supply of motion sensors) that can support the clinical evaluation remotely by the clinician is desirable, to monitor the situation of patients by reducing the number of accesses at health facilities; for this purpose, it is necessary to use the available technological resources to identify the most suitable tools. At the same time, it is also necessary to guarantee proper classification and financial rewards of these services (27).
- in case of previous BoNT-A treatment (14), we suggest considering a clinical assessment in the health facility if two or more of these issues are present at screening:
  - Last inoculation date with BoNT-A $>$ 3 months (yes/no)
  - Increased spasticity in the muscles previously treated with BoNT-A, which can affect the patient's function or autonomy (yes/no)
  - Presence of hypertonus in untreated muscles, which can affect the patient's function or autonomy (yes/no)
  - Severe degree of spasticity conditioning a potential risk of long-term damage (e.g., myotendinous retractions) (yes/no)
  - Significant presence of pain, potentially related to spasticity (yes/no)
  - Impossibility of wearing orthoses/aids in use due to the presence of spastic hypertonicity (yes/no).
- We also suggest to carefully consider each of the above-reported points on patients treated with ITB due to the potentially life-threatening risk of pump emptying or malfunction (13).

Access to the Health Facility

- Set a screening station at the entrance to identify subjects potentially affected by COVID-19 (e.g., targeted medical history, contactless temperature measurement) to minimize the risk of exposure to COVID-19; prepare an adequate clinical pathway in case of suspected infection (e.g., SARS-COV-2 swab test, according to the local guidelines) (18, 24)
- verify that all staff are trained to recognize possible clinical signs compatible with COVID-19 and that

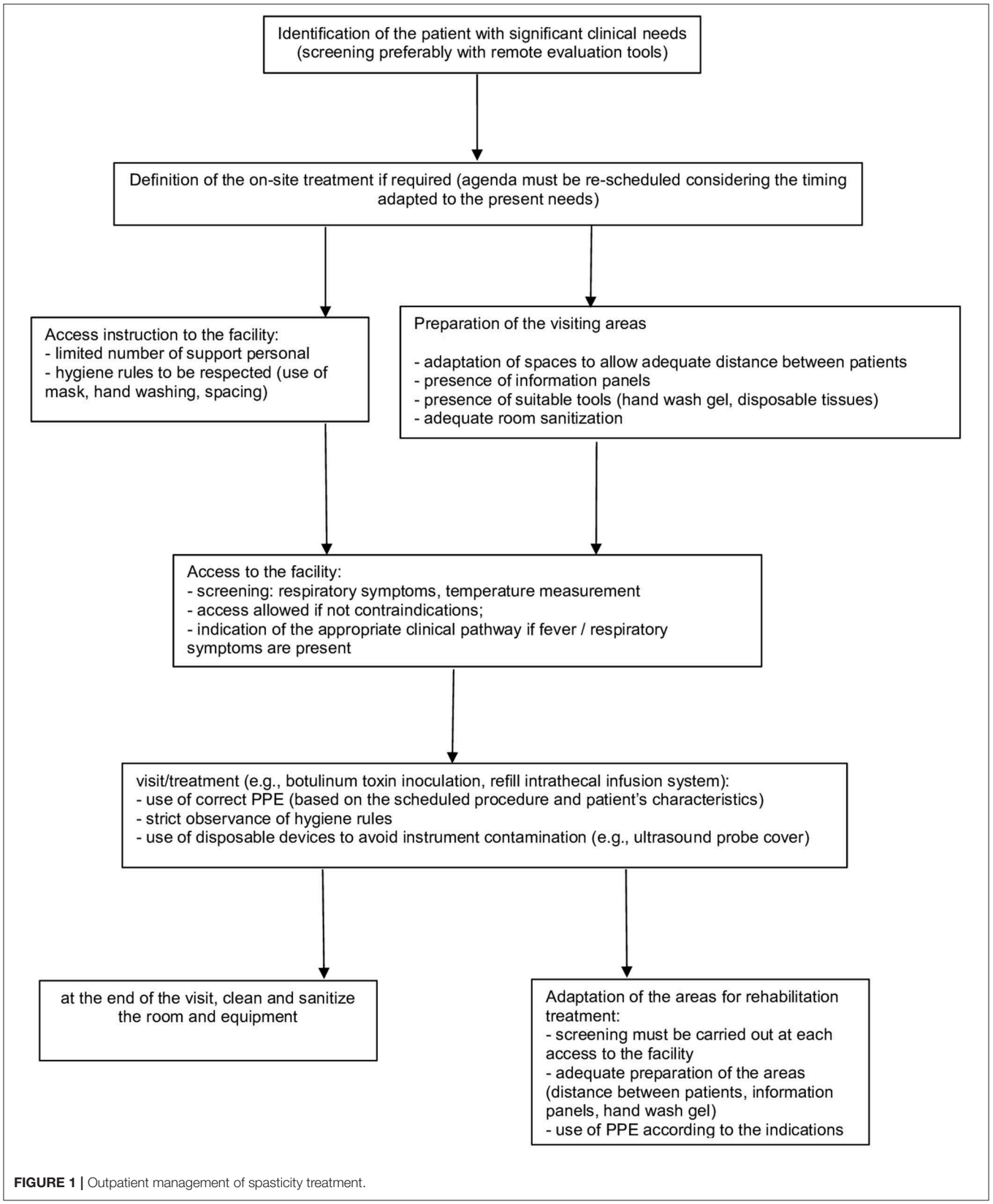


FIGURE 1 | Outpatient management of spasticity treatment.

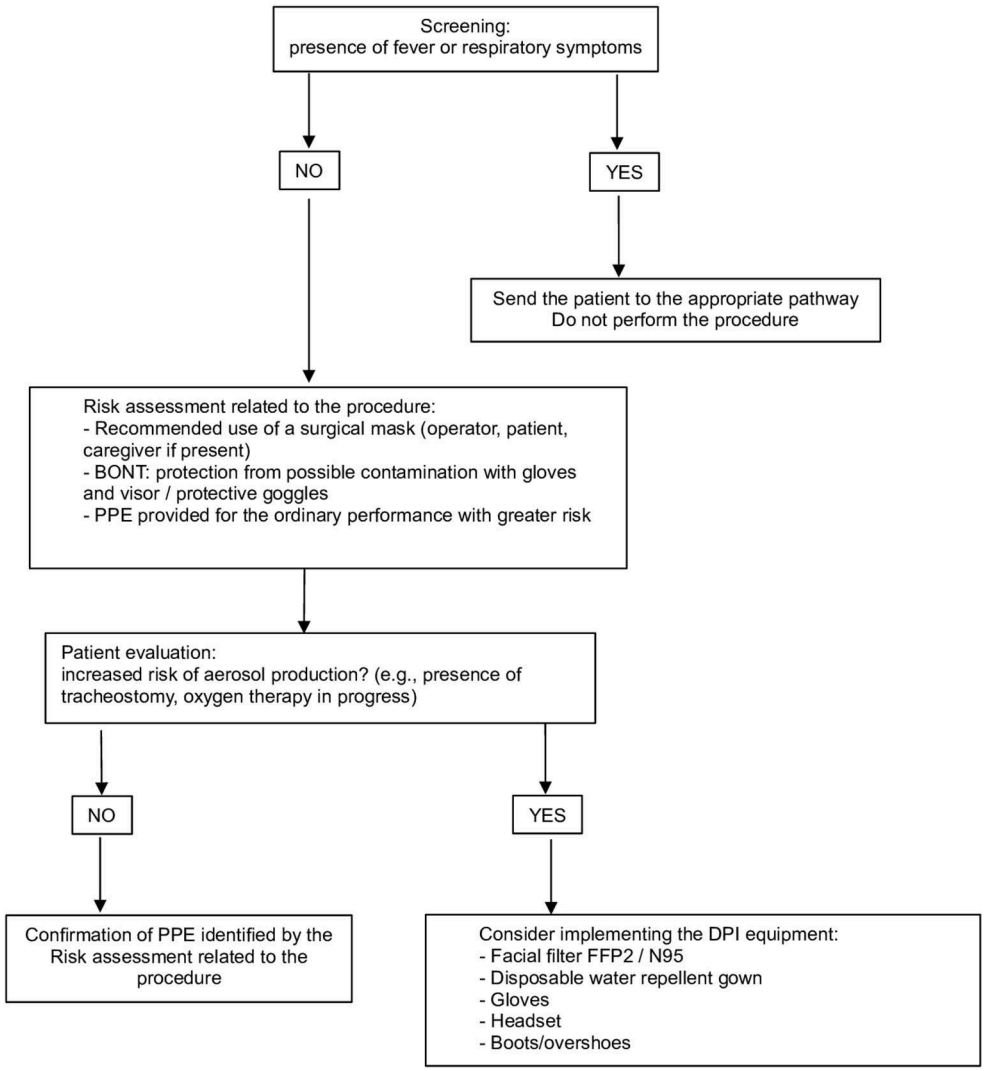


FIGURE 2 | Personal Protection Equipment (PPE) management: risk assessment related to the procedure and patient characteristics.

they can provide the correct indications to the patient (18).

Health Service Provision

- The provision must be adapted to the general indications (24), with attention to specific aspects of the treatment of patients affected by spasticity.
- It may be necessary to remodel the interventions' planning to allow the implementation of all the appropriate procedures. In particular, patients must be properly scheduled in order to avoid gatherings of people (24)
- Reorganization of waiting rooms (18, 24, 28, 29):
  - prepare the presence of information panels relating to COVID-19, highlighting the standards to be respected
  - prepare the presence of tools such as hand wash gel and disposable tissues
  - there must be as few people as possible in this area: where necessary, the service provision must be re-modulated. In particular, access to carers must be limited
  - consider the adaptation of common areas to allow an adequate spacing of patients (>1 m) (28).

Adaptation of Treatment Procedures

- Considering the need to distance patients, the possible use of PPE with relative dressing/undressing procedures and the time required for the room cleaning, it is reasonable to set an agenda with scheduled appointments adapted to these needs (18, 22, 23)
- the use of correct PPE must be planned based on the scheduled procedure and the characteristics of each patient (**Figure 2**); in consideration of the potential risk of contagion even in asymptomatic subjects, the use of a surgical mask by both the

healthcare professional and the patient is mandatory to limit the spread of the virus (18, 22, 23)
- strict observance of the usual hygiene rules (e.g., hand washing) is necessary to minimize the risk of virus transmission (18, 28–30)
- cleaning and sanitizing of instrumentation and environments are mandatory (18):
  - the environmental sanitation procedures must be implemented as per institutional or company indications by the dedicated staff, equipped with the appropriate PPE
  - in general, surfaces frequently touched by a large number of people (such as doorknobs, chairs, desks) must be cleaned at least daily and if possible more frequently; the use of regular detergents can be considered sufficient if there has been no contact with confirmed or suspected COVID-19 patients
  - However, it is conceivable to arrange additional cleaning of the surfaces and devices used during the procedures between one patient and another (e.g., ultrasound or electrical stimulation devices in injections with botulinum toxin, examination table). For this purpose, after removing any visible traces, a suitable product should be used wherever possible. Current evidence suggests (31) the use of a standard detergent associated, where possible, with a virucidal product or sodium hypochlorite 0.05% or ethanol 70%
  - the use of disposable devices that avoid contamination of the devices is desirable (e.g., probe cover when using ultrasound for injection procedures with BoNT-A).

Adaptation of Areas for Rehabilitation (if Applicable)

As previously stated, spasticity treatment requires multidisciplinary management. In particular, adjunctive treatment might improve the clinical effect of BoNT-A, and they should be applied in the health care facility immediately after the BoNT-A injection (12).

However, in order to minimize the risk during COVID-19 pandemic, several issues must be carefully considered:

- it must be highlighted that the screening procedures must be implemented at each access to the facility (24)
- we suggest that the rules of distancing between patients (>1 m) (28) must also be applied in the organization of the areas where the patient's rehabilitation treatment takes place (e.g., gyms, areas dedicated to the occupational therapy)
- the correct use of PPE for the staff involved must be considered based on the patient's characteristics (18, 22, 23)
- consider information panels and provide suitable material (e.g., hand wash gel) within the area (18, 24)
- prepare adequate plans for cleaning and sanitizing rooms and tools; in particular, attention must be paid to cleaning the equipment used by patients (e.g., electrical stimulation devices, dedicated equipment, and machinery, beds) (18, 31)
- if appropriate, exposure risk should be limited by implementing communication technologies which can support remote rehabilitation treatment (27, 32).

CONCLUSIONS

The treatment of the patients suffering from spasticity, while not showing the characters of urgency except for some procedures such as ITB refill or monitoring, is worthy of particular attention in this phase of the COVID-19 pandemic.

It must be highlighted that this prolonged suspension of deferred activities has potentially exposed many patients to the disabling consequences of untreated spasticity.

Given these aspects, close monitoring of patients is recommended in order to plan an adequate schedule for the resumption of patients' treatment, in compliance with the rules for reducing the spread of the COVID-19 pandemic.

The use of remote assessment tools can support the identification of patients who require treatment in a short time to prevent the onset of complications that may further limit their level of activity and participation.

Looking ahead and considering the foreseeable need to adopt these precautions in the medium term, using these technologies can also allow adequate planning of patients' follow-up and rehabilitation treatment.

AUTHOR CONTRIBUTIONS

AB: conception of the document, document draft and revision. PF, SP, NS, GM, AP, and AS: conception of the document and document revision. All authors contributed to the article and approved the submitted version.

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REVIEW
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Intensive Care Admission and Early Neuro-Rehabilitation. Lessons for COVID-19?

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Coronavirus disease 2019 (COVID-19) requires admission to intensive care (ICU) for the management of acute respiratory distress syndrome in about 5% of cases. Although our understanding of COVID-19 is still incomplete, a growing body of evidence is indicating potential direct deleterious effects on the central and peripheral nervous systems. Indeed, complex and long-lasting physical, cognitive, and functional impairments have often been observed after COVID-19. Early (defined as during and immediately after ICU discharge) rehabilitative interventions are fundamental for reducing the neurological burden of a disease that already heavily affects lung function with pulmonary fibrosis as a possible long-term consequence. In addition, ameliorating neuromuscular weakness with early rehabilitation would improve the efficiency of respiratory function as respiratory muscle atrophy worsens lung capacity. This review briefly summarizes the polymorphic burden of COVID-19 and addresses possible early interventions that could minimize the neurological and systemic impact. In fact, the benefits of early multidisciplinary rehabilitation after an ICU stay have been shown to be advantageous in several clinical conditions making an early rehabilitative approach generalizable and desirable to physicians from a wide range of different specialties.

Keywords: COVID-19, early rehabilitation, ICU, immobilization, mechanical ventilation, neurological complications

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major burden on Intensive Care Units (ICU) because of the high number of patients eventually requiring respiratory support measures. Although most COVID-19 patients are asymptomatic or experience mild illness, ∼15% become severely ill, requiring oxygen therapy. A further 5% are admitted to an ICU, where they require invasive ventilation for acute respiratory distress syndrome (ARDS) (1).

Regardless of the underlying pathology, prolonged ICU stay frequently involves sedation and immobilization (often in a prone position). This is associated with musculoskeletal, pulmonary, cardiovascular, immunological, endocrine, and metabolic complications (2). Musculoskeletal consequences are especially relevant and include muscle atrophy, decreased strength, reduced protein synthesis, joint contractures, bone density decrease, and pressure ulcers. Nearly 50% of ICU

patients show critical illness-associated neuromuscular abnormalities (3). If ventilatory support is maintained for longer than 14 days, a tracheotomy is recommended (4). As a result, a high proportion of COVID-19 patients undergo this procedure in their extended ICU stay.

The complexity of ICU patient management is compounded if the underlying disease touches the central and/or peripheral nervous system (CNS, PNS). In the case of COVID-19, emerging preliminary evidence points toward significant neurological involvement (5–8). Actually, possible nervous system infection could occur by direct entry of the virus via the cribriform plate (8) or, through systemic circulatory dissemination following infection of the lungs. COVID-19 patients admitted to ICU should therefore be considered as especially critical given the potential nervous system involvement. A higher risk of developing transient or persistent neuromuscular and/or neurological sequelae/deficits is consequently conceivable (**Figure 1**).

In this respect, early (defined as during and immediately after ICU discharge) rehabilitative interventions are fundamental in reducing possible added neurological burden to a disease that already greatly affects lung function, potentially causing pulmonary fibrosis in the long-term. In addition, managing neuromuscular weakness would improve the efficiency of respiratory function, as respiratory muscle atrophy worsens lung capacity.

Here, we first briefly summarize the current knowledge on the repercussions of COVID-19, mainly focusing on the neurological manifestations and complications. We compiled the available literature by performing computer searches of English-language databases (Medline, PubMed Central, Google Scholar) combining the relevant keywords ("COVID-19," "Coronavirus," "early rehabilitation," "neurological complications") up to 1st May 2020. Then, we address early rehabilitative interventions that could minimize the neurological impact of COVID-19. Many lessons can be learnt from the cumulative experience of early rehabilitation strategies applied in the acute stage on severely and critically ill patients. However, it is pertinent to point out that this knowledge continues to evolve as new data is being shared regularly, and new recommendations may be provided as more evidence emerges.

WHY COVID-19 IMPAIRS RECOVERY

Several features, comorbidities, and complications of COVID-19 are associated with adverse effects on multiples organs and systems other than the respiratory system, which may then lead to high levels of physical, cognitive, and functional impairment. Rehabilitation treatment plans for patients with COVID-19 or recovering from it, ought to take into consideration these implications to restore impaired functions and prevent long-term consequences.

CNS Involvement

Adverse cerebrovascular events have been reported in COVID-19 patients who developed severe respiratory complications (1). In one study, hypoxic/ischemic encephalopathy was reported in ∼20% of 113 patients who all died from COVID-19 (9). Additionally, a recent investigation from China found that among 214 COVID-19 patients, approximately one third experienced neurological manifestations, including acute cerebrovascular disease, and impaired consciousness (10). Hemorrhagic necrotizing encephalopathy and medio-temporal epileptic encephalitis have also been reported (11, 12). In a French consecutive cases series of 58 severe acute-COVID-19 patients, encephalopathy with prominent agitation, confusion, and corticospinal tract signs were observed in almost two thirds of cases. Eight out of 13 patients who received a brain MRI in this series showed an enhancement of the leptomeningeal spaces. Furthermore, in the 11 patients who underwent perfusion imaging, all showed bilateral frontotemporal hypoperfusion (13). Importantly in this cohort, enduring dysexecutive symptoms accompanied recovery, identifying a target for late rehabilitation effort and follow-up treatment.

The link between COVID-19 and cerebrovascular disease remains controversial but many findings suggest that ischemic stroke occurs in the context of a systemic, highly pro-thrombotic state. An increase in the number of large vessel occlusion malignant strokes has been independently reported (14–16), combined with a higher number of life-threatening thrombotic complications (17). Post-mortem observations have demonstrated multi-organ endothelitis with significant micro-vascular impairment (18).

Although based on a limited amount of data, some evidence suggests that coronaviruses may cause damage to the dopaminergic system. A selective affinity of coronaviruses for the basal ganglia and limbic system has been reported in rodent models of encephalitis induced by intranasal inoculation (19). Specifically, intraneuronal transport was posited as the spreading mechanism of the viruses (20). In humans, high anti-coronavirus antibody titers were observed in the cerebrospinal fluid of Parkinson's disease patients (21). Furthermore, using electron-microscopy the virus was detected in frontal-lobe tissue (22). Prolonged confusion after sedation withdrawal and impaired consciousness have also been described in COVID-19 patients (23). This is not surprising given that functional disturbance of the forebrain systems (frontal/prefrontal, cortical-striato-pallidal, and thalamocortical loop systems) are known to be associated with cognitive-motor dissociation in severe brain injuries. Cognitive-motor dissociation is characterized by blocked motor preparation and action (24). Of note, the possibility that dopaminergic systems may become deregulated suggests that in some COVID-19 patients, altered consciousness may reflect a functional akinetic mutism (25); in such instances a more marked alteration of resting metabolism could be diagnostic or the direct evaluation of altered dopaminergic transmission (26). In summary, COVID-19 can induce neurological sequelae by attacking the CNS in a multifaceted way. This includes vascular, inflammatory, and/or direct neuronal injury. Furthermore, this neurological intrusion may be clinically silent because of sedation and avoidance of certain diagnostic procedures to reduce the risk of cross infection including lumbar puncture, brain imaging, and electromyography/nerve conduction velocity.

PNS Involvement and Critical Care Illness

Several cases of post-COVID-19 acute polyneuropathy have been reported (7, 27–32) with electro-clinical characteristics of Guillain Barré syndrome. These include acute inflammatory demyelinating and motor-sensory axonal subtypes. In the largest case series to date, Toscano et al. (32) demonstrated that of five Italian patients, an axonal variant was observed in three of them and a demyelinating form in two. Furthermore, two cases of Miller-Fisher variant, a Guillain Barré subtype with cranial nerve involvement, have also been described (33). Mao et al. (10) first proposed that anosmia and ageusia in COVID-19 patients reflected involvement at the cranial nerve level. In line with this theory, a large case-controlled study of COVID-19 patients presenting with smell and/or taste disorders, found that < 15% reported concomitant nasal obstruction indicating a primary dysfunction of the olfactory tract (34).

Data are still lacking to prove a specific association between critical illness–related myopathy or neuropathy (CRIMYNE) and COVID-19. However, data from the severe acute respiratory syndrome (SARS) outbreak in 2003 indicated that myopathies with severe muscle wasting and myalgias, were very frequently associated with coronavirus infections (35). As previously stated, nearly 50% of ICU patients present critical illness-associated neuromuscular abnormalities (3). It is therefore arguable that COVID-19 patients are especially at risk of PNS damage.

Respiratory Impairment and Tracheotomy

COVID-19 causes varying degrees of lung complication. These range from mild to severe pneumonia, ARDS, and sepsis. In mild or uncomplicated illness, patients present with symptoms of upper respiratory tract viral infection. These symptoms include mild fever, a dry cough, sore throat, nasal congestion, malaise, headache, and muscle pain. In severe pneumonia, fever is associated with serious dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air) (36). Chest imaging results may be normal in early or mild disease, however, in patients requiring hospitalization, 69% have abnormal chest X-Rays at admission (37). The most frequent findings on X-Ray and CT scans are airspace opacities including ground-glass opacity or consolidation. Distribution is most often bilateral, peripheral, and lower zone predominant (37). In some patients, major alveolar damage results in hypoxemic acute respiratory failure (ARF), requiring mechanical ventilation and ICU admission. Moreover, respiratory viral infections predispose to co-infections resulting in increased disease severity and mortality. Zhou et al. (38) showed that 50% of patients who died from COVID-19 had secondary bacterial infections. Additionally, Chen et al. (9) recorded bacterial and fungal co-infections in COVID-19 patients. Although 71% of patients admitted with COVID-19 receive antibiotics, no information is available on the antimicrobial sensitivities of the organisms identified or on the type and duration of antimicrobial treatment (39).

Chronic obstructive pulmonary disease (COPD) is a risk factor for severe COVID-19. Many patients with COPD have underlying chronic bacterial infections prior to the SARS-CoV-2 infection; however, this important information is not being reported. Given the neuro-invasive potential of SARS-CoV-2 and the peculiar severity of respiratory failure observed in COVID-19 patients, researchers have suggested involvement of the CNS respiratory centers (40). However, to date, there are no data proving SARS-CoV-2 invasion of brainstem dorsal root neurons; furthermore, recovery is typically longer and more difficult in patients having neuroinflammation or neurodegeneration in these areas than in COVID-19 disease (41). While the majority of patients recover from pneumonia without any lasting lung damage, the lasting effects of COVID-19-associated pneumonia may be drastic. Following recovery from acute COVID-19, lung injury may lead to shortness of breath that takes months to get better. Indeed, COVID-19 patients who recover from ARDS may have lasting pulmonary scarring/fibrosis.

In a typical non-COVID-19 ICU patient cohort, early tracheotomy is often performed for critically-ill ventilated patients based on several arguments, including decreasing the duration of mechanical ventilation and ICU stay. However, the ensuing reduction in mortality rate described in several studies, remains a matter of controversy (42–45). It is widely accepted that tracheostomy presents various drawbacks with delayed effects. These include swallowing disorders, mucous plugs, and granulations. Cuff inflation, which causes irritation or damage to the tracheal mucosa, is related to these consequences. In addition, the lack of air-flow induces deafferentation of the oropharyngeal region, which perturbs the swallowing process (46).

Tracheostomy patients requiring repeated aspirations might need continual monitoring and significant support, which incurs additional costs. Rapid and safe weaning of tracheostomy patients is therefore an important goal. Several recent studies have confirmed that a multidisciplinary approach significantly reduces weaning time in acute care (47).

Cognitive Impairment

Neurocognitive impairments in COVID-19 patients have not yet been widely reported. Nonetheless, the tendency of SARS-CoV-2 to invade and disseminate into the CNS through a synapse-connected route, similarly to other coronaviruses, may lead to severe neurological consequences (48, 49). A recent systematic review suggested that a substantial proportion of patients with severe COVID-19 were highly likely to experience a impaired mental status (5). Furthermore, recent findings of a retrospective study of 214 COVID-19 patients described various neurological manifestations. Among the severe cases, impaired consciousness was observed in 14.8% (10). Neuro-radiological investigation of the first meningitis/encephalitis case associated with SARS-CoV-2 demonstrated inflammation in brain structures supporting memory functions, namely the medial temporal lobe including the hippocampus (12). Early case reports from Italy highlighted the importance of recognizing the development of encephalopathy both as a risk during hospital stay and, as a symptom of COVID-19 (50). In addition, older age and preexisting

cognitive conditions were highlighted as enhancing the risk of developing encephalopathy during acute infection and critical illness. Indeed, neurological dysfunction, including delirium and cognitive impairment, is extremely common following critical illness and its pharmacological management (51, 52).

The majority of the literature concludes that several mechanisms such as hypoxemia, glucose dysregulation, and the effects of sedation contribute to development of neurological dysfunction. Studies regarding cognitive outcomes following critical illness report damage over a range of domains including attention, memory, processing speed, and executive function (52–54). A large cohort study of 821 patients in medical and surgical ICUs estimated a high risk of long-term cognitive impairment following critical illness (55). They reported a significant positive correlation between longer duration of delirium with worse global cognition and executive function scores at 3 and 12 months. Moreover, deficits in executive abilities are prominent in patients suffering from conditions such as ARDS, which include symptoms resulting from hypoxemia. This is coherent with the evidence suggesting that structures within the frontal circuits are sensitive to hypoxia (56).

Literature specifically regarding the long-term outcomes in ARDS survivors reported that 1 year after discharge, the majority experienced neuropsychological disabilities including impaired memory, attention, concentration, and mental-processing speed and a global intellectual decline. Prevalence ranged from 25 (57) to 78% depending on the severity of the ARDS (51). A prospective multicenter study in 174 ARDS patients found that at 12 months, 25% of survivors had cognitive impairment in their executive functions, language, immediate, and delayed memory, verbal reasoning and concept formation, and attention and working memory. However, 36% showed significant improvement at 6 months (58). In another study, 82 ARDS survivors self-reported a high prevalence of depressive symptoms and a low prevalence of memory deficits 6–48 months after ICU discharge (59).

As new data on the novel coronavirus SARS-CoV2 continue to reveal its involvement in the CNS, primary deficits in executive functions, attention, and memory may be expected and should be addressed immediately in the acute phase. In this respect, early (unpublished) clinical data from post-acute COVID-19 infected patients in our Swiss hospital are consistent with the expectations. They exposed that executive deficits ranged from light to severe, that attention disturbances were observed in all patients, and more than two-thirds presented memory alteration. Furthermore, from our clinical neurological examination of acute COVID-19 patients in the ICU, severe forms of akinesia were frequently encountered. This may lead to clinical underestimation of conscious awareness in the acute phase, a condition described as cognitive-motor dissociation (60). Indeed, in cases of severely impaired motor output, a patient's cognitive capacity to interact may be hampered and misdiagnosed as reflecting forms of severe altered consciousness carrying unfavorable prognosis (61, 62).

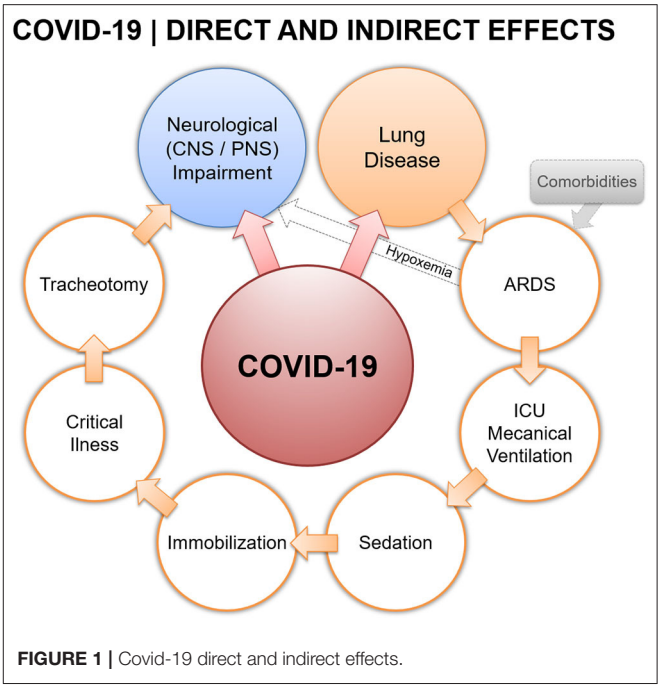


FIGURE 1 | Covid-19 direct and indirect effects.

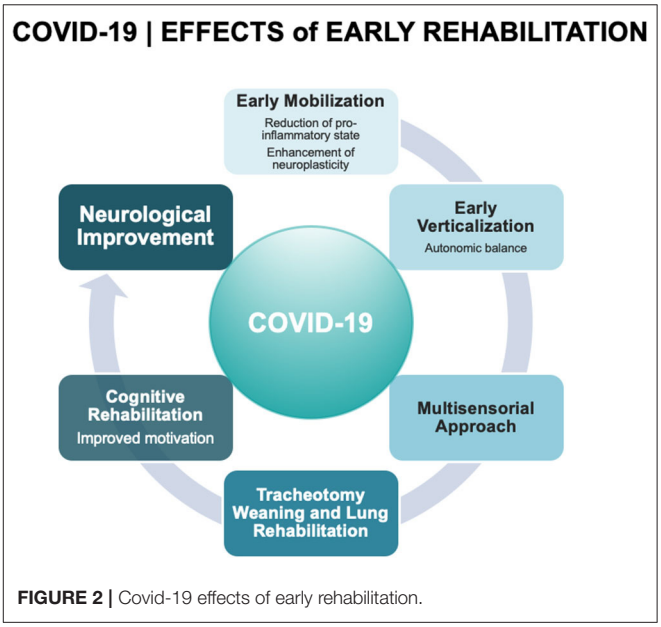


FIGURE 2 | Covid-19 effects of early rehabilitation.

REHABILITATION STRATEGIES TO ENHANCE RECOVERY AFTER COVID-19

Rehabilitation is a complex intervention that focuses on reducing disability, decreasing dependency, and increasing the quality of life. Early rehabilitative interventions following COVID-19 could be similar to those of patients with severe brain injuries or critical illnesses also requiring a prolonged ICU stay. In this respect, they should target recovery of the respiratory system and cardiovascular reconditioning

but also recovery of mobility, functioning, and cognition (**Figure 2**). Rehabilitative intervention programs should be implemented according to the framework of the International Classification of Functioning, Disability, and Health (63, 64), which integrates an individualized treatment plan addressing personal functioning, disease and disability. This promotes and optimizes functional independence thus maximizing a return to participation in society.

Early Mobilization

Muscle deconditioning occurs very early with bed rest, involving a decline in muscle mass, strength, and aerobic efficiency. ICU-acquired weakness is found in in ∼25% of patients (65). This worsens acute morbidity and increases the mortality risk at 1 year (66). Mechanically ventilated patients warrant close attention because of the increased risk of developing ICU-acquired weakness (67). In this respect, COVID-19 patients needing ventilator support for extended periods should be considered especially at risk. Evidence of benefit from early mobilization and physiotherapy comes from numerous randomized controlled trials, systematic reviews, and recommendations (68, 69) and is proven to be a safe and effective intervention. Early mobilization (70), can be initiated during the mechanical ventilation to counteract ICU-acquired weakness. However, an agreed method of early mobilization in mechanically ventilated patients is currently lacking, thus limiting reproducibility and dissemination of shared protocols (71). While official guidelines suggest the use of early mobilization protocols, they do not recommend a specific one (72) and international practices are heterogeneous (61). Unfortunately, there is also limited awareness of the clinical benefits of early mobilization and physiotherapy techniques and when used, disagreement on the sustainable maximal level of activity in these critically-ill patients. However, several factors including multidisciplinary rounds, setting daily goals for patients, day-to-day availability of dedicated physiotherapists, and an adequate nurse/patient ratio are becoming significantly associated with the practice of early mobilization in ICUs.

In our Swiss University Hospital, we adopt a pre-specified procedure for early mobilization with clear entry and exit points. In the ICU, mobilization of mechanically ventilated patients is achieved using MOTOmed Letto® (Reck & Co. GmbH, Germany; an automatic system for leg movement in a supine position, mimicking a bicycle, allowing passive, active, or assisted mobilization) and Erigo® (Hocoma AG, Switzerland; a tilting table with an integrated leg movement system, allowing progressive verticalization of the patient, adjustable to the patient's needs, and possibilities) as soon as cardiovascular stability of the patient is attained. Many animal and human studies suggest that intermittent exposure to gravity throughout long periods of bed rest is sufficient to prevent deconditioning (73) and improve outcome after awakening from a coma (74). Verticalization is now integrated into a neuro-sensorial approach in acute neuro-rehabilitation and improves the results of tracheostomy weaning (75). In addition, a multidisciplinary approach (physiotherapists, nurses, physicians) allows a rapid and pertinent adaptation to the different stages as it takes into account the great variability in neurological deficits and the considerable intra-individual requirements for patient management (75). A prospective randomized study on patients with severe brain injuries showed that mobilization with the lower-body ergometer MOTOmed®, was able to prevent polyneuromyopathy in critical-care illness and to improve awareness in disorders of consciousness. Of note, the use of the robot Erigo® proved to be safer in patients with subarachnoid hemorrhage as it has no effect on the production of catecholamines (76). Futhermore, mobilization has potentiation effect on arousal that may support cognitive recovery as well (77).

Neurosensory Stimulation Approach

The restricted mobility, impaired communication, and social isolation that COVID-19 patients experience in the ICU due to mechanical ventilation may lead to severe sensory deprivation. Environmental (i.e., sensory) deprivation is described as a reduction in variety and intensity of sensory input (78) and can slow down the recovery and development of CNS function (79). Sensory deficits may have additional negative effects of majorly stressing the body and so altering its physiological balance (80). A rationale for treatment is to enrich the environment, promoting the brain's plasticity processes, thereby enabling organizational, and functional modifications. Interventions use multisensory-stimulation programs, which promote arousal, and behavioral responsiveness from controlled exposure to environmental or sensory-specific stimuli (81). Sensory stimuli include visual, auditory, tactile, olfactory, gustatory, and proprioceptive stimulation that can vary considerably in form, intensity, and number of modalities but are typically variations of multisensory stimulation, including the presentation of stimuli that are structured, meaningful, multimodal, familiar, and with emotional content. This maximizes the probability of cognitive engagement (82). For instance, affective auditory stimulation can be achieved by providing information about a time and place, using the patient's favorite music, playing the voice of a loved one, talking to the patient about happy daily events in his/her family or pleasant memories and enjoyable experiences; a tactile and proprioceptive stimulation can be applied by massaging the patient's hands and legs and performing passive range-of-motion activities several times; a visual stimulation can be applied by using a picture of a family member, a family film, or a picture with high positive valence; an olfactory stimulation can be applied using aromatic stimuli including the patient's favorite aromas; a gustatory stimulation can be applied by placing different kinds of food and flavors on the patient's tongue with a cotton bud.

In the clinic, multisensory stimulation is the core of basal stimulation, a therapeutic concept developed by Andreas Fröhlich (83) and subsequently transferred into nursing. Basal stimulation aims to provide a structured and accessible perceptual experience through stimulation of the body and its movements. In addition, it aims to develop an individual, non-verbal form of communication with people whose own activity is limited by their lack of mobility and whose ability to perceive and communicate is significantly impaired. Sensory

stimulation is a non-invasive, safe, inexpensive, and simple-to-apply rehabilitation approach, which has been widely studied in patients with severe brain injuries experiencing alterations in consciousness (84). Despite the lack of high-quality clinical trials, the literature suggests that applying a sensory stimulation protocol enhances the recovery process and improves outcomes in severely brain-injured patients (84–86).

Cognitive Rehabilitation

Alongside respiratory physiotherapy and functional rehabilitation, additional cognitive rehabilitation may be required for COVID-19 patients who present neuropsychological alterations in cognitive performance in the acute and immediate post-acute phases. Formal rehabilitation pathways, comparable to those used in stroke and traumatic brain injury patients, do not yet exist for survivors of acute COVID-19 (87, 88). However, as awareness of COVID-19-induced cognitive impairments grows, rehabilitation strategies should also focus on cognitive recovery.

Cognitive rehabilitation is a broad term referring to therapeutic approaches that address the cognitive deficits caused by lesions or illnesses affecting the brain's optimal functionality. Most methods use either a restorative or compensatory approach (88). The restorative approach aims at rehabilitating cognitive functions by reinforcing, strengthening, or re-establishing previously learned patterns of behavior. It includes repeated exercise of standardized cognitive tests of increasing difficulty that target specific cognitive domains (e.g., selective attention, memory for new information). In contrast, the compensatory approach uses alternative strategies (e.g., internal residual strengths or external compensatory mechanisms including environmental structure and support) that compensate for the decline in cognitive function. Several principles underpin its process and effectiveness (89). Therapeutic interventions have shown greater benefit when integrated as part of a multidisciplinary rehabilitative approach (90) and tailored to the individual needs with goals regularly reassessed (91). Additionally, if interventions are of increasing intensity (92) and begin as soon after injury as possible (89), they are more likely to be successful. In patients with acquired cerebral lesions including traumatic brain injury and stroke, successful cognitive rehabilitation has previously been demonstrated. Systematic reviews on evidence-based cognitive rehabilitation emphasize the importance of functional, patient-centered outcomes. They advise developing individualized and motivational interventions documented by more subjective outcome measures (93).

As previously hypothesized, patients with severe, and critical COVID-19 may present with disturbances primarily in executive functions including severe akinesia (as seen in cognitive-motor dissociation), as well as in attention and memory. Moreover, attention and memory deficits may be exacerbated following periods of delirium. This can lead to additional disturbances in other complex cognitive functions, such as interpersonal communication skills. Similar to patients with severe brain injuries, the acute rehabilitative treatment of COVID-19 patients should aim to improve attention and stimulate the networks responsible for conscious perception and environmental interaction. Promoting motivational stimulation (94, 95) and increasing sensory input (84) may increase adequate goal-oriented behaviors, enhance the recovery process, and minimize the risk of functional disability (88). Post-acute rehabilitation of COVID-19 patients should focus on interventions that improve everyday functioning. They should directly apply compensatory strategies to functional contexts while considering appropriate infection-control measures. This may necessitate the use of remote support services such as tele-rehabilitation, virtual care platforms, and communication devices (96).

Respiratory Support and Physiotherapy

Severely and critically ill patients suffer varying degrees of dysfunction, especially respiratory insufficiency during the acute and recovery stages. The goal of early rehabilitation intervention is to reduce breathing difficulties, relieve symptoms, ease anxiety and depression, and lower the incidence of complications.

Rehabilitation interventions in severely or critically ill COVID-19 patients can only begin when the minimum clinical stability has been achieved. Treatments should be immediately withdrawn in cases of high fever, worsening dyspnea, a respiratory rate $>$ 30 breaths/minute, pulse oximetry $<$ 93% on oxygen therapy or requiring FiO2 $>$ 50% during non-invasive ventilation (NIV), positive end expiratory pressure (PEEP)/continuous positive airway pressure (CPAP) $>$10 cm H2O, respiratory distress, arterial hypertension, brady- or tachycardia, intercurrent arrhythmias, shock, deep sedation, or evidence of radiological lesion progression ($>$50%) within 24–48 h. Rehabilitation therapy in these cases mainly includes position management, respiratory training, and mild physical exercise. Frequent changes of posture, passive mobilization, and/or neuromuscular electrical stimulation should be planned especially in the unconscious patient (97). In addition, evaluation of peripheral muscle strength trends [by the Medical Research Council [MRC] scale and dynamometers] should be recorded as soon as practicable. Airway clearance techniques are not recommended in the acute phase. Indeed, the hypothetical benefits do not outweigh the contamination risk for operators. The risk/benefit ratio should be evaluated on a single-case basis in patients with bronchiectasis or with evident bronchial encumbrance using tools at a safe distance from the patient, which can be maintained.

After discharge from intensive care or an intermediate care, patients may present with disability and functional damage (respiratory function, critical illness myopathy, and neuropathy), reduced participation, and deterioration of quality of life, either in the short- and long-term following discharge. Recovery time is variable depending on the degree of normocapnic respiratory failure and associated physical (asthenia, peripheral muscle weakness) and emotional (anxiety, depression, sense of abandonment, post-traumatic stress syndrome) dysfunction (55). Comorbidities make longer the return to the former condition. Evaluation of exercise capacity and oxygenation response on effort (by the 6-min walk test) and at nighttime should be planned as soon as possible. For patients bedridden for extended periods, an assessment of balance function is

especially recommended. Further suggestions include: evaluation of peripheral muscle strength by the MRC scale, measurement of joint range-of-motion (ROM), and manual and isokinetic muscle tests. Simple and repeatable treatment protocols for weaning patients from oxygen therapy are indicated. Reconditioning interventions are advised in weaned patients and those requiring prolonged weaning from mechanical ventilation and oxygen use, to improve the physical status and to rebalance the motor, and cognitive consequences of prolonged immobilization (72, 98). Exercise involving a gradual load increase is recommended to regain normal function. Low intensity exercise (< 3.0 metabolic equivalents), daily patient counseling, and education are urged. Patients discharged home or to other facilities in the community should receive instruction on physical activity plans. These must be closely monitored regarding function, capacity, and participation once the patient is no longer contagious.

Concerning tracheotomy weaning, our experience emphasizes the importance of patient positioning (head in high flexion) and regular tracheostomy care (cleaning the stoma, changing the inner cannula, aspirations). We use the Facial Oral Tract Therapy (FOTT®) concept and patient positioning according to the Bobath® concept (99) as stimulation techniques that we start immediately on patient admission. Deflation of the cuff is performed during treatment sessions, as soon and as often as possible, with the longest permissible duration, depending on the patient's tolerance. Cuff deflation, even in patients with altered consciousness, avoids deafferentation of the oropharyngeal region. The cuff is inflated during respiratory physiotherapy when ventilation is required and humidification is constantly provided. An appropriate stimulation (cuff deflation, stimulation of upper airway respiration, swallowing, coughing, and verbal communication) it's helpful to avoid sensory deafferentation. Physicians and physiotherapists must work closely with the Ear Nose and Throat (ENT) specialists. The timing of the first trans-cannulation depends on the type of tracheostomy in question. Use of the open surgical approach is recommended between the second and fifth days while the percutaneous dilatational approach is favored after 10 days. A fenestrated outer cannula is inserted at this moment, with the cuff deflated to allow air to flow over the vocal folds when the orifice is plugged by a finger, speaking valve, or stopper. The stimulation from airflow passing over the vocal cords is essential for laryngeal re-afferentation. When saliva-flow management seems to be safe and ventilation treatment is no longer need, the tracheostomy tube can be removed.

Several studies have confirmed that intervention by a multidisciplinary team reduces weaning time (47, 99, 100). Although several individualized, non-comparative, and non-validated decannulation protocols exist, there is no universally accepted protocol. Additionally, randomized clinical trails are lacking on this critical issue. However, our group has demonstrated the benefits of the interdisciplinary neurosensory weaning program in a retrospective study. It showed a reduction in weaning failure rate from 27 to 9%. Furthermore, the time to decannulation after admission decreased from 19 to 12 days (101).

Early and intensive treatments conducted by a specialized team reduce the complications associated with bed rest therefore improving patient outcomes (102). Defining specific guidelines for individual patient pathways will enable creating treatment plans suitable for multiple settings (75). Ineffective cough and secretion retention can play a significant role in weaning failure. In this respect, evaluation of cough strength by peak expiratory flow rate can predict extubation failure and may reduce the length of ICU stay and as a result, costs, morbidity, and mortality may also decrease. Cough stimulation techniques, including lung volume recruitment or manually and mechanically assisted cough are used to facilitate extubation and prevent post-extubation respiratory failure. However, the sub-standard quality of studies on this topic make it difficult to draw conclusions regarding the effectiveness of the techniques (103).

CONCLUSIONS

Although our understanding of COVID-19 is still incomplete, a growing body of evidence indicates potential deleterious effects on CNS and PNS function. This may lead to complex and long-lasting physical, cognitive, and functional impairments. Beginning rehabilitation in the acute stage of the disease is required to combat this.

COVID-19 is associated with a cascade of negative concurrent factors, including some unrelated to the disease *per se,* all having a potentially heavy impact on disability and global functioning. This additive effect with ability to induce multi-organ dysfunction is peculiar to COVID-19 and differentiates it from CNS, PNS, heart and lung diseases for example, which, even when very severe, rarely display such a pleiotropic effect. Patients with severe COVID-19 are likely therefore, to present with a variety of serious sequelae associated with the viral illness, including prolonged stay in the ICU, immobilization, mechanical ventilation, tracheotomy, sedation, delirium, all aggravated by preexisting comorbidities.

Given the high proportion of hospitalization in critical care units, it is likely that a considerable number of survivors will require rehabilitation due to these sequelae. Hence, rehabilitation will be a key component in the continuum of patient-centered care and rehabilitation professionals will have a critical role in assisting patient recovery from COVID-19-associated disabling effects. Indeed rehabilitation by a multidisciplinary team should start as early as possible since prompt intervention has proven efficient in counteracting the vicious circle of disease-related and indirect ICU side-effects. Accordingly, individualized treatment plans should be implemented.

Based on the experience of our acute interdisciplinary neuro-rehabilitation team in managing severely brain-injured patients, we would recommend applying an early and intensive rehabilitation program for severe COVID-19 patients that aims at maximizing patient function to achieve the highest possible level of independence (**Figure 2**). Such programs consist of a combination of approaches including early mobilization, multimodal sensory, and cognitive stimulation,

tracheotomy-weaning strategies, cardiovascular training and monitoring and respiratory management. These have been shown to improve functional outcomes and quality of life, reduce the social and emotional burdens for the patient and family, and reduce the length of hospitalization and related costs.

AUTHOR CONTRIBUTIONS

AP, JJ, LL, LD, PR, NS, and KD contributed to the conception and design of the review. AP, JJ, and LP contributed to the literature review, drafting the text, and preparing the figures. All authors contributed to the article and approved the submitted version.

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Pain Assessment and Treatment in Dementia at the Time of Coronavirus Disease COVID-19

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INTRODUCTION

The infection of severe acute respiratory syndrome coronavirus (SARS-CoV) 2 has raised rapidly from the outbreak in Wuhan within the Chinese Hubei province all over the world resulting in a pandemic emergency, which has remarkably affected the Italian population since February 21, 2020 (1). COVID-19 (COrona VIrus Disease 2019) presents the highest rate of severity and mortality in the elderly, characterized by several comorbidities contributing to a worse prognosis (2). This is exacerbated by the circulation and spread in long-term care facilities (3). Among the concurrent chronic conditions affecting the aged patients and the oldest old, one of the most frequent is represented by cognitive impairment in dementia, known as Alzheimer's disease and related dementias (ADRD) (4). It is known that age represents a highest risk factor for pain and dementia (5). In addition, about half of the people suffering with dementia experience regular pain (6). Pain can be encountered in different types of dementia, such as Alzheimer's disease (AD), vascular dementia (VaD), fronto-temporal dementia (FTD), and Parkinson's disease (PD), and it could appear in different forms (e.g., nociceptive pain, neuropathic pain, and central pain) (5). Importantly, the occurrence of pain in dementia could lead to further complications in the patients' healthcare routine. At this moment, due to the COVID-19 emergency, a large amount of old people presenting dementia and pain cannot attend to the hospital to receive their usual healthcare routine to manage pain. In this regard, the introduction of new digital technologies in the field of medicine—commonly known as "telemedicine" or "telehealth" (7)—can pave the way for treating pain in patients with dementia from the comfort of their own home (8).

DEMENTIA, PAIN, AND COVID-19

ADRD affect some 50 million people worldwide (9) and 900–1,000 per 100,000 inhabitants in Italy (10). The 12% of COVID-19 positive dead patients in Italy suffered from dementia (11), and 43% of deaths occurs in the oldest old (12). Apart from being aged, demented patients may have difficulties to remember preventative measures, thus resulting in a higher risk of infection, even more in nursing-home residents (4). Moreover, the mental and cognitive health of demented patients can be worsened by COVID-19. These patients suffer from several behavioral symptoms, like agitation and aggression, known as behavioral and psychological symptoms of dementia (BPSD), which can be enhanced by social distancing (13). A greater concern is for patients in need of hospitalization for COVID-19, since a new environment is proven to increase BPSD (14). Losing face-to-face contact

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with people familiar to the patients can bear a remarkable burden (4), in terms both of anxiety and of cognition. Moreover, COVID-19 induces delirium due to hypoxia, which can exacerbate dementia (4). Cognitive deterioration is common in course of acute respiratory distress syndrome (ARDS) and it can last also in the long term, complicating several aspects, such as memory and attention (15, 16). In particular, COVID-19 seems to be associated with neurologic manifestations as confusion (9%), dizziness (17%), impairment of consciousness (8%), risk of stroke (3%), anosmia (6%), hypogeusia (6%), and ataxia (1%) (17). Moreover, neuropathies can also occur (16). This issue can play a pivotal role in patients affected by ADRD, since they often present mixed pain states like osteoarthrosis and diabetic neuropathy, due to their advanced age (18). Mobility, already impaired by these conditions, can result in being very difficult to recover after hospitalization, mainly in intensive care units (ICU). The issue of worsened conditions is even more worrying in this period in which follow-up and accurate review of therapy against BPSD are postponed in order to reduce the risk of contagion (13).

In this field, pain is considered one of the most important causes of BPSD (19). In particular, the BPSD can arise as a result of pain through agitation or aggression, representing a stressful factor for both the patients and the caregivers (6). Another important issue is the impact of neuropathological changes occurring in dementia, which could affect patients' pain perception (20). Concerning this, it is known that in patients with ADRD the neuropathological changes occurring after the onset of the clinical condition have a greater impact in the medial pain system than on the lateral pain system (20). This means that in patients presenting ADRD, there is a higher impairment of the cognitive-evaluative and motivational-affective aspects of pain than in sensory-discriminative ones (20). However, in patients with VaD, lesions in white matter lead to several disconnections between brain areas in a neurobiological process known as "deafferentation" and provokes an increase in the motivational-affective aspects of pain (6). This type of pain—commonly known as "central neuropathic pain" —has also been shown in patients with stroke (21), and with VaD (22, 23). Nevertheless, in FTD patients the atrophy in the prefrontal cortex can lead to a decrease in the motivational-affective aspects of pain, similarly to those presenting ADRD (24). Overall, the alterations in both the afferent transmission pathways and the endogenous descending inhibitory transmission control systems lead to an altered pain processing in patients with dementia (25). Moreover, it has been shown that the more severe the cognitive impairment, the bigger the difference in pain experience between demented and non-demented populations (5).

PAIN ASSESSMENT AND NEURO-REHABILITATION: THE CONTRIBUTION OF TECHNOLOGY AT THE TIME OF COVID-19

The 72% of patients older than 85 years suffer from pain (26, 27), and this amount can reach the 80% for nursing-home guests with ADRD (6) and definitely increase in ARDS and intubation. Pain diagnosis and assessment through self-report represents the gold standard, but it cannot be applied in patients with severe ADRD because of their limited communication skills (28). In these patients, underdiagnosed pain may induce BPSD like agitation (29, 30), requiring the use of neuroleptics increasing cardio cerebrovascular accidents (31) and, hence, predisposing to increased risk in course of COVID-19. In this situation, the ABCDEF bundle can be recommended: assess, prevent and manage pain; both spontaneous awakening and breathing trials; choice of sedation; delirium monitoring and management; early mobility and exercise; and family engagement and empowerment (16, 32). Although telemedicine can be not suitable to provide virtual neurologic examination (13), it can be very useful to manage BPSD (13) and pain (33). It can indeed represent an important option to provide accurate treatment also with drugs like opioids endowed with serious adverse reactions (34), including immune system, and thus involved in COVID-19 management (33). Therefore, the assessment of pain is fundamental to improve the quality of life and reduce the risk of death of demented patients, even more in this difficult scenario. For patients with severe dementia observational assessment tools can be applied. In particular, the Mobilization–Observation–Behavior–Intensity–Dementia (MOBID)-2 pain scale that allows the caregiver to rate the intensity of both the musculoskeletal pain, through the observation of pain behavioral indicators (pain noises, facial mimics, and defense moves) during the execution of five guided movements to unravel also hidden conditions, and the visceral pain (35). Furthermore, some reviews highlighted that the same motor rehabilitative treatment, delivered from afar or face to face, produces the same results, suggesting that telerehabilitation is not inferior in comparison with in-person therapy (36, 37). In this situation, motor telerehabilitation can be very useful to improve motor activity, according to the ABCDEF bundle, and tele-care may also allow to establish a safe contact with the caregiver whom can be instructed in streaming by the health assistant (38). The use of mask may prevent the assessment of facial expressions. Moreover, another assessment test for intubated patients, with specific non-verbal pain scales examined in ICU, is the Critical-Care Pain Observation Tool (CPOT) (39). This pain scale allows to observe pain also in the presence of the endotracheal tube and to evaluate the compliance with the ventilator, and it has proven to have good validity, reliability, feasibility, and clinical utility (39–41). The main features of the proposed pain assessment tools are reported in **Table 1**.

Interestingly, previous investigations have described the use of telemedicine as a useful tool to follow or treat clinical populations in catastrophic situations or in public health emergencies (42). Through telemedicine systems, patients can be efficiently screened, and this could represent an effective approach in the current worldwide emergency of COVID-19. By using telemedicine systems, it is also possible to protect patients, clinicians, and the community from virus exposure (8). Moreover, telemedicine systems allow physicians and patients to be in contact anytime (24/7) through smartphones, tablet, or webcam enabled computers (8) and tackle some clinical issues related to expenses, prevalence, and other treatment barriers associated with the patients' management. In particular,

TABLE 1 | Characteristics of the pain assessment tools useful for non-communicative patients with severe dementia and intubated.

Pain assessment tool	Authors and year of first publication	Type of scale	Number of items	Time of execution	Qualification of rater	Validity and reliability
Mobilization–Observation–Behavior–Intensity–Dementia (MOBID)-2.	(35)	Observational scale.	It consists of two parts of 5 items each. Part 1: assessment of musculoskeletal pain observing pain behavior during the execution of five guided movements. Part II: assessment of pain from internal organs, head and skin pain behavioral indicators, and localization of pain crossing on pain drawing.	Time-efficient in use (mean 4.37 min, range 2.0–7.0).	Trained nurse.	Moderate to excellent agreement was demonstrated for behaviors and pain drawings ($\kappa = 0.41$–0.90 and $\kappa = 0.46$–0.93). Inter-rater and test–retest reliability for pain intensity: ICC 0.80–0.94 and 0.60–0.94. Internal consistency: Cronbach's α ranging 0.82–0.84. Good face-, construct- and concurrent validity. Correlation of overall pain intensity with physicians' clinical examination and defined pain variables (rho = 0.41–0.64).
Critical-Care Pain Observation Tool (CPOT).	(39)	Observer rated scale.	It consists of 4 items: facial expression, body movement, ventilator compliance, and muscle tension.	The patient is observed for 1 min at rest and during and after nociceptive procedure.	Trained nurse.	Inter-rater reliability: $k = 0.52$–0.88. Acceptable reliability and validity, with significant discriminant validity (paired *t*-tests, $P \leq 0.001$). Criterion validity: analyses of variance ANOVA ($P \leq 0.001$) and Spearman correlations (0.40–0.59, $P \leq 0.001$).

telemedicine has been used for pain assessment through digital diaries or personal digital assistants (43, 44), to provide an accurate and easy monitoring of pain symptoms. Regarding treatment delivery in pain patients, novel telemedicine strategies have been found effective to facilitate consultation and talk therapy and to provide rehabilitation pain trainings (45–49). For instance, telemedicine systems have been proposed to provide behavioral medicine interventions in chronic pain patients through a self-regulation training targeting both the sensory and affective components of pain (50). In addition, training programs through video-conferencing have been also used for pain treatments (46, 50).

DISCUSSION

The SARS-CoV 2 has changed the management of chronic conditions often occurring in the main target of COVID-19 represented by the aged population. One of the most common comorbidities in these patients is dementia, often accompanied by chronic pain. The assessment and management of pain in demented patients is necessary during COVID-19 pandemic emergency, and the use of telemedicine can allow a safe handling reducing the access to hospitals and clinics to contain contagion. We suggest pain management to improve the quality of life of patients and to reduce agitation (51): accurate review of analgesic and antipsychotic therapy of BPSD can reduce cardiocerebrovascular events, an important risk factor for bad prognosis of COVID 19. Pain is often misunderstood and undertreated; therefore, educational programs for physicians and caregivers are needed (52, 53) to improve "pre-habilitation," the process of optimizing general health fundamental to cope better with the stress condition (16), and neurorehabilitation of demented patients after COVID 19. Furthermore, novel telemedicine systems should be also taken in consideration to provide assessment and rehabilitation pain trainings to improve neurorehabilitation of patients suffering from dementia in the new era of COVID-19.

AUTHOR CONTRIBUTIONS

DS, MC, GB, and PT have conceived the work. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Telemedicine and Virtual Reality for Cognitive Rehabilitation: A Roadmap for the COVID-19 Pandemic

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The current COVID-19 pandemic presents unprecedented new challenges to public health and medical care delivery. To control viral transmission, social distancing measures have been implemented all over the world, interrupting the access to routine medical care for many individuals with neurological diseases. Cognitive disorders are common in many neurological conditions, e.g., stroke, traumatic brain injury, Alzheimer's disease, and other types of dementia, Parkinson's disease and parkinsonian syndromes, and multiple sclerosis, and should be addressed by cognitive rehabilitation interventions. To be effective, cognitive rehabilitation programs must be intensive and prolonged over time; however, the current virus containment measures are hampering their implementation. Moreover, the reduced access to cognitive rehabilitation might worsen the relationship between the patient and the healthcare professional. Urgent measures to address issues connected to COVID-19 pandemic are, therefore, needed. Remote communication technologies are increasingly regarded as potential effective options to support health care interventions, including neurorehabilitation and cognitive rehabilitation. Among them, telemedicine, virtual reality, augmented reality, and serious games could be in the forefront of these efforts. We will briefly review current evidence-based recommendations on the efficacy of cognitive rehabilitation and offer a perspective on the role of tele- and virtual rehabilitation to achieve adequate cognitive stimulation in the era of social distancing related to COVID-19 pandemic. In particular, we will discuss issues related to their diffusion and propose a roadmap to address them. Methodological and technological improvements might lead to a paradigm shift to promote the delivery of cognitive rehabilitation to people with reduced mobility and in remote regions.

Keywords: augmented reality, cognitive, COVID-19, rehabilitation, telemedicine, virtual reality

INTRODUCTION

Disorders of cognitive functions (language, perception, attention, memory, executive functions, and praxis) are frequent following neurological damage of different etiology, with a significant impact on independence, social relationships, school attendance, and employment opportunities, ultimately leading to reduced quality of life. Cognitive impairment is a critical determinant of

overall neurorehabilitation outcome, and cognitive rehabilitation is an expanding clinical and research field.

Cognitive rehabilitation encompasses a wide range of therapeutic cognitive interventions to achieve functional changes by reinforcing, strengthening, or reestablishing previously learned patterns of behavior or establishing new patterns of cognitive activity or mechanisms to compensate for impaired neurological systems (1). These interventions are based on psychological theories and models of behavior and behavioral change and on neuropsychological models of brain–behavior interactions (2, 3), and can be conducted with paper–pencil tools, computer programs, or, more recently, virtual reality (VR).

Several works explored the effectiveness of cognitive rehabilitation. While some studies adopted a pragmatic clinical focus, supporting the efficacy of neuropsychological interventions (4, 5), other reports emphasized the lack of methodological rigor of trial design, concluding that there is insufficient evidence to guide the clinical practice (6–10). To overcome these limitations, the Cognitive Rehabilitation Task Force (CRTF) of the American Congress of Rehabilitation Medicine, Brain Injury Special Interest Group, recently published a systematic review of studies addressing cognitive rehabilitation for people with two of the most frequent clinical conditions, namely, stroke and traumatic brain injury (TBI) (11). The authors evaluated 491 articles and made 29 recommendations for evidence-based practice of cognitive rehabilitation that support practice standards for (1) attention deficits after TBI or stroke; (2) visual scanning for neglect after right-hemisphere stroke; (3) compensatory strategies for mild memory deficits; (4) language deficits after left-hemisphere stroke; (5) social communication deficits after TBI; (6) metacognitive strategy training for deficits in executive functioning; and (7) comprehensive–holistic neuropsychological rehabilitation to reduce cognitive and functional disability after TBI or stroke (11).

To be effective, cognitive rehabilitation should be intensive and prolonged over time, but social events that reduce access to care facilities hamper intensive and prolonged cognitive rehabilitation, unless current protocols are modified. This is the case we have been dealing with since December 2019, when a pneumonia epidemic of previously unknown etiology in China was related to SARS-CoV-2 infection. In March 2020, the World Health Organization declared the COVID-19 pandemic (12). Since then, the virus has spread widely and rapidly. On June 4, 2020, more than 6 million cases of COVID-19, and nearly 380 hundred deaths have been reported worldwide (13). In the absence of an effective treatment against SARS-CoV-2, the outbreak containment strategies mainly rely on hygienic measures, extraordinary sanitization, and reduction of interpersonal contacts through social distancing and quarantine for infected people and their contacts (14). In this scenario, healthcare systems need to reorganize quickly and deeply both in the wards hosting COVID-19 patients and in the services for patients with chronic diseases. Social distancing and quarantine, indeed, abruptly interrupted access to routine medical care for frail and vulnerable people, who are at an increased risk of SARS-CoV-2 infection and related morbidity and death. Patients with neurological diseases are among such frail patients because of advanced age, comorbidities, or immunosuppression due to treatments (15). In addition, the best medical practices have also been suspended for patients whose doctors have been in quarantine or for people with stroke and myocardial infarction, who have not sought medical treatment for fear of social contact (16, 17).

Therefore, timely measures are required to mitigate the potentially harmful consequences of quarantine, and telemedicine approach to achieve non-face-to-face consultations has been proposed (18).

We will review features of telerehabilitation, VR, and other technologies to achieve cognitive telerehabilitation (**Table 1**); provide some suggestions to enhance cognitive rehabilitation interventions during the COVID-19 pandemic; and propose future implementations based on telemedicine and VR.

TELEMEDICINE AND TELEREHABILITATION FOR COGNITIVE DISORDERS

Telemedicine is a general term, first introduced in the 1970s, to indicate the practice of medicine without the usual physical interaction between a healthcare professional and a patient using an interactive multimedia communication system (23). Telemedicine includes the application of information and communication technology (ICT) to the medical field to guarantee remote assistance services based on the exchange of clinical information and data within a network of professionals or between professionals and clients (24). In parallel to the classical doctor–patient relationship, telemedicine must comply with all the rights and duties of any health act for prevention, diagnosis, treatment, rehabilitation, and monitoring. Telemedicine is not meant to replace traditional health services but rather to integrate them to improve effectiveness, efficiency, and appropriateness (25).

Stemming from the broader approach of telemedicine, telerehabilitation is an alternative method of delivering conventional rehabilitation services via ICT to patients allowing them access to care at their homes or other locations (19, 26). Telerehabilitation systems provide therapists with the possibility of selecting the most appropriate approach for each individual patient, monitoring execution and outcomes remotely, and modifying the treatment accordingly. The COVID-19 pandemic has accelerated this process and forced researchers and clinicians to reshape the neurorehabilitation strategies with the use of technologies (27) and to accelerate the development of telemedicine for home care purposes, e.g., the use of low-cost technologies such as smartphones or tablets for virtual medical examination, counseling, and rehabilitation (15, 28).

Tele-health approaches were demonstrated to be feasible, well-accepted, and effective in providing rehabilitation to chronic neurological patients, increasing participation, and allowing the continuity of care in an ecologic environment (29).

Telerehabilitation was initially aimed to improve motor outcomes, but the interest in the treatment of cognitive deficits has increased over the years. Studies ranged from pilot reports,

TABLE 1 | Main methods and technologies for cognitive telerehabilitation.

	Definition	Advantages	Limitations
Telerehabilitation	The provision of rehabilitation services via telemedicine methods and techniques (19)	Increases frequency of healthcare professional contact Facilitates intensive and prolonged programs Allows the access to home-delivered care	Barriers to accessing technologies (e.g., lack of computer or internet connection) in specific patient groups (e.g., elderly people)
Virtual Reality	A computer-based, interactive, multisensory environment that occurs in real time, with which the user can directly interact (20)	Provides immediate feedback Allows the adaptation to patient's performance Highly engaging High level of ecological validity Can be combined with other tools/devices (e.g., electroencephalography, physiological activity registration tools)	Technology requirements are often cumbersome Limited availability (i.e., outpatient clinics) Expensive hardware and software tools
Augmented Reality	The overlaying of computer-generated imagery atop the real world using a see-through display (21)	Employs wearable devices Allows the adaptation to patient's performance High patient engagement Available for home-delivered care	Limited user's immersion Barriers to accessing technology
Serious Games	Digital games whose purpose is to reach a specific goal (e.g., cognitive rehabilitation) other than entertainment (22)	Allows the adaptation to patient's performance High patient engagement Affordable costs Available for home-delivered care	Lack of immersion Limited flexibility and customizing

assessing the feasibility of postoperative telerehabilitation programs to improve cognitive outcomes in adult patients with primary brain tumors (30), to systematic reviews and meta-analyses focused on neurodegenerative disorders (31, 32), stroke (33), and multiple sclerosis (34).

Telemedicine interventions were found not to be inferior to conventional face-to-face approaches in terms of efficacy, validity, reliability, and patients' satisfaction, but the low number of randomized controlled trials hampered definitive conclusions (35, 36). Based on these promising results and forced by COVID-19 contingency, new studies and a larger diffusion of cognitive telerehabilitation approaches are expected.

VIRTUAL REALITY FOR COGNITIVE REHABILITATION

Over recent years, researchers and clinicians proposed VR as a new technology to implement innovative treatments in a broad range of clinical areas, including mental health disorders (e.g., anxiety disorders, depression, schizophrenia, eating disorders), pain management (37–41), motor and cognitive rehabilitation of neurodegenerative disorders, TBI and stroke (42), and cognitive domains (43–46).

VR allows the user to interact with, and become immersed in, a computer-generated environment in a naturalistic way. The key concepts that define VR are immersion (i.e., the extent to which the user perceives himself in the virtual environment rather than the real world), sense of presence (i.e., the subjective experience of the user as being in the virtual world), and the possibility to interact with the computer-generated environment (20, 47, 48).

VR has a number of advantages over traditional rehabilitation approaches. First, VR has a high level of ecological validity because of the sensorimotor interaction between the user and the virtual environment, allowing to transfer skills from virtual to real word. Second, the compliance and the satisfaction of the patient when interacting with the enriched computer-generated environment are higher than those with conventional rehabilitation (49). Third, VR has the great advantage of providing an immediate and direct feedback, so that the level of difficulty of the therapy can be easily adapted to the patient's needs and severity (50), with positive effects on their sense of efficacy. By providing quantitative outcome measures to patients, VR supports better adherence to neurorehabilitation programs than to traditional rehabilitation (51). Fourth, VR rehabilitation programs can be applied without the direct supervision of the therapist, but only with the presence of a caregiver (44), addressing the patient's need of autonomy. Fifth, VR allows patients to perform basic daily living activities in a safe and controlled environment, increasing engagement and motivation (52). This is particularly important, considering that traditional training programs are often repetitive and monotonous. VR may engage the patient in an enriched environment and stimulating activities, thus activating attention and motivation, and facilitating neuroplasticity and functional recovery (53, 54). VR research protocols are increasingly applied to rehabilitation, as technology becomes more accessible and affordable, but VR is not yet routinely used in clinical rehabilitation settings because of several issues. The term VR is frequently used in the wrong way, as some studies improperly define computer-based devices providing stimuli on a monitor (e.g., video games), which clearly lack two out of the three key features of VR, i.e., immersion and presence. As gaming consoles are widely available, clinicians have indeed started to use low-cost commercial immersive systems designed for recreation as an alternative way of delivering VR (55–57), but the lack of specific VR features may result in

a limited therapeutic effect of these devices. Moreover, VR systems are often cumbersome and expensive, thus hampering the possibility to perform VR rehabilitation interventions outside the outpatient clinics (44). The possibility to perform immersive VR-based rehabilitation programs at home is an important challenge that should be addressed in the near future. Moving from a single-user VR setting available in the clinic to a multiuser one with remote connection between patients/caregivers and therapists could be an important step toward the dissemination of VR technologies (58).

Among graphic immersive techniques, augmented reality (AR) is another novel technological system that enhances the sensory experience of the real environment by inserting virtual elements to the view of the physical environment, usually using a camera, smartphone, or other vision devices (21). In contrast to VR, AR environment is not completely computer generated but is a combination of real and virtual objects in a physical environment (59). The amplification of sensory experience through AR was found to be associated with a significant improvement of the ecological validity of treatments of various health disorders (60). AR-based treatment has been proposed for phobic disorders and stroke (61, 62).

More recent approaches include serious games (SGs), i.e., interactive computer applications, in which education and learning, not entertainment, are the primary goals (63, 64). Due to their design, games can offer challenging, rewarding, motivating, and engaging experiences that can be shared with other players in the form of points or ranking. Indeed, the interactive nature of the games enables constructive, situational, and experiential learning opportunities that can be easily adopted for rehabilitation purposes, despite not having been fully designed for rehabilitation goals (65). SG-based treatments derive from the combination of specific elements of computer cognitive training with motivational aspects of games (66). Similar to AR, SGs are characterized by an immersive level of each environment that can range from the complete VR to the real environment (67). Hence, the smaller computation time required to model the 3D environment of AR and SG may make them more cost effective in comparison to VR (61). Most SG-based cognitive treatments have been directed to healthy older adults or patients with mild cognitive impairment or Alzheimer's dementia (68). The fact that elderly people could have difficulties in interacting with tools designed for the game (69) has determined a recent interest to develop SGs specifically designed for these populations (66). Since cognitive rehabilitation adopts a restitution-based approach, in which impaired functions, either physical or cognitive, are recovered through intense and continuous stimulation (70), SG-based interventions are particularly useful to this end, being available also for home-based rehabilitation (71). Cognitive treatments using SGs have been developed also for stroke, TBI, brain tumors (72) and cerebral palsy (73). In conclusion, even if SG systems are appealing because of their low cost, their diffusion is partially limited because of the lack of customization and of rehabilitation theoretical models behind their development. The smaller computation time required to model the 3D environment of AR and SG may make them more cost effective in comparison to VR (61), overcoming some VR limitations and providing another option for remote cognitive rehabilitation.

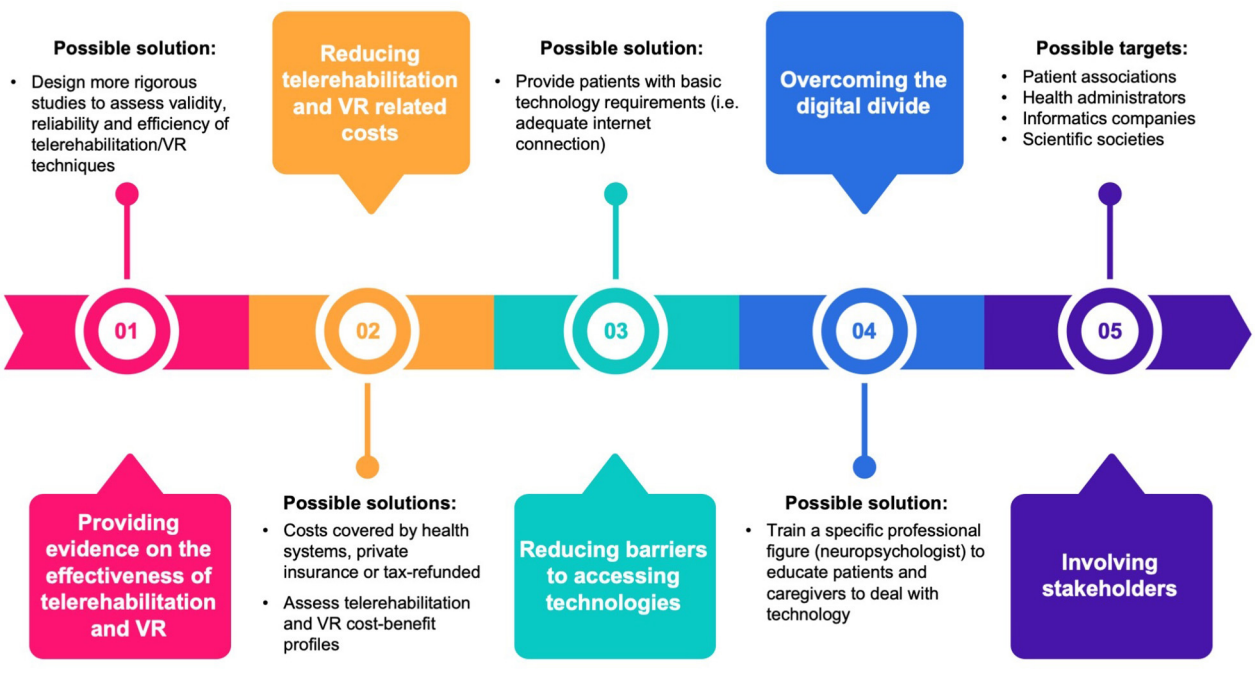


FIGURE 1 | Issues related to cognitive telerehabilitation and possible solutions. VR, virtual reality.

DISCUSSION

The current health system contingency due to the COVID-19 pandemic requires an acceleration in the use of telemedicine to enable cognitive neurorehabilitation outside the traditional settings (e.g., hospital, rehabilitation centers, private practice) and in an ecologic environment. Teletherapy may replace and complement in-person treatment to mitigate constraints on service delivery that currently limit access to cognitive rehabilitation care. Telemedicine, VR, AR, and SGs are promising tools for remote-delivered cognitive rehabilitation programs. There are, however, a number of open questions that hamper these approaches to become a valid complement to standard care of patients with cognitive deficits. We propose a roadmap to address these issues (**Figure 1**).

First, evidence supporting telerehabilitation and VR for cognitive rehabilitation is still preliminary, and a larger number of studies focusing on the validity, reliability, effectiveness, and efficiency of these techniques and approaches are needed. The use of VR therapy is indeed far from becoming widespread beyond the research setting, thus limiting its translation into the ordinary clinical setting (74). Another point that limits the spread of telerehabilitation and VR for cognitive rehabilitation beyond the research setting is that these techniques have no specific effect on a single (e.g., executive, visuospatial, and memory) domain, but they are rather intended to stimulate at the same time multiple domains to achieve high levels of ecological validity. The development of more targeted and specific VR and telerehabilitation techniques to be compared with "traditional" ones could offer challenging opportunities for future research. Moreover, the lack of specific clinical training in VR therapy could be another issue that hampers its diffusion (75). The identification of specific health professional figures (e.g., neuropsychologists) to be adequately trained could be a possible solution. An important point to be investigated to contribute to the dissemination of VR therapy is the tolerance of VR interventions, i.e., the gradual decrease in effect due to the lack of novelty of the experience. A critical component is safety and tolerability: VR sickness and boredom should be monitored to avoid dropouts and lack of compliance.

Second, the high cost of the hardware and software required for these techniques is still a bottleneck that impedes their wide application outside the experimental setting. Moreover, these costs are covered neither by health systems and private insurance nor by tax refund. Studies exploring their cost–benefit profiles in terms of reduced direct and indirect costs related to cognitive deficits might help overcome this issue. A wider diffusion of hardware platforms and the use of open software might consistently reduce these costs, in analogy to what happened in recent years with mobile phones and consumer technology.

Third, a high-speed Internet connection is of paramount importance to improve telerehabilitation and remote monitoring from the therapist, but in some areas, it may not be available.

Fourth, the digital divide in some countries/regions, in older adults, and in some classes of people might reduce the wide application of cognitive telerehabilitation. A specific figure, i.e., the neuropsychologist with expertise in these techniques, including the ability to remotely monitor the correct application of cognitive telerehabilitation at home, educate caregivers, and help them to solve technical issues, would be important to reduce the effects of this digital divide.

Addressing these points requires the involvement of a number of stakeholders, including patient associations, health, informatics, and scientific societies, but may result in a consistent improvement in cognitive rehabilitations strategies in that carrying out interventions at home is even more important because the generalization of the results to daily life activities is one of the most critical elements for the success of the intervention. Addressing the abovementioned issues may lead to a wider application of teletherapy, e.g., to the still unexplored area of behavioral and psychological symptoms of dementia (BPSD) management. Because of the limited benefits of the pharmacological and nonpharmacological interventions (e.g., environmental redesign, validation therapy, and behavioral management techniques) for BPSD (64), telemedicine, and VR may offer new options for this condition. Preliminary results are, indeed, encouraging, either for patients (76, 77) or caregivers (78–80).

Methodological and technological improvements might survive the end of the COVID-19 pandemic and result in a cost-effective and sustainable paradigm shift for remote delivering of health services to people with reduced mobility and access to hospitals and rehabilitation centers, and in remote regions not covered by these facilities. Adapting healthcare facilities during the COVID-19 pandemic through new technology could help support the cognitive and psychosocial needs of both patients and their families (81).

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets generated for this study are available on request to the corresponding author. Requests to access these datasets should be directed to ST, stefano.tamburin@univr.it.

AUTHOR CONTRIBUTIONS

The study has been designed by EM, CZ, CC, and ST. Data have been gathered and analyzed by EM, CZ, SB, AF, RG, GS, CC, and ST. The manuscript has been drafted by EM, CZ, SB, AF, CC, and ST. SB, RG, GS, CC, and ST revised the manuscript. All Authors approved the final version of the manuscript.

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REVIEW
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Acute Ischemic Stroke in COVID-19: A Case-Based Systematic Review

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Corona virus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) is recognized as a global pandemic by WHO 2020 with 5,934 936 infections, 367,166 deaths and affecting over 200 countries as of 30th May 2020. Acute Ischemic Stroke (AIS) in brain is also emerging as an important neurovascular/neurological complication of COVID-19, associated with extreme immune responses leading to dysregulated coagulation system and generalized thrombo-embolic status and increased risk of AIS especially among usually less vulnerable younger adults in this cohort. Thus, in early June 2020, we aimed to review the clinical data on all published cases of COVID-19 and concomitant AIS, with a view to understanding the pertinent clinical, laboratory and imaging features. The neutrophil-lymphocyte ratio (NLR) at time of hospital admission for COVID infection correlates positively with the duration of time before onset of clinical features of AIS. Higher NLR, C-Reactive protein, serum ferritin, D-dimer and fibrinogen levels are associated with poor prognosis of AIS in COVID-19 with 75% of patients dying or being severely disabled at present. Currently it is too early to comment on the long-term outcomes for survivors.

Keywords: acute ischemic stroke, COVID-19, neurorehabilitation, white blood cells, neutrophil lymphocyte ratio, hyper coagulopathy, D-dimer, ferritin

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KEY FINDINGS

- Acute ischemic stroke is an important, but an under recognized complication of SARS-CoV2 infection, that leaves most recovered patients with significant disabilities as of present stage July 2020 of the pandemic.
- Hypercoagulation markers such as D-dimer are substantially elevated among all patients early in the disease progression.
- Neutrophil to lymphocyte ratio, C-Reactive protein, and Serum Ferritin levels appear to be prognostic markers.
- Patients with higher admission neutrophil-lymphocyte ratios demonstrate a shorter interval between infective symptoms of COVID-19 and the clinical manifestation of Acute Ischemic Stroke.
- Large vessel occlusion is the main etiologic subtype, with only a minority of patients receiving standard of care treatment.

- Seventy five percent of the patients with COVID-19 and Acute Ischemic Stroke died or are still severely disabled.
- The COVID-19 pandemic has created a unique opportunity to advance the whole field of neurorehabilitation based on a better biological and scientific underpinning of precision neurorehabilitation protocols.

INTRODUCTION

In December 2019, a novel corona virus associated with a series of acute, atypical respiratory diseases was first detected in Wuhan China. Since then the virus, now known as SARS-CoV2 (Severe Acute Respiratory Syndrome coronavirus two), has spread to over 200 countries and is now recognized as a major world pandemic (1). As of May 30th 2020, the mortality rate of COVID-19 was reported with the number of confirmed deaths with recorded cases worldwide. Since the pathogenesis of SARS-CoV2 first began to emerge, numerous other clinical system manifestations have been identified.

Neurological manifestations of SARS-CoV 2 infection were first reported in a series of patients in Wuhan, China by Zhou et al. (2). Acute ischemic stroke (AIS) was diagnosed in 5% of the cases (2). However, a much lower rate of only 0.9% imaging confirmed AIS i.e., 32/3,556 total patients case number with COVID-19 was reported in New York USA (3). Subsequent retrospective reports from Europe have also confirmed AIS as a common neurovascular complications of SARS-CoV2 (4, 5). Interestingly Oxley et al. noted an increased occurrence of younger SARS CoV2 virus-infected patients with no significant traditional risk factors for AIS, presenting with large vessel occlusion (6). Putative mechanisms suggested as inducing AIS in association with SARS CoV2 have included systemic inflammation, inflammatory cytokine storm, hyper-coagulability, and imbalances in the classical and alternative Renin Angiotensin System (RAS) in relation to SARS-CoV-2 spike glycoprotein-ACE2 binding related molecular mechanisms (3, 7–19). The RAS system comprises both a plasma-based RAS regulating cardiovascular system and tissue-based RAS regulating long term changes via a complex hormonal system, endocrine, paracrine, and autocrine in action. Thus, the RAS controls renal, adrenal and cardiovascular systems with important implications on blood pressure control as well as fluid/electrolyte control which are critically important to maintain life being very susceptible to damage by SARS-CoV 2. The inflammatory pathway is core to the various clinical manifestations of SARS-CoV2 infection. Also referred to as the "cytokine storm," it triggers an upsurge of various inflammatory cytokines such as IL-2, IL-7, IL-10 (20, 21), induces a state of lymphocytopenia (22–24) and also activates a spike of acute phase reactants such as CRP and ferritin (25, 26).

Various parameters have been proposed to predict prognosis and outcomes among patients with COVID, including the neutrophil to lymphocyte ratio (NLR) (27–30). A metanalysis of six studies involving 1,141 patients has demonstrated that an elevated NLR is associated with severe disease manifestation (28). The same meta-analysis has also revealed that along with ESR and IL-6, CRP was correlated with increased severity among patients with SARS-CoV2 infection (28). The role of ferritin as a predictor of mortality among confirmed SARS-CoV2, has also been confirmed in another metanalysis of 10 studies involving more than 1,400 subjects (31). Furthermore, elevated D-dimer and hyperfibrinogenemia, which are both biomarkers of inflammation and hypercoagulable state, have also been shown to predict the severity of the said infection (31, 32). Interestingly, similar biomarkers predict outcomes in stroke (33–39). In particular, it is known that patients who show elevated NLR, ferritin, CRP, D-dimer and fibrinogen have a higher risk for stroke and equate to potentially poorer clinical outcomes (33–39).

To date, despite the theoretical association of inflammatory and procoagulable states linking stroke and SARS-CoV2 infection, there is limited published literature on the actual co-occurrence of both. There is also limited information on the biological markers which may be associated with poor neurological outcomes. Thus, this study aims to describe the clinical characteristics of patients with acute ischemic stroke and concomitant SARS-CoV2 infection. By further analysis of available laboratory data, this will look at the trend of inflammatory biomarkers such as NLR, CRP, serum ferritin, fibrinogen and D-dimer and hospital discharge outcomes.

Currently, there is limited information about the clinical characteristics and specific neurorehabilitation issues of AIS patients with SARS-CoV 2 infection (40–43). However, it is expected that the surge in patient numbers, on-going issues with personal protective equipment (PPE) shortages, and associated health care workers anxiety and stress about the potential of getting infected with COVID-19 (and actual infection of health care workers and mandatory self isolation for 14 days even if these members are demonstrating minimum or no symptoms) will create a significant challenge to traditional neurorehabilitation practices and pathways, at least during the pandemic, possibly for a long time to come. Thus, these circumstances argue a strong case for converting the catastrophe [Complex rearrangement of hospital facilities as part of the preparation for the pandemic has also occasioned significant problems and added resource problems for health care systems across the world (44–50) into an opportunity for revamping of rehabilitation protocols]. Currently evidence is emerging for further expansion of telemedicine type paradigms, with incorporation of tablet based remote monitoring technology (Melbourne Rapid Field visual fields, wearable devices and artificial intelligence) suggesting as the way forward in neurorehabilitation of AIS in COVID19 pandemic era, at least for the foreseeable future (43, 51–53).

Thus, this systematic review aims to identify and collate the clinical and laboratory features, acute and long term treatment, and outcomes of all published reports on patients with concomitant diagnosis of confirmed SARS-CoV 2 infection and

acute ischemic stroke and with a special emphasis on clinical and laboratory features.

PURPOSE

The present study was conducted to provide a systematic review of AIS and COVID-19 with respect to definition, prevalence, pathophysiology, clinical characteristics, acute, subacute features, prognostic markers outcomes.

Participants

Information regarding ischemic stroke patients with confirmed SARS-CoV2 infection and radiologically or clinically Confirmed AIS included in published studies from November 2019 to May 30th 2020 using the search strategy detailed below will be considered here.

Types of Studies

All types of studies including qualitative, systematic reviews, meta-analyses, case reports and case series, were included.

Search Methods

Published articles in English and on human subjects that were published from November 2019 until 30th May 2020 were the inclusion criteria for the search. The following search strategy was adopted:

1. In the first step MEDLINE, Cochrane and CINAHL databases were searched, followed by title and abstract search.
2. In the second step, the keywords were used when searching on Ovid MEDLINE, Cochrane, PubMed, CINAHL, and EMBASE databases.
3. In the third step, a manual search was carried out to ensure no study was inadvertently left out.

The keywords used to conduct the search were: Stroke, thrombosis, coronavirus, neurological complication, neurorehabilitation, COVID19, SARS-COV2.

Data Extraction

The Arksey and O'Malley methodological framework was employed in this review (54).

The bibliographies of individual studies were further hand-searched. Articles were screened by two independent investigators.

4. In the fourth step the secondary analysis was carried out as follows.

Clinical and laboratory data of every patient was extracted. Demographics and details of their respective laboratory details were also investigated. In particular, the following routine laboratory values were of interest to the researchers: NLR, CRP, ferritin, fibrinogen, and D-dimer. Individual patient outcomes were also accounted for and classified as good [with modified Rankin Scores (mRS) of 0, 1, 2, and 3 and poor mRS of 4, 5, 6]. Patients with no available laboratory data and outcomes were excluded in the quantitative analysis.

SEARCH RESULTS

Extensive database search yielded 595 citations, and four studies were added by manual searching. A total of 257 duplicates were excluded resulting in 342 citations. These titles and abstracts were further screened yielding 90 final publications of relevance to consideration of stroke and SARS-COV2 infection, during the second screening process. One publication was non-existent despite being cited by multiple authors in their publications. Further evaluation of the full texts of the 89 studies by two independent neurologists (TW and CS) excluded 74 citations with 15 studies. Three further studies were added from hand-held search by TW and CS with 18 publications that were deemed to be included in this systematic review by all authors.

Year and Country of Study

The studies published from 2019 to 2020, Included literature were originated from North America, Europe, and Asia.

Study Population

This study included all patients with SARS-COV2 infection and a concomitant diagnosis of acute ischemic stroke and/or acute/subacute outcomes where available.

An electronic search performed on May 10 to 30th, 2020 using the identified keywords yielded 342 citations after removal of duplicates. This was further assessed at the title and abstract level which resulted in 90 articles. After full assessment of the full text of each, 18 were deemed relevant to the study, in addition to the three articles which were added from hand-held research. **Figure 1** summarizes the search process.

There were 18 articles included in the study consisting of 87 patients from USA, Italy, Turkey, France, Philippines, and United Kingdom. Most of the studies were case reports and case series while three of the included studies were retrospective and prospective cohorts. **Table 1** outlines the characteristics of the individual studies.

Clinical characteristics of patients are described in **Table 2**.

The majority of the patients were within the 50–70 age group while almost one-third of the patients were <50 years old. The most common comorbidity was hypertension followed by diabetes, dyslipidemia and less frequently, atrial fibrillation. Mean hematologic parameters are also described. Neurovascular imaging either with magnetic resonance angiography (MRA) or computer tomographic angiography (CTA) was available for 35 patients, of whom the majority presented with anterior circulation, large vessel occlusion. Treatment regimens were also described for the majority of the patients and among whom a significant number received systemic anticoagulation, intravenous thrombolysis and mechanical thrombectomy. Of the 87 patients described, 72 outcomes are available, with almost 75% resulting in poor neurological outcomes of Modified Rankin score (mRS) 4 and above.

Inflammatory and coagulation markers of individual patients were also analyzed. Neurological outcomes were classified as either good (mRS 3 and below) or poor (mRS 4 and above). Respective inflammatory parameters such as neutrophil to lymphocyte ratio, C-reactive protein and serum ferritin

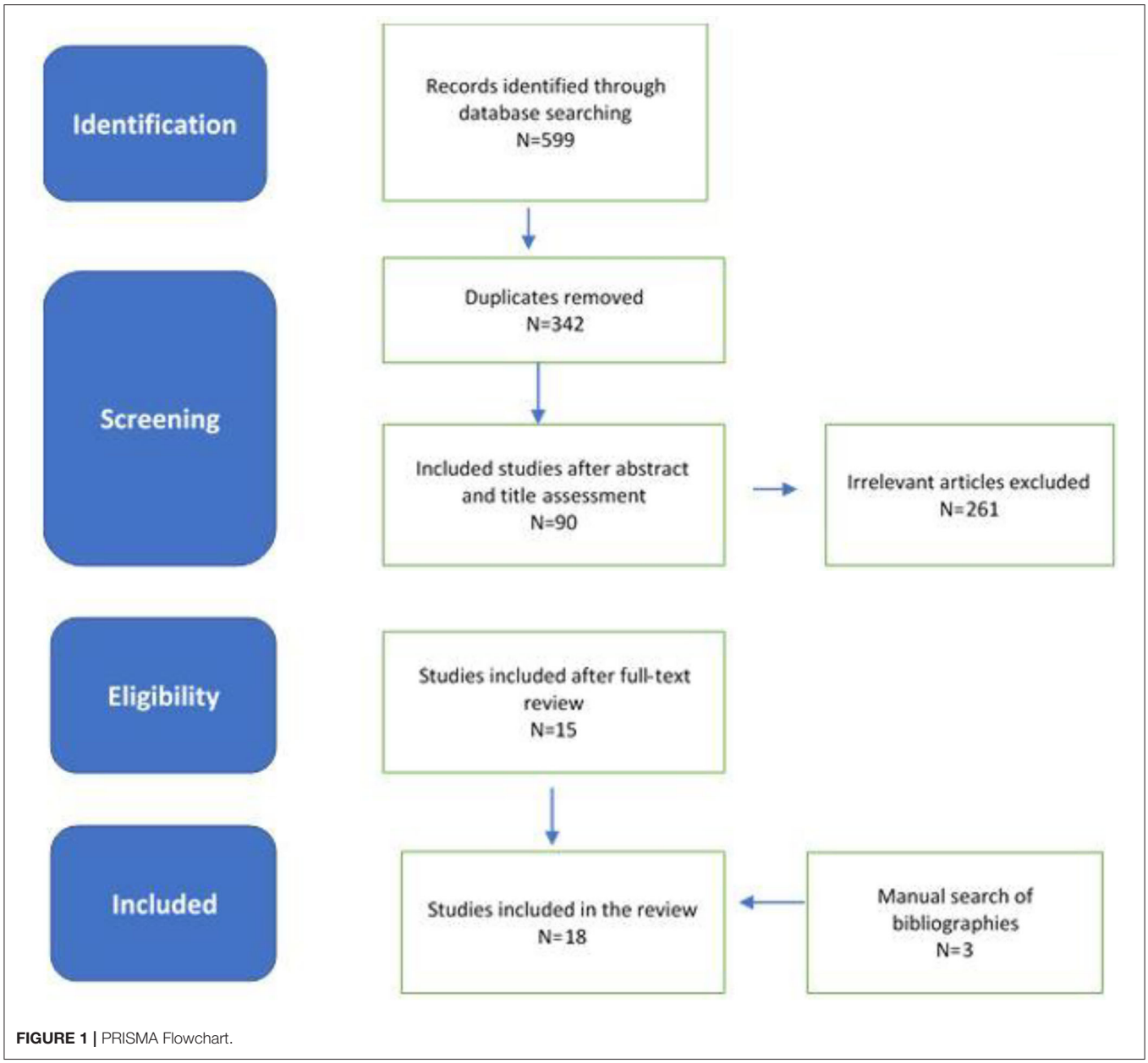


FIGURE 1 | PRISMA Flowchart.

were analyzed for each group. The same was performed for coagulation markers such as D-dimer and fibrinogen. Patients with good neurological outcomes had lower mean NLR, CRP and serum ferritin (4.39 ± 1.44, 53.09 ± 92.70 mg/L, 449 ± 482.3 ug/L, respectively), compared to patients with mRS 4 and above (7.51 ± 5.84, 88.69 ± 70.45 mg/L, 1,086 ± 1,220 ug/L, respectively). Similar trends were observed in terms of coagulation markers, with D-dimer and fibrinogen showing levels of 2,509 ± 4,093 ug/L and 4.70 ± 1.70 g/L, respectively, for patients with mRS 3 and below, while values for patients with poor neurological outcomes were 7,223 ± 6,781 ug/L for D-dimer and 6.086 ± 2.69 g/L for fibrinogen respectively. Summary of the said values are plotted in **Figures 2A–E**.

The relationship between the NLR on admission and the time interval from onset of SARS-CoV2 symptoms to the appearance onset of symptoms of stroke was established. As shown in **Figure 3**, patients who have higher NLR at the onset have a shorter time interval between infective symptoms and the occurrence of the ischemic event.

DISCUSSION

To date, there is no comprehensive review describing the potential role of inflammatory and coagulation biomarkers in determining the clinical outcomes of patients with SARS-CoV2

TABLE 1 | Characteristics of studies included.

Author	Country	Study design	Number of patients with confirmed SARS-CoV2 infection and AIS
Yaghi et al. (3)	USA	Retrospective cohort	32
Lodigiani et al. (4)	Italy	Prospective cohort	8
Berekashvilli et al. (55)	USA	Prospective cohort	10
Wang et al. (38)	USA	Case series	5
Beyroutti et al. (56)	UK	Case series	6
Avula et al. (57)	USA	Case series	4
Tunc et al. (58)	Turkey	Case series	4
Oxley et al. (6)	USA	Case series	5
Morassi et al. (59)	Italy	Case series	4
Viguier et al. (60)	France	Case report	1
Co et al. (61)	Philippines	Case report	1
Deliwala et al. (62)	USA	Case report	1
Al Saiegh et al. (63)	India	Case report	1
González-Pinto et al. (64)	Spain	Case report	1
Gunasekaran et al. (65)	USA	Case report	1
Valderrama et al. (66)	USA	Case report	1
Moshayedi et al. (67)	United Kingdom	Case report	1
Goldberg et al. (68)	USA	Case report	1

infection and concomitant acute ischemic stroke. The data presented will also supplement currently limited information on the occurrence of neurovascular events among patients with SARS-CoV2 infection.

To date a number of theoretical models have been proposed to account for the occurrence of neurovascular events among SARS-CoV2 patients. Most build on the idea of the SARS-CoV2 virus infection inducing inflammation and associated immunological release of cytokines from blood and endothelial cells and the concurrent activation of platelets resulting in micro thrombosis (69). The depletion of the cardioprotective and neuroprotective ACE-2 receptors throughout the body and on microglia in the brain, as a result of the receptors being the preferential cellular target of the virus invasion, has also been proposed as another neuropathologic mechanism irrespective of age (8). However, the hypercoagulable state of SARS-COV2 infection as the sole basis of this mechanism is debateable given that vascular workups for cryptogenic stroke have not been detailed in most of the case studies. Furthermore, the increase in "burden of disease" especially in the elderly is likely to be further exacerbated by the expected age-related depletion in ACE-2 receptors resulting in the predominance of the end-organ damaging effects of increasing the ACE-1/Angiotensin II ratio (70–72).

To date, the majority of AIS lesion sites in the patients described in the literature, are related to large vessel occlusion. However, it remains unclear whether this is due to a mechanism related to thrombosis or embolism or the lack of brain imaging. Unfortunately, there are no studies to date, which fully report autopsy findings of the deaths recorded among the stroke patients with SARS-CoV infection. In a different, though recent, study describing the autopsy results of 12 SARS-CoV2 patients in a German center, the majority of cases showed massive venous thromboembolism with no arterial thrombosis being reported (73). Mechanisms which may contribute to intracranial arterial thrombosis include the cytokine-induced initiation of thrombin formation that triggers the activation of platelets that subsequently result in the development of micro and macrothrombi (74–87). This is worsened by the free conversion of fibrinogen to fibrin and inflammation-induced depletion of physiological anticoagulants such as antithrombin III, tissue factor pathway inhibitor, and the protein C system (74–88). In terms of treatment, while 30 cases were reported to have large vessel occlusion, only 20 mechanical thrombectomies were performed. A comprehensive stroke center in Barcelona, Spain reported an 18 and 23% drop in the number of strokes codes and mechanical thrombectomies during the start of the pandemic, respectively, albeit without any changes in reperfusion and clinical outcomes (89) The World Stroke Organization recognizes the said difficulties and emphasizes the utility of telemedicine as well as best practice sharing to further optimize and streamline stroke processes (90, 91).

While not depictive of the true epidemiologic picture, it is clear that patients with AIS and SARS-CoV2 infection have poor neurologic outcomes of either death or severe disability. Aggarwal et al. (92) concluded in a point analysis of four studies that patients with a previous history of stroke have a 2.5-fold increase in the odds of severe COVID infection but did not show any significant association with mortality (92). A retrospective cohort study of ischemic stroke reports a mortality rate close to 50% (3) while a prospective study involving 10 AIS patients resulted in four deaths (55) Clearly, more prospective studies involving a larger number of individual patients is necessary to ascertain the true mortality rate in this population.

In this study, there is a trend that patients with good outcomes have lower NLR, CRP, and serum ferritin compared to patients who died or remained critically ill. NLR has been shown to have a good predictive value in assessing patients who are likely to have severe SARS-CoV2 infection (30, 93–96). In particular, it has been proposed that patients who are older and have NLR values of more than 3 are likely to require intensive care (27). Yan et al. also predicted that high NLR values on admission is associated with greater odds of complications related to COVID-infection (97). On the other hand, it is known that high NLR is used as a poor prognosticating factor for patients with cerebral ischemia, intracerebral hemorrhage and post-stroke complications (98–107). The dual consequence of COVID-related lymphopenia along with migration of the neutrophils to the ischemic tissue may contribute to the significant increase in the NLR levels in patients with stroke and concomitant SARS-CoV2 infection (107).

Another hyperinflammatory biomarker which has been shown to stratify outcomes in patients with SARS-CoV2

TABLE 2 | Clinical characteristics of patients described.

Age (years) ($N = 87$)	>70	29 (33%)
	50–70	38 (43%)
	<50	21 (24%)
Comorbidities ($N = 87$)	Hypertension	46 (53%)
	Diabetes	32 (37%)
	Dyslipidemia	21 (24%)
	Atrial Fibrillation	8 (9%)
Time from SARS-CoV2 symptoms to onset of stroke (days) $N = 60$	> 14	19 (31%)
	7–14	17 (28%)
	<7	24 (40%)
Laboratories	Mean hemoglobin (g/L)	129 (94–155)
	Mean white cell count (/mm^3)	10.23 (0.5–23.05)
	Mean platelet count (/mm^3)	269.41 (135–408)
	Neutrophil to lymphocyte ratio (NLR)	6.99 (0.91–17.4)
	Mean creatinine (umol/L)	129.81 (55–537)
	Mean fibrinogen (g/L)	5.52 (1–9.7)
	Mean D-dimer (ug/L)	9,800.47 (52–000)
	Mean INR	1.48 (0.99–3.6)
	Mean APTT (s)	31.66 (24–42.7)
	CRP (mg/L)	131.817742 (4–366)
Neuroimaging $N = 35$	Any stenosis	5 (13%)
	Middle cerebral artery occlusion	15 (43%)
	ICA/CCA occlusion	8 (23%)
	Anterior cerebral artery occlusion	1 (3%)
	Tandem occlusion	2 (6%)
	Posterior cerebral artery occlusion	2 (6%)
	Basilar artery occlusion	1 (3%)
	Posterior inferior cerebellar artery occlusion	1 (3%)
Treatment $N = 69$	Alteplase only	4 (6%)
	Thrombectomy	3 (4%)
	Alteplase and thrombectomy	8 (12%)
	Alteplase and thrombectomy and antiplatelet/anticoagulation	5 (7%)
	Thrombectomy and antiplatelet	4 (6%)
	Anticoagulation only	32 (46%)
	Antiplatelet only	8 (12%)
	Anticoagulation and antiplatelet	5 (7%)
Outcomes $N = 72$	MRS 3 and below	17 (24%
	MRS 4 and above	55 (76%)

infection is CRP. Aside from predicting severity and mortality, it has prognosticating value in determining which patients will eventually require mechanical ventilation (108–110). Published literature noted that elevated CRP is associated with poor outcomes in patients with neurovascular conditions (111, 112). There is also evidence to suggest that CRP is not just a "marker" but a "maker" of the atherogenesis (110). It has been demonstrated in experimental studies that exogenous CRP promotes atherogenesis by promoting the expression of adhesion molecules and cell mediators along with the decrease of arterial vasodilators (113–115). A meta-analysis of nine studies also provides evidence on the dose-dependent relationship of CRP and increased risk of venous thromboembolism (112). Whether the elevation of CRP is the causative etiology or the sequelae of a multifactorial process linking SARS-CoV2-infection to inflammation, atherogenesis or embolism needs further exploration.

Hyperferritinemia, which implies a heightened state of immunologic reactivity has also been associated with increased mortality in recent publications related to the SARS-CoV2 infection (116). It signals the activation of the macrophages and the reticuloendothelial system resulting in end-organ damage (117). Patients with SARS-CoV2 treated for pneumonia with Toculizumab had a marked decrease in the inflammatory markers such as CRP and ferritin, along with significant clinical improvement post-infusion (118). In patients with acute stroke, this iron storage protein can potentially worsen the iron-dependent oxidative stress in the ischemic penumbra which can

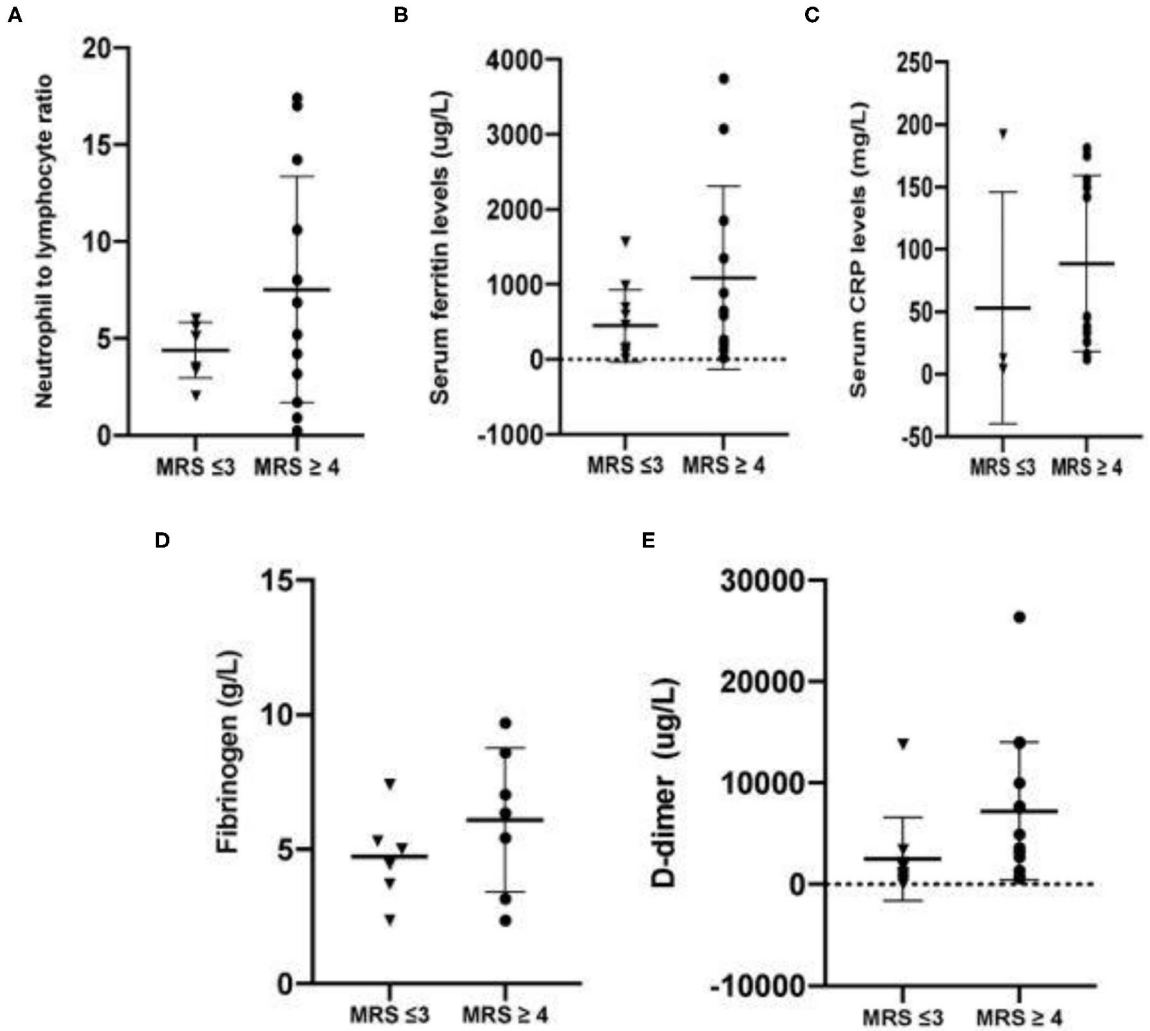


FIGURE 2 | (A–C) Mean inflammatory markers among patients with stroke and confirmed SARA-CoV2 infections. **(D–E)** Mean coagulation markers among patients with stroke and confirmed SARS-CoV2 infection.

lead to further neurologic decline (119). This is further validated in a study which shows a direct correlation between serum ferritin and markers of neural and blood-brain barrier disruption such as glutamate, interleukin-6, matrix metalloproteinase-9 and cellular fibronectin among patients receiving thrombolysis (39). The complementary inflammatory sequelae of SARS-CoV2 infection and ischemic stroke is the likely culprit of hyperferritinemia in SARS-CoV2 related strokes.

SARS-CoV2-related coagulopathy is responsible for various thrombotic events linked to mortality. Described as a fibrinolytic "shut-down," SARS-CoV2 infection promotes a pro and hypercoagulable states resulting in disseminated (intravascular coagulation (DIC), microthrombi and other venous and arterial thrombotic phenomena (4, 120–122). D-dimer and fibrinogen are both recognized as important biomarkers of the severity of coagulopathy in patients with SARS-CoV 2 infection (123, 124). Olive et al. in a retrospective analysis of 21 patients with SARS-CoV infection concludes that D-dimer was associated with increased risk of pulmonary embolism (125). A similar observation was made in a larger study that suggests that D-dimer levels above 1 μg/mL may help in stratifying patients with poor prognosis at the onset (26). Fibrinogen increase was also observed among patients with severe SARS-CoV2 related pneumonia compared to mild presentation (126). The disproportionate increase of these biomarkers, especially at the early stages, warrant screening of thromboembolic events and initiation of thromboprophylaxis (124). The trend in these coagulation biomarkers are similarly observed in non-COVID related strokes. In the ARISTOTLE trial, patients with AF and increased D-dimer values had higher incidence of stroke, systemic embolism and all-cause mortality (127). Choi and colleagues also propose that D-dimer can be used as a biomarker for recurrence among patients with previous AF and non-AF related strokes (128). The EUROSTROKE study likewise

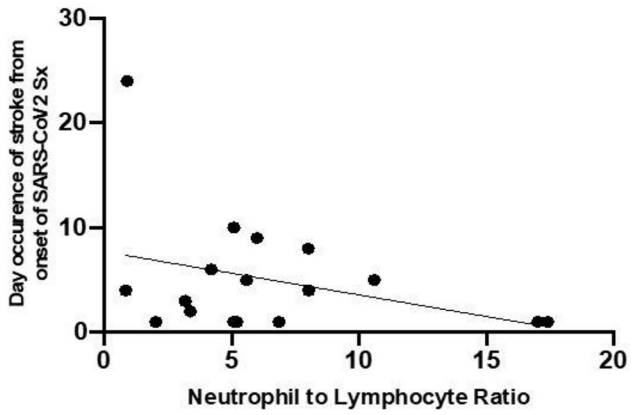


FIGURE 3 | Relationship between NLR and the occurrence of stroke from onset of SARS-CoV2 symptoms.

confirms the utility of fibrinogen in predicting patients who are at risk for stroke (36). The said risk is equated to various clinical risks such as smoking, DM, MI, and HDL cholesterol (36). In this study, we have provided a scaffold on the potential trend between outcomes and coagulation parameters for SARS-CoV2 related strokes. While the most accepted mechanism behind this phenomenon is sepsis-induced disruption of the coagulation system, Iba et al. propose that more complex procoagulant responses resulting in a distinct interaction between the host's immunologic and the coagulation systems (124).

This study also highlights the occurrence of the ischemic event days to weeks after the onset of SARS-CoV2 symptoms. More importantly, we have established an inverse relationship between the inflammatory biomarker, NLR on admission and the duration between the stroke and the onset of SARS-CoV2 symptoms. This is likely related to the inflammatory burden which triggers a pro-coagulable cascade. Furthermore, Amiral et al. relate this to the alloimmune hypothesis, which has been demonstrated in rodents (129). The development of auto-antibodies to other ACE-2 receptors such as on the microglia in the brain after the onset of viral infection presumably resulted in the exponential increase in the cytokine storm and significant tissue destruction which may be linked to the delayed onset of the vascular event after the viral prodrome (129).

Lastly as the COVID-19 pandemic is distressing national health systems worldwide, a tsunami wave of neurorehabilitation needs and challenges regarding the long-term effects of the pandemic must be expected to begin to unfold soon. Thus, we believe that with strong humanity and collaboration across disciplines, this is the time to convert this situation into an opportunity that with vision, creativity, innovation, and use of smart technology can be harnessed with the aim of surviving this global health crisis (43, 130).

CONCLUSION

Stroke is an important neurovascular complication of SARS-CoV2 infection. The aetiopathogenesis of cerebral ischemia is related to the overactivation of immune and hypercoagulable mechanisms. This is supported by the disproportionate increase of biomarkers such as NLR, CRP, serum ferritin, D-dimer and fibrinogen among patients who died or were critically ill. An elevated NLR on admission also implies an increased burden of inflammation at the onset of SARS-CoV infection which may result in early manifestation of cerebral ischemic events.

AUTHOR CONTRIBUTIONS

TW and LK conceived of the presented idea. TW, SC, and LK developed the theory. TW and CS performed the literature search. TW wrote the manuscript with support from CS, LK, and SC. All four authors 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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An Italian Neurorehabilitation Hospital Facing the SARS-CoV-2 Pandemic: Data From 1207 Patients and Workers

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Objective: The aim of the present observational study is to report on the data from a large sample of inpatients, clinical staff and other workers at an Italian neurorehabilitation hospital dealing with SARS-CoV-2 infections, in order to analyze how it might have affected the management and the effectiveness of neurorehabilitation.

Methods: The data on infection monitoring, obtained by 2,192 swabs, were reported and compared among 253 patients, 722 clinical professionals and 232 other hospital workers. The number of admissions and neurorehabilitation sessions performed in the period from March-May 2020 was compared with those of the same period in 2019.

Results: Four patients and three clinical professionals were positive for COVID-19 infection. Six out of these seven people were from the same ward. Several measures were taken to handle the infection, putting in place many restrictions, with a significant reduction in new admissions to the hospital ($p < 0.001$). However, neither the amount of neurorehabilitation for inpatients ($p = 0.681$) nor the effectiveness of treatments ($p = 0.464$) were reduced when compared to the data from 2019.

Conclusions: Our data show that the number of infections was contained in our hospital, probably thanks to the protocols adopted for reducing contagion and the environmental features of our wards. This allowed inpatients to continue to safely spend more than 3 hours per day in neurorehabilitation, effectively improving their independence in the activities of daily living.

Keywords: coronavirus, COVID-19, rehabilitation, molecular test, swab, SARS-CoV-2, hospital design and construction

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INTRODUCTION

The World Health Organization (WHO) characterized the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak as a pandemic on March 11th 2020 (1). In response to this, many governments implemented a series of emergency containment measures, including social restrictions and the quarantine of positive and suspect cases. Italy was the first Western country with a wide diffusion of coronavirus disease (COVID-19), so it could be important for other countries to analyze in depth the Italian case-study (2). In April, Iosa and coworkers suggested

a dynamic analysis of the Italian case-fatality ratio to gain deeper insight into the course of the COVID-19 pandemic, and we anticipated the need to prepare rehabilitation units. Both people with COVID-19 sequelae related to motor and respiratory functions and patients with neurological disorders (3), not infected but needing neurorehabilitation in the time of this pandemic, could not wait to be treated (4–6). Several measures, including those imposed by the Decrees of the Italian President of the Council of Ministers, were taken to tackle the infection in rehabilitation hospitals with the aim of monitoring the insurgence of epidemic outbreaks (4). As nosocomial transmission is a severe problem in relation to the condition of inpatients, any action should be taken to minimize the risk of transmission among patients and clinical staff (7). However, an analysis of the impact of these measures is lacking in the literature. A recent study analyzed the outcomes of outpatients with pre-existing neurological disorders reporting the prevalence of symptoms of COVID-19 infection (8). The authors found that the presence of neurological chronic diseases did not increase the prevalence of COVID-19 infection, but the burden of neurological disorders was worsened by the lockdown. These problems could be even more dramatic for inpatients. Indeed, hospital access to people with neurological impairments due to brain or spinal cord injury in the subacute phase was often postponed as a consequence of infection. However, the neurorehabilitation of these patients is time-dependent and cannot be delayed, nor can it be reduced in intensity (9, 10). Furthermore, in Italy, there was an increased pressure on high specialty neurorehabilitation wards to admit patients with severe neurological disabilities (sometimes even with unstable vital functions and a high risk of medical complications) due to the sudden need for intensive care units to free up beds for COVID-19 positive patients with respiratory insufficiency. Other countries are now facing the same problem. In this scenario, there is a need for a quantitative analysis of the impact of the adopted restriction measures on inpatients needing neurorehabilitation, especially in hospitals exposed to the risk of COVID-19 infection.

The aim of the present observational study is to report on the data regarding COVID-19 infection monitoring in a large sample of inpatients needing neurorehabilitation, clinical staff and other hospital workers, analyzing how it might have affected the management and the efficacy of neurorehabilitation.

MATERIALS AND METHODS

This was an observational study performed on data collected during the monitoring of hospitalized inpatients and people working in our hospital from April 30th to May 26th 2020. People were classified into three categories: inpatients, clinical staff (medical doctors, psychologists, nurses, therapists, health care assistants, etc.) and other hospital workers (administrative staff, cleaners, etc.). They underwent repetitive series of swabs related to the program monitoring at out hospital during the COVID-19 pandemic.

Protocols

During the SARS-CoV-2 pandemic, the Italian Society of Neurological Rehabilitation indications were followed for the reorganization of neuro-rehabilitation activities (4). Moreover, we also changed our protocols in the following aspects:

- Our neurorehabilitation units admitted patients with subacute neurological impairments due to severe acquired brain lesions or stroke coming from an acute unit only if they were not affected or suspected to be infected with COVID-19 (with two negative nasal swabs performed within the last 48 h before discharge from acute wards).
- Our hospital is formed by six identical wards for inpatients, with 26 bedrooms having only two beds each (each room was 46 square meters with a bathroom inside), according to the requirements defined by Italian law, plus one room with negative pressure, and the availability of a gym in each ward (as shown in **Figure 1**). We planned three different pathways for human traffic within each ward: one for entering, one for exit, and one specific for isolated patient with different elevators just used for them, as shown in **Figure 1**. This figure also shows that each ward has a gym in which there were two rooms for speech therapy. The detail of one bed-room and of the isolation room with negative pressure were also shown in that figure.
- Healthy people, such as workers and allowed visitors, could enter into the hospital only if their body temperature was lower than 37.5°C (if higher, home isolation was suggested). Employees commute from home, no specific restrictions to social activities were required by the hospital direction, but they were required to strictly follow the restrictions of the lockdown programmed by Italian government for all the citizens (for example, in the study period, in Italy most of the shops were closed, restaurants were closed, religious meetings were forbidden).
- Posters with behavioral/health general rules (such as about social distancing in rooms, maximum number of people allowed into elevators at the same time, hand hygiene recommendations, use of protective devices, and so on) were positioned at each entrance and within all the complex operative units and the number of hand-sanitizing gel dispensers in the whole hospital was increased.
- A specific guideline has been drawn up describing prevention and control measures during the management of suspected and confirmed cases of COVID-19 in our facility, and several training sessions have been held with the health care professionals for the correct use of SARS-CoV-2 personal protective equipment (PPE) such as surgical masks, whereas suspected cases were cared by clinical staff using medical cap, eye-visor, face shield, N95 respiratory mask, double disposable gloves, medical protecting coverall, leg cover waterproof boots.
- Reorganization of work shifts (medical and non-medical staff) with a reduction in some activities in order to reduce contact and movements (for example, encouraging staff to work from home for administrative activities).
- After the first case of a positive swab in our hospital (April 30th), neither new admissions (up to May 21st) nor visitors

(for the entire month of May and the first weeks of June, with only a few exceptions for caregivers staying in the same room of patients needing continuous assistance after two consecutive negative swabs) were allowed. An extraordinary plan for daily cleaning and sanitization of the wards was putted in action.
- Outpatient activities and/or day hospital rehabilitation were reduced (only activities that cannot be postponed according to regional guidelines were maintained in different areas and different clinical staff from those of inpatients to avoid contacts between these two populations).
- Strengthening of patient and caregiver support networks, also through information technologies and an emphasis on the role of tele-rehabilitation.
- Seven sessions of swab analyses for monitoring patients and workers were carried out from the end of April to the end of May.

Epidemiological Analysis

From 30th April, we started an epidemiological analysis on the inpatients and employers of our hospital with the main aim to identify asymptomatic subjects. The whole sample was formed of 1,207 people: 253 inpatients, 722 clinical professionals and 232 other hospital workers. Among the patients, 153 were affected by stroke, 54 by traumatic brain injury, 31 by spinal cord injury, 9 by multiple sclerosis, 2 by Parkinson's disease, and 4 by orthopedic problems. Our hospital provides six wards for inpatients. Workers and patients were assigned to the same ward for the entire investigation period, in order to limit transfers.

Data Analysis

Data are reported in terms of mean and standard deviation for continuous measures, absolute frequency for counted discrete measures, median and interquartile range (IQR = third–first quartiles) for ordinal measures of clinical scales and not normally distributed variables. Odds ratios were computed together with relevant 95% confidence intervals (95% CI) and inferred by the chi-squared test. Paired *t*-tests were performed to compare the data related to March, April and May 2020 and 2019 in terms of time spent in neurorehabilitation activities. Mann–Whitney *U*-tests were performed for comparing the Barthel Index (BI) score at admission and discharge, effectiveness and length of stay in the period from March to May 2020 vs. the same period in 2019. The effectiveness was computed as the percentage improvement obtained in terms of the BI-score with respect to the maximum achievable one. The level of statistical significance was set at 5%.

RESULTS

Epidemiological Data of Swab Analysis

During the study period, the statistics of the outbreak in Italy reported 104,664 new contagions in March, 99,671 in April, and 27,534 in May. In Lazio (the Italian region of our hospital and in which resided our employees) the number of contagions were 3,092 in March, 3,521 in April and 1,112 in May, on a population of about 5.9 million of people (11).

In our hospital, a total of 2,192 nasal swabs were performed in <1 month: 13 swabs on April 30th finding one nurse positive; 62 swabs on May 2nd finding another nurse and two stroke patients positive (these patients came from the same ward as the first positive case); 1,093 swabs on May 4th and 5th with positive findings in other two stroke patients (from the same ward) and one therapist (from another ward); no more positive cases were found in the subsequent analysis of 31 swabs on May 7th, 151 swabs between 11th and 12th, 738 between 18th and 19th, 104 swabs on 26th May. All seven positive cases (corresponding to a prevalence of 0.6%) were asymptomatic. Familiars were advised. According to the regional guidelines, positive patients were immediately isolated in the special room with negative pressure and transferred within 6 h to a regional dedicated Covid-hospital (during this short time, the patients did not receive any rehabilitation session). After the recovery in that hospital and the following negativization of two consecutive swabs, two out of the four patients were discharged at home and the other two were re-admitted to our hospital to continue the neurorehabilitation. The cases of positive employers were notified to the competent authorities, and these subjects were quarantined at home for 14 days in charge to family physician, and they were allowed to return to work after 2 negative nasal swabs performed within the last 48 h.

The cumulative data are reported in **Table 1**. The odds ratio of being infected by SARS-CoV2 was not statistically different between patients and clinical staff, although it was close to the significance threshold (OR = 3.85; 95% CI: 0.86–17.3; $p = 0.0588$). Conversely, an odds ratio of 64.8 (95% CI: 7.7–545; $p < 0.001$) was found in favor of being hospitalized or working in the same ward. For a comparison with the data of the outbreak during the study period, in Italy there were 104,664 new contagions in March, 99,671 in April and 27,534 in May. In Lazio (the Italian region of our hospital and in which resided our employees) the number of contagions were 3,092 in March, 3,521 in April and 1,112 in May.

Number of Treated Patients

The admission of patients to the hospital was stopped immediately after the first positive swab. This measure implies a reduction in inpatients, as shown in **Figure 2**. During the period from March to May 2020, 89 patients were admitted (median BI-score = 12, IQR = 26). In the same period of 2019 the number of admissions were 180; however, the median BI-score was not significantly different (BI-score = 13, IQR = 30, $p = 0.468$).

The hospital bed occupancy was significantly different in the entire period from March to May 2020 with respect to the same period in 2019 ($p < 0.001$), especially after the first positive case, when the temporary halt to new admissions occurred, as shown in **Figure 2**. The rehabilitation of outpatients (day hospital) was even more significantly decreased: it was 36% of planned occupancy in March, 3.8% in April and 8.6% in May, whereas the matching percentages in 2019 were 106, 102.1, and 103.6%, respectively ($p = 0.010$).

From an economic point of view, the amount of loss of income related to the reduction of Day Hospital was 64% in March, 96% in April, and 92% in May; whereas that of inpatients was 5, 6,

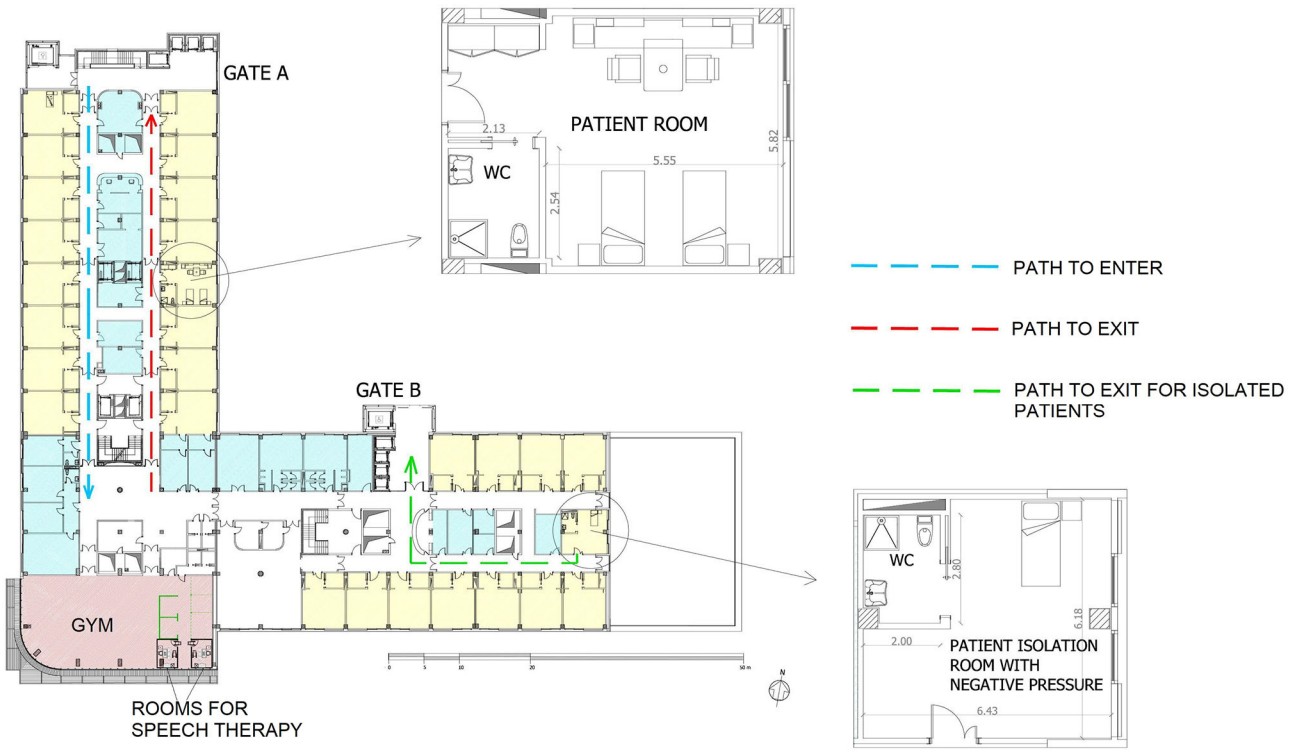


FIGURE 1 | The planimetry of one of the six identical wards of our hospital. In details are also shown the planimetry of one of the twenty-seven standard patient's rooms of the ward (in yellow) and the special isolation room with negative pressure. In blue the rooms of doctors and in pink the gym. Stairs and elevators are located in proximity to each gate. The dotted rows show the pathway defined for human traffic during the analyzed period: the blue pathway is that for entering into the ward, the red one for exit from the ward, and the green one that related to a patient isolated in the special room. All the measures are expressed in meters.

TABLE 1 | Data on subjects classified as patients, clinical staff or other hospital workers.

Categories of people	Age (years old)	Sample *N*	Gender (female %)	Number of tests	Positive swab
Patients	66.3 ± 16.2	253	35%	560	4
Clinical staff	44.0 ± 11.8	722	64%	1,361	3
Other workers	47.6 ± 12.4	232	59%	271	0
Total	50.7 ± 16.4	1207	57%	2,192	7

15%, respectively. The loss related to other outpatient hospital services were 73, 81, and 61%, respectively.

Number of Treatments and Their Effectiveness in Inpatients

The mean time spent by each patient in neurorehabilitation activities was not reduced in the period from March to May 2020 (global mean: 213 ± 15 min) with respect to the same period in 2019 (211 ± 10 min, $p = 0.558$), nor in the period after the first positive cases with the temporary halt to new admissions (211 ± 11 vs. 215 ± 10 min, $p = 0.681$). The number of patients discharged in the period from March to May 2020 was 71; their median BI-score was 69 (IQR = 50) with a treatment effectiveness of 48 ± 40% and a median length of stay of 49 days (IQR = 42). In the same period in 2019, the number of discharged patients was much higher at 233, with a median BI-score of 54 (IQR = 67, $p = 0.049$), an effectiveness of 47 ± 36% ($p = 0.464$) and a median length of stay of 63 days (IQR = 52, $p = 0.001$), as shown in **Figure 3**.

DISCUSSION

The aim of the present observational study was to report on how COVID-19 infections were monitored and contained in a large sample of inpatients and workers, and how infection management might have affected neurorehabilitation activities. Our results highlight three important findings about the management of the COVID-19 outbreak in neurorehabilitation.

First of all, the safety protocol and continuous monitoring performed with nasal swabs allowed us to identify 7 cases in 1,207 screened people. All the positive cases were asymptomatic, and only the planned monitoring allowed us to discover the presence

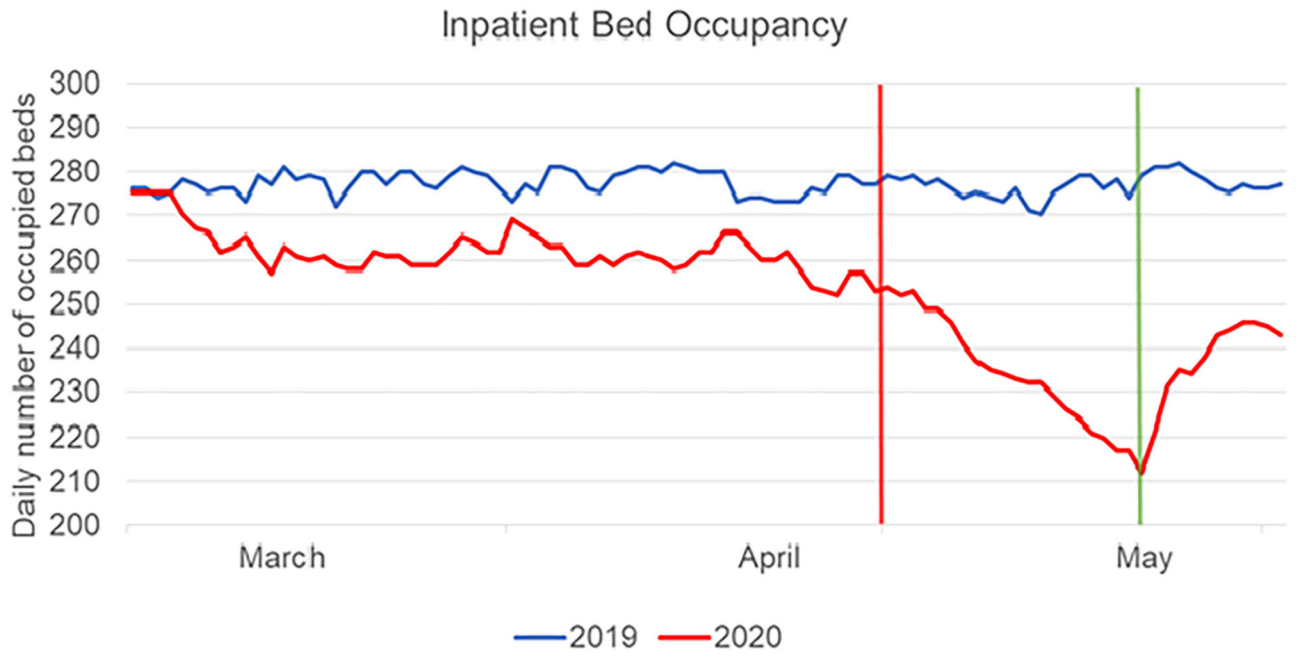


FIGURE 2 | Hospital bed occupancy in 2019 (blue line) and in 2020 (red line) for the period from March to May. The vertical red line represents the day of the first positive case in our hospital, corresponding to the beginning of the temporary halt to new admissions. The green line represents the last day of this period of halted admissions.

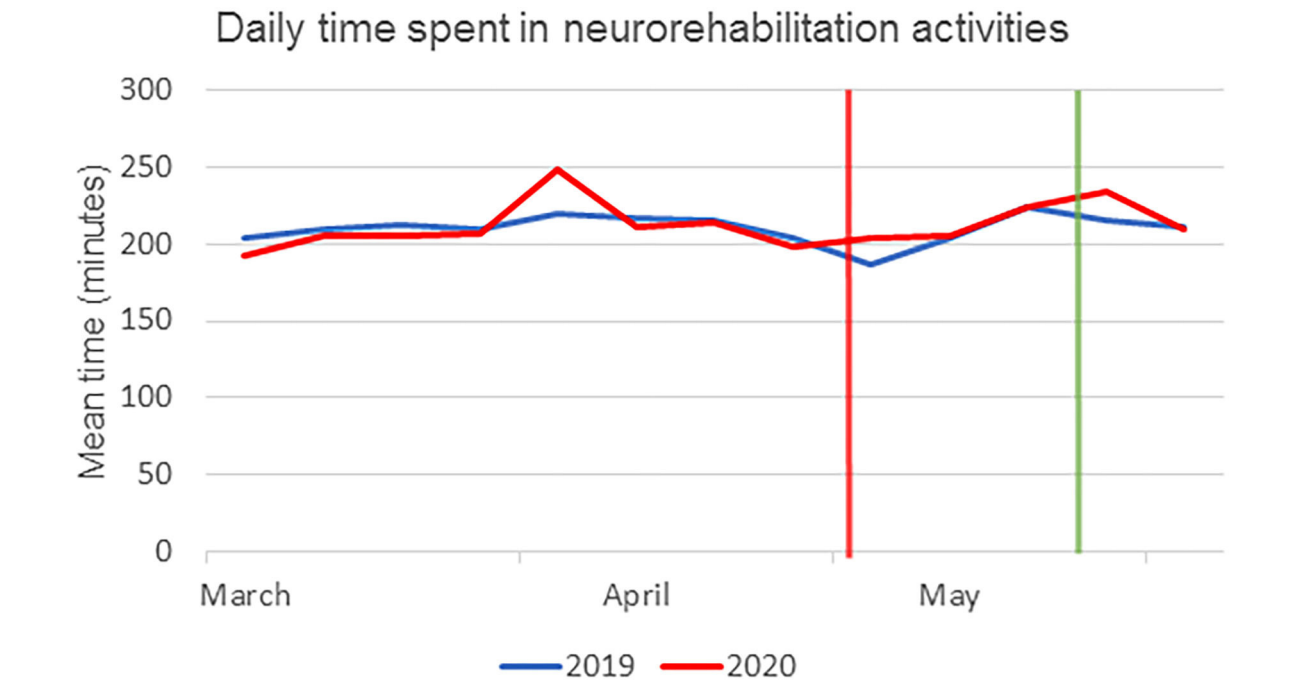


FIGURE 3 | Mean time spent by patients in neurorehabilitation activities (in minutes), averaged by week in 2019 (blue line) and 2020 (red line). The vertical red line represents the day of the first positive case in our hospital, corresponding to the beginning of the temporary halt to new admissions. The green line represents the last day of this period of halted admissions.

of positive cases in the hospital. The prevalence of COVID-19 on the screened population in our hospital (0.6%) was slightly higher than that of the Italian population at 0.2% (11), but this was due to the fact that our sample was related to a hospital population.

The second finding is related to the clusterization of positive cases, with 6 out of 7 coming from the same ward. The odds ratio related to the environmental factor was 64.8 vs. an odds ratio of 3.85 for the category of persons (patients vs. clinical staff). This effect was already well-known and at the basis of social distancing and isolation of infected patients (12). Furthermore, this odds ratio may suggest the need to isolate the different wards of a hospital, reducing possible contacts among patients and/or workers in different wards. The protocols related to internal transfers, inspired by the Decrees of the Italian President of the Council of Ministers together with the scientific literature (4, 10), adopted severe measures and allowed us to counteract the pandemic. Among the adjunctive measures, it is important to mention the requirement of two negative nasal swabs within the last 48 h before discharge from acute wards for being admitted in our hospital, even if this was not required by the World Health Organization guidelines.

Moreover, the prompt interdiction of visitor entry, although this rule enormously overwhelmed nursing staff and neurorehabilitation professionals regarding the management of daily activities and the psychological isolation of inpatients with severe neurological disabilities and common neuropsychological disorders. Another factor that may have contributed to containing the outbreak could be the architectural structure of our wards, with wide bedrooms having only two beds each and the availability of a wide gym in each ward. Before COVID-19, some authors (13) reported that the architecture of hospital facilities does not influence nosocomial infection rates, concluding that there is a lack of stringent evidence to link hospital design and construction with the prevention of nosocomial infection. However, further studies (14–16) support the opposite idea, i.e., that the design of the physical environment influences nosocomial infection rates. The safety protocols, the large rooms and the presence of a gym in each ward, together with the presence of six isolation rooms with negative pressure, could be the key factors that limited the outbreak of SARS-CoV-2 in our hospital.

Finally, the third main finding of our study was that, during the containment of the pandemic in our hospital, the admissions were significantly reduced due to the temporary halt on admissions, but the mean time spent by inpatients in rehabilitation was not reduced by the emergency. It allowed us to provide the same level of treatment effectiveness. Despite many difficulties in discharging patients from our neurorehabilitation hospital due to the problems with managing the chronic phase of neurological diseases, the length of stay was shorter than that in 2019, according to a general process of reduction of length of stay already occurring before pandemic. The main problem was the dramatic reduction in amount of care reserved to outpatients, as also observed elsewhere (8).

Our study has some limits, the main of which is that the present study is an observational study based only on one hospital, without a population-based analysis and with some populations (i.e., stroke patients) that could be overrepresented. However, our study is similar to a previous one analyzing rehabilitation of outpatients, although ours is more focused on inpatients. The presence of COVID-19, its management and the contemporary management of neurorehabilitation makes this study important for other similar hospitals.

In conclusion, the prevalence of COVID-19 infection in our inpatient neurorehabilitation hospital was effectively managed, affecting the number of admissions and the rehabilitation of outpatients, but not that of inpatients, who achieved a good level of independence in the activities of daily living, similar to that of hospitalized patients in the same period in 2019. Six out of seven positive cases of SARS-CoV-2 were recorded in the same ward, and wide screening allowed us to contain the infection by isolating and transferring positive professionals and patients, respectively. These results suggest the need for repetitive and systematic screening of patients and clinical staff in neurorehabilitation hospitals to prevent outbreaks and to maintain a high amount of effective neurorehabilitation for inpatients.

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 Fondazione Santa Lucia ethics committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GM and MI wrote the first draft of this manuscript. MI and SP performed all the data analysis. CC, AS, and AR conceptualized and supervised the study. SP, MG, MT, UN, RF, and MM revised the manuscript and provided important contributions. MB was responsible of all the swab analysis. 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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OPINION
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Neuropsychology in the Times of COVID-19. The Role of the Psychologist in Taking Charge of Patients With Alterations of Cognitive Functions

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Keywords: neuropsychology, COVID-19, healthcare, cognitive impairment, neuropsychological assessment, neurorehabilitation, neuro-COVID

INTRODUCTION: STATE OF THE ART AND THE ROLE OF THE PSYCHOLOGIST

From the very beginning of this severe pandemic, the intervention of psychologists in managing and containing the spreading infection has been essential. Now that, in some respects, the emergency for protection of human lives is receding, another opportunity for psychologists' intervention has emerged: the neuropsychological field.

Recent scientific publications highlight the cognitive sequelae in neuro-COVID syndromes: tropism of this type of virus for central nervous system and prolonged periods of hypoxia due to severe desaturation represent highly significant factors in determining dysfunctional alterations of cognitive functioning. Indeed, it is widely known that protracted hypoxemic episodes cause cognitive impairments. For instance, Hopkins et al. (1) have pointed out that about 50% of patients with acute respiratory distress disorder (ARDS) shows cognitive alterations up to 2 years after the acute event. Consistently, the authors recommend carrying out an assessment of memory and executive functions in order to foster long-term monitoring processes.

Concerning the etiopathogenetic nature of COVID-19, the virus' distinctive features favor its access up to the blood–brain barrier via retrograde axonal transport along cranial nerves—in particular, the olfactory nerve, which explains one of the most frequently reported symptoms. The alteration of the blood–brain barrier determines the onset of neurological conditions known as necrotizing acute encephalopathies (2–4). Moreover, patterns of brain lesions have been documented, with hemorrhagic effusions at well-defined hemorrhagic rims around the thalamus, in subregions of the medial temporal lobes, and in subinsular regions (4).

Clinical features of COVID-19 are to be considered according to the severity of their manifestation: the clinical picture is defined as *mild* or *asymptomatic* when the disease occurs in the absence of dyspnea or desaturation; *moderate* when the O_2 saturation is between 94 and 98% and there are signs of pneumonia on radiological examination; *severe* in case of O_2 saturation below 93%, increased of respiratory rate, interstitial pneumonia, and need to add O_2 to the natural respiratory process; and *critical* when, in addition, mechanical ventilation is required.

Generally, patients with mild COVID-19 symptomatology recover with no need of specific interventions, whereas in moderate, severe, and critical forms, several systems, first and foremost the CNS, suffer from implications of the infection. Persistent desaturation levels are associated with worsening dyspnea, which, in turn, has serious repercussions on brain metabolism (5). In their work, Carda et al. (5) also report the clinical experience with a sample of Italian COVID-19 patients, which have presented cognitive alterations such as memory disorders, deficits of executive functions and, among older subjects with severe forms, confusion [see also (6, 7)]. These impairments are due to the effect of the viral infection on the central nervous system, as previously mentioned, and to long periods of hypoxygenation and brain injuries, as clearly reported by Girardini et al. (8). Likewise, Li et al. (9) report, in a study conducted on a sample of 211 patients, that patients with severe infection develop cerebrovascular impairment syndromes. In a systematic review, it was confirmed that one out of four patients with ARDS consequent to COVID-19 infection develops neuropsychological symptoms as a manifestation of CNS involvement (10). Hence, it is strongly recommended that early identification and care of cognitive deficits should be performed. Neurological deficits involve, among others, severe changes in the state of consciousness and consequent alterations of cognitive functions (7).

What has been so far highlighted by scientific evidence seems sufficiently convincing to demonstrate that this type of lung disease can remarkably affect the CNS and that cognitive, emotional, and behavioral functions may be severely compromised (11, 12). Indeed, behavioral alterations compatible with delirium and loss of control have also been found as a consequence of hypoxemia and cerebral lesions. On the other hand, thymic alterations, such as dysphoria and mood tone deflection, are frequently associated with isolation and sudden loss of meaningful social contacts with significant family members. **Figure 1** reports main neuropsychological and neuropsychiatric symptoms in COVID-19 patients.

PROPOSAL FOR THE CURRENT SITUATION: NEUROPSYCHOLOGICAL ASSESSMENT

Field experience shared by colleagues working in these areas points out that, in these days, neuropsychologists are facing a constantly increasing number of requests for assessment and care of patients showing cognitive outcomes as a result of the new coronavirus infection.

It is reasonable to think that when all concerns about the potential risk for transmission of the contagion and isolation have ceased and people are to resume their usual working activities, the invalidating cognitive consequences will emerge with strength and the demand for neuropsychological intervention will further increase.

In our opinion, it is necessary to boost neuropsychological services and, consequently, the number of psychologists serving in the neuropsychology field, in order to cope with the increase in demand. Effective measures to be taken with this kind of patients involve—in addition to the dissemination of information concerning the high risk of cognitive repercussions—neuropsychological assessment, rehabilitation treatment, and the role of the psychologist/neuropsychologist in managing cognitive issues. **Table 1** summarizes recommendations for neuropsychologists' practice.

Neuropsychological assessment, which cannot be considered as the mere administration of psychometric tests, provides a profile of residual abilities, emerging difficulties, and potential trend of cognitive decline, just as it occurs for other neurological diseases. The assessment procedures, then, provide relevant information to outline opportunities for intervention. The

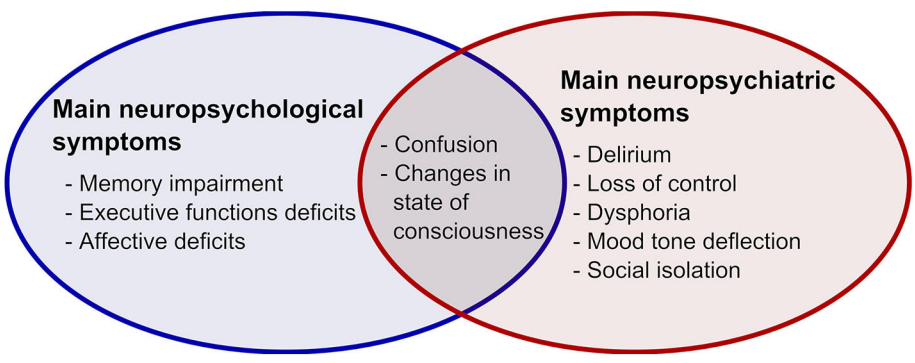


FIGURE 1 | Main neuropsychological and neuropsychiatric symptoms in COVID-19 patients.

TABLE 1 | Summary of recommendation for neuropsychologists.

Assessment process	Online neuropsychological assessment vs. in presentia assessment	Benefit	Limitations	Recommendations
		- Simpler test administration when online - Observance of safety norms even in critical conditions	- Impossibility of making adequate clinical and qualitative observations of emotional–cognitive–behavioral alterations - Limitation in socio-relational factors	- A vis-à-vis approach is recommendable, unless urgent conditions imply that the evaluation cannot be postponed
	Tests administration	Measures	Test administration condition	Recommendations
		- Global functionality, cognitive flexibility, problem-solving skills, working memory, and praxis abilities, as well as mnesic, learning, and attention skills - Assessment of patient's residual abilities - Detection and quantification of possible affective alteration	- Compatibility with patient's clinical conditions - Retention of minimal attention levels	- Be sure that COVID-related clinical condition (i.e., SARS, neurological and motor deficits) is emended - Adequate psychometric properties of selected tests
Rehabilitative intervention	Online neuropsychological intervention and in presentia rehabilitation: features	In presentia rehabilitation	Online intervention	Recommendations
		- Calibrating the commitment required from the patient for an effective rehabilitation - Support deficit recovery or maintenance over time	- Planning of teletherapy intervention - Remote administration of exercises - Modulation of gradients of difficulty based on the actual level of impairment - Constant monitoring by the neuropsychological expert	- Both solutions are strongly recommended, especially with effective and planned exercises aimed at functional cognitive recovery - Choose between online and in presentia rehabilitation based on both sanitary global condition (quarantine, lockdown, etc.) and patient's/caregiver's needs and resources

psychologist is called to take part into this clinical decision-making process based on specific neuropsychological expertise and competence. In the backdrop of this epidemic, the possibility to carry out an online neuropsychological assessment, by using telematic administration of tests, has also been brought to attention.

In a special note sent to the National Council of the Order of Psychologists on May 8, 2020 (13), we had the chance to express our opinions and some recommendation concerning remote neuropsychological assessment by referring to the scientific literature and by following the Guidelines of the American Psychological Association. Online assessment exhibits a number of limitations in the process of evaluating cognitive functions. In particular, remote procedures miss crucial steps because of the impossibility of making adequate qualitative clinical observations concerning patients' affective–cognitive–behavioral skills, as well as specific socio-relational dimensions. Having said that, while it has to be acknowledged that a few specific tools for remote assessment have already been presented in peer-reviewed journals, we argue that they should be used for such purpose if, and only if, the values of the normative sample can be properly applied to and compared with the patient. For these and other reasons—referring to which we suggest to read the abovementioned note—we conclude that a vis-à-vis approach is still recommendable, unless urgent conditions imply that the evaluation cannot be postponed.

The assessment of COVID-19 patients cannot be limited to the administration of screening batteries that provide scores mirroring the so-called "global functionality" or, at the very least, it cannot stop at such level of analysis because this would mean denying the patients the right and possibility to undergo a proper evaluation of the cognitive profile. According to the extant literature, the assessment should include the administration of tests that accurately evaluate cognitive flexibility, problem-solving skills, and working memory, as well as mnesic, learning, and attention skills. Nonetheless, the assessment session should also be compatible with patient's clinical conditions, which could affect appropriate maintenance of attention levels. Furthermore, it is recommended, if possible, to deepen the evaluation via tests that qualify as accurately as possible the patient's residual abilities and via the use of scales for the detection and quantification of potential affective impairments.

NEUROPSYCHOLOGICAL REHABILITATION

One of the targets of the neuropsychological assessment is to provide baseline data for the implementation of individualized rehabilitation programs, in which it is possible to draw up an intervention plan including cognitive exercises of increasing complexity and adequately calibrated to the difficulties that have arisen. A well-defined program examines and takes into account

those factors that allow calibrating the level of commitment asked to the patient for an effective rehabilitation intervention that aims at recovering a deficit or maintaining current abilities over time. The cognitive sequelae of COVID-19 might also benefit from a specific and calibrated intervention on the symptoms profile of each patient. Even in this case, a vis-a-vis intervention allows controlling for relational variables that might be missed during online briefings. Yet, in the field of neuropsychological rehabilitation, it is certainly possible to think at activities that can be provided via teletherapy interventions without losing their effectiveness (5). Today, different tools are available to psychologists for the implementation of rehabilitation projects appropriate to the circumstances: such tools allow, for example, to remotely deliver the exercises, which are modulated in gradients of difficulty so that they can be adjusted to the actual level of impairment, and whose results can be monitored remotely by the psychologist with neuropsychological expertise.

THE ROLE OF THE NEUROPSYCHOLOGIST

The number of patients affected by moderate and severe forms of COVID-19 raises serious considerations about the actual and forthcoming role of the psychologist with neuropsychological expertise. Based on the above, we believe that the contribution of the neuropsychologist should be considered in the phases that follow COVID-19 infection: in the course of neuropsychological intervention, which should be carried out as soon as possible in post-acute departments or rehabilitation facilities; in the implementation of cognitive treatment and behavioral deficits management, not only during the inpatient rehabilitation program but ensuring continuity of these interventions also after the discharge in outpatient facilities or via tele-monitoring; last but not least, the neuropsychologist must ensure the correct dissemination of information about the existence, the extent, and the consequences of patients' cognitive deficits to their caregivers and should provide them with adequate support also to cope with alterations of the emotional states.

SOME CONCLUSIVE REMARKS

As scientific society of psychologists with neuropsychological expertise, we believe it is appropriate to point out the need for neuropsychologists' intervention in taking care of COVID-19 patients, considering that this pandemic, in its manifestation as neuro-COVID, may result in a variation of the epidemiological data on the incidence of cognitive alterations, in addition to the peculiarity of cognitive and behavioral alterations that follow acute necrotizing encephalopathy.

Also, all structures in which COVID-19 patients are hospitalized should be provided with information on cognitive, affective, and behavioral alterations resulting from this pathology.

Neuropsychological assessment of those patients should, then, be fostered, with the aim to correctly understand the deficit, implementing rehabilitation programs, managing cognitive problems in the family environment, and providing support for emotional difficulties.

We also believe that it is necessary to build a "network" of neuropsychologists in order to develop intervention protocols and collect data in the context of observational studies. Such research action could help define a better framework to understand and explain the cognitive consequences of the pathology, as well as enhance virtuous circles of cooperation and increase the homogeneity across neuropsychological interventions, with a view to drafting appropriate guidelines.

It should be finally underlined that the neuropsychologist, as psychologist, operates in close collaboration with colleagues dealing with other aspects of the human mind, aiming at an integrated and complete psychological care of the patient, her/his family system, and the social environment.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it 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.

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REVIEW
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Applications of Non-invasive Neuromodulation for the Management of Disorders Related to COVID-19

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Background: Novel coronavirus disease (COVID-19) morbidity is not restricted to the respiratory system, but also affects the nervous system. Non-invasive neuromodulation may be useful in the treatment of the disorders associated with COVID-19.

Objective: To describe the rationale and empirical basis of the use of non-invasive neuromodulation in the management of patients with COVID-10 and related disorders.

Methods: We summarize COVID-19 pathophysiology with emphasis of direct neuroinvasiveness, neuroimmune response and inflammation, autonomic balance and neurological, musculoskeletal and neuropsychiatric sequela. This supports the development of a framework for advancing applications of non-invasive neuromodulation in the management COVID-19 and related disorders.

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Results: Non-invasive neuromodulation may manage disorders associated with COVID-19 through four pathways: (1) Direct infection mitigation through the stimulation of regions involved in the regulation of systemic anti-inflammatory responses and/or autonomic responses and prevention of neuroinflammation and recovery of respiration; (2) Amelioration of COVID-19 symptoms of musculoskeletal pain and systemic fatigue; (3) Augmenting cognitive and physical rehabilitation following critical illness; and (4) Treating outbreak-related mental distress including neurological and psychiatric disorders exacerbated by surrounding psychosocial stressors related to COVID-19. The selection of the appropriate techniques will depend on the identified target treatment pathway.

Conclusion: COVID-19 infection results in a myriad of acute and chronic symptoms, both directly associated with respiratory distress (e.g., rehabilitation) or of yet-to-be-determined etiology (e.g., fatigue). Non-invasive neuromodulation is a toolbox of techniques that based on targeted pathways and empirical evidence (largely in non-COVID-19 patients) can be investigated in the management of patients with COVID-19.

Keywords: coronavirus, COVID-19, non-invasive vagus nerve stimulation, taVNS, tDCS, TMS, neuromodulation, NIBS

INTRODUCTION

The first cases of novel coronavirus disease (COVID-19) were reported in Wuhan, China, in December 2019 (1). The disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly worldwide and affected more than three million people, and killed more than 750 thousand up to July 2020 (1). The virus spreads by droplet transmission and via direct contact with people while they are infectious in both the pre-symptomatic and symptomatic phases, although a potential transmission *via* fecal, urine, aerosol, and fomite have been reported (2, 3).

COVID-19 presents a variety of clinical symptoms from asymptomatic to severe respiratory dysfunction and death. Key symptoms include fever, anosmia, ageusia, vertigo, nausea, headache, lower limb pain, cough, fatigue, shortness of breath, sore throat, arthralgia, chills, vomiting, and others. In more severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, and kidney failure (4), and on rare occasions, stroke (5, 6), and encephalitis (7–9). Systemic issues such as coagulation disturbances/thrombosis (10, 11) and cytokine storm (12, 13) are also relevant, especially to understand how COVID-19 would be associated with nervous system pathology. Risk factors to severe complications are age (more than 65 years old), and comorbidities, such as systemic arterial hypertension, chronic obstructive pulmonary disease, cardiopathies, morbid obesity, diabetes mellitus, and cancer (14, 15). COVID-19 may not only be restricted to the respiratory system but would possibly affect the peripheral (PNS) and central (CNS) nervous systems which appear to have an influence on morbidity and mortality (16). However, this topic is still a matter of debate.

SARS-CoV was detected in the cerebral cortex and hypothalamus of six out of eight confirmed patients, but not in unconfirmed or control patients (17). The virus may invade the CNS via olfactory nerves, and from the guts via the vagus nerve, reaching brainstem nuclei associated with cardio-respiratory control (18), and thalamus, causing autonomic dysfunction and/or neurogenic respiratory failure (19). Inflammatory waves and particles may reach in the supraspinal nuclei in the brainstem and trigger "the inflammatory reflex," a pathway that has both immunosensing and immunosuppressive functions (20). Thus, the neuroinvasive potential of the SARS-CoV-2 could be related to the severity of some cases (21, 22), and also extend the impact of the disease on cognitive and behavioral aspects. While a growing body of evidence suggests that COVID-19 is associated with neurological diseases (2–4, 23), the potential neuroinvasiveness of the virus and its relation to COVID-19 pathophysiology continues to be deliberated. There are few documented cases of encephalitis (24). It is not clear if CNS pathological findings are a consequence of direct virus infection or consequent to hypoxia (25), and the controversy of SARS-CoV-2 neuroinvasiveness is not resolved

Although it is not clear if COVID-19 affects the nervous system directly, and how this would impact the severity of some cases, the inflammatory nature of the disease is well-recognized (26–29). Despite the uncertainty of the direct involvement of nervous system pathology in the pathophysiology of COVID-19, it is clear that patients present other necessities such as respiratory care and rehabilitation (22, 30–32) and the management of fatigue, and pain (33, 34), for instance. Strategies to control inflammation usually include pharmacological approaches (35–37), but especially given incomplete efficacy and complications in many patients, alternative treatments approaches are relevant. Non-invasive brain stimulation (38–40) and vagus nerve stimulation (41) have the potential to reduce inflammation. These techniques can be used in the management of psychiatric symptoms associated with the COVID-19 pandemic (39, 42, 43). Non-invasive neuromodulation has also shown to be a potent resource

in cognitive and physical rehabilitation (44, 45) and could serve additional goals in the management of COVID-19 patients (30).

Here, we review aspects of the SARS-CoV-2 pathophysiology and its relation to the immune response, autonomic balance, neurological, musculoskeletal and respiratory symptoms, and neuropsychiatric aspects of COVID-19. We highlight the potential applications of non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) in the treatment of patients with disorders related to COVID-19. We link specific non-invasive neuromodulation techniques to the management of targeted disease aspects.

Non-invasive neuromodulation may manage disorders associated with COVID-19 through four pathways:

(1) Direct infection mitigation through the stimulation of regions involved in the regulation of systemic anti-inflammatory responses and/or autonomic responses and prevention of neuroinflammation and recovery of respiration;
(2) Amelioration of COVID-19 symptoms of musculoskeletal pain and systemic fatigue;
(3) Augmenting cognitive and physical rehabilitation following critical illness; and
(4) Treatment of outbreak-related mental distress including neurological and psychiatric disorders exacerbated by surrounding psychosocial stressors related to COVID-19.

The above pathways may be linked. For example, systemic inflammation can occur alongside brain inflammation and fatigue and/or pain, which will all indirectly aggravate psychiatric symptoms (e.g., isolation provoked anxiety). These pathways both in the context of COVID-19 etiology and specific non-invasive neuromodulation therapeutic targets are addressed here, alongside practical considerations for NiN deployment.

MATERIALS AND METHODS

This targeted view (5) was steered by groups of authors involved with research in the fields of inflammation and immune responses to infections, autonomic nervous system activity, neurology, psychiatry, psychology, physiotherapy, rheumatology, neuroscience, bioengineering, and non-invasive neuromodulation. All the groups reviewed the literature using relevant keywords in their specific areas, in search for relevant texts, mainly peer-reviewed articles, to describe a rationale on the use of NiN in the treatment of patients with disorders related to COVID-19. The key problems to be addressed were described by clinicians in reference hospitals in Brazil dealing with COVID-19 patients, and were summarized as: (a) how to help patients who arrive at hospitals with high levels of inflammatory markers, many of which are sent after a short time to intensive care units, and some die after a few days? (b) how to help weaning from mechanical ventilation, intra-hospital rehabilitation, and discharge of patients with COVID-19, who seem to present a slower pattern of recovery, compared to patients without COVID-19? (c) how to approach patients and health teams who are presenting elevated levels of distress, including outbreaks of anxiety; (d) how to prepare for the post-COVID-19 phase, where some patients will need to be rehabilitated because of the consequences of the infection?

After searching the peer-reviewed and pre-print literature and summarizing their findings, key authors from each group joined to integrate their findings, aiming to describe which pathophysiological mechanisms would be approached by the use of NiN. Finally, three authors (BWB, JAC, and MB) externally reviewed the manuscript. The non-invasive neuromodulation tools found to be of relevance were tDCS, rTMS, and VNS. The basis for its use and practical aspects of the application in patients with COVID-19 are described.

Rationale for the Use of Non-invasive Neuromodulation Techniques in the Treatment of COVID-19 Patients

This section presents the theoretical basis that would underpin the use of non-invasive neuromodulation techniques in the management of COVID-19 patients. The potential neuroinvasiveness of COVID-19 represents the first avenue where these nervous system stimulation techniques would act in the control of the disease. In addition, non-invasive neuromodulation can also stimulate the neuroimmune response to the virus, a key factor to determine the severity of the symptoms. Non-invasive neuromodulation techniques may also be useful in the physical and cognitive rehabilitation of the patients, as well as in the management of the mental health both in patients and healthcare teams.

Potential Neuroinvasiveness of COVID-19

SARS-CoV-2, such as MERS-CoV and SARS-CoV can be transmitted through infectious droplets, via angiotensin-2 converting enzyme (ACE2) and transmembrane serine protease 2 (TMPRSS2), which are important to cell viral invasion (46–48). SARS-CoV-2 can directly access the central nervous system (CNS) through the circulation or cranial nerves and the olfactory bulb (18, 49), by synapse-connection (**Figure 1**) (50–52). In addition, direct endocytotic infection (similar to that demonstrated for the ZIKA and TBEV viruses) may also be a pathway for CNS invasion. Once within the CNS, coronaviruses affect astrocytes, neuroblasts, and neurons (53–55). The neurobiological mechanism involves a direct binding of SARS-CoV-2 to the ACE2 receptor leading to a fall in ACE2, which is responsible for mediating neuroinflammation, neurodegeneration, and neurotoxicity processes related to CNS disorders. Invasion of the brainstem may be also clinically relevant, since the nucleus of the solitary tract (NTS) and nucleus ambiguous are crucial for the maintenance of cardiorespiratory homeostasis (22, 51). Afferents of the vagus nerve convey peripheral inflammation information to the CNS, specifically in the medullary NTS and nucleus ambiguous (56, 57). The NTS responds to hypoxia and hypercapnia by activating or inhibiting the sympathetic activity (58–61). This autonomic response is a

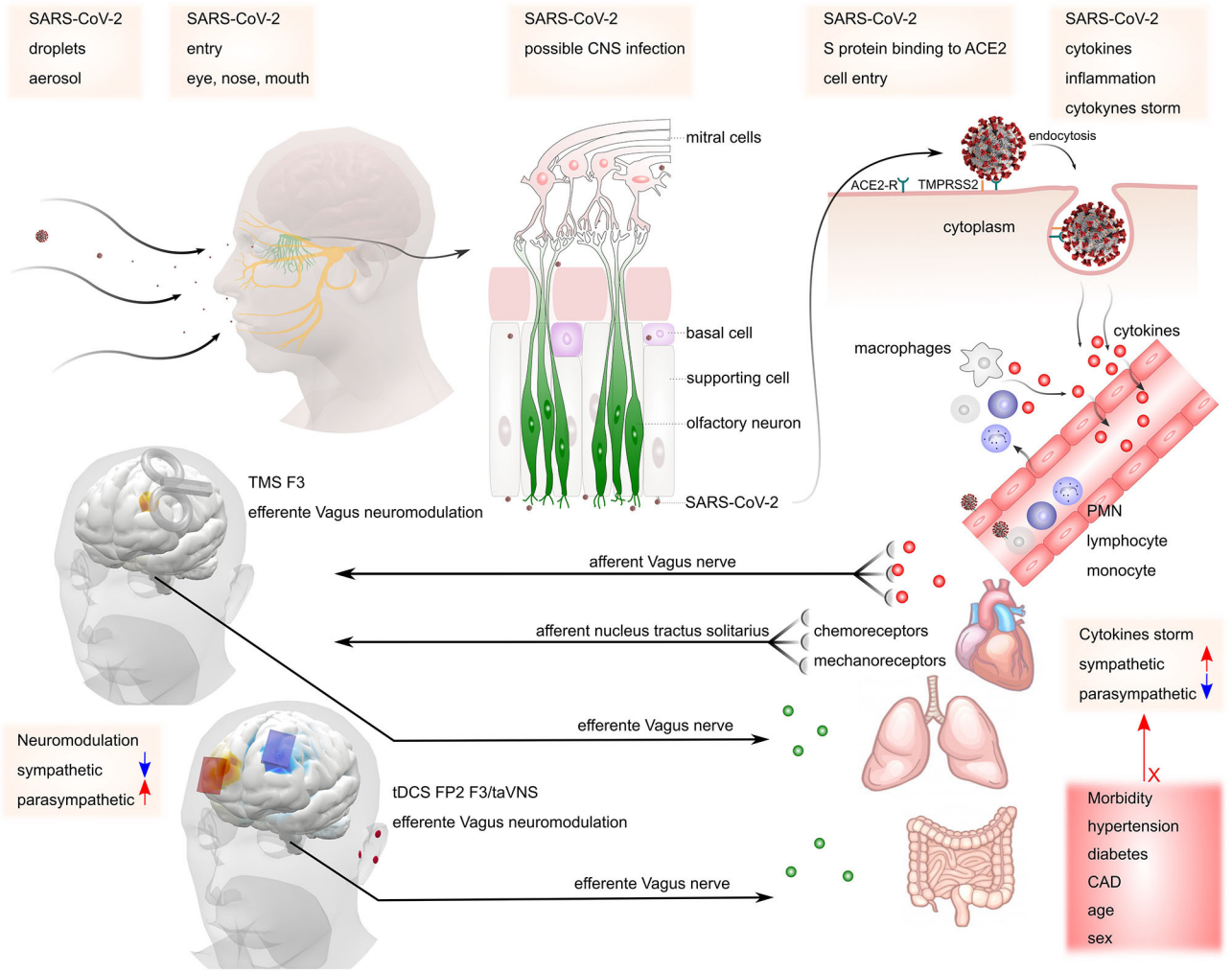


FIGURE 1 | Possible mechanisms of SARS-CoV-2 invasion in the nervous system. SARS-CoV-2 may gain access to the central nervous system via peripheral nerves such as olfactory and vagus nerves. The virus binds to ACE2 receptors, starting the release of cytokines (cytokine storm). This process increases sympathetic activity, which may be responsible for maintaining the inflammatory condition. The presence of co-morbidities such as hypertension, diabetes, coronary artery disease (CAD), increased age, and male sex may contribute to the increased risk of complications. Stimulation of parasympathetic activity *via* TMS or tDCS at the left dorsolateral prefrontal cortex (F3) or transcutaneous vagus nerve stimulation at the ear may counteract increased sympathetic activity mediated inflammation.

powerful regulator of the innate and adaptive immune system (62, 63).

The sympathetic nervous system promotes pro-inflammatory responses, *via* catecholamine release and beta-adrenergic stimulation, and the parasympathetic nervous system promotes anti-inflammatory effects (64). Besides, primary and secondary immune organs have substantial sympathetic innervation and almost all immune cells express receptors for neurohormones and neurotransmitters (65). These factors suggest that COVID-19 may be a systemic disease associated with systemic inflammation and trigger a massive neuroinflammatory response, manifested by reactive astrogliosis and microglial activation (66).

Although respiratory (nasal/oral cavity, pharynx, larynx) to nervous system transmission is still under investigation in the case of COVID-19 pandemic, the reports of neurological symptoms in infected patients support the potential neuroinvasiveness of SARS-CoV-2. Patients with COVID-19 in hospitals of Wuhan presented acute CNS symptoms, such as dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and convulsions (67). Earlier studies also reported the presence of SARS-CoV within the brain of infected individuals (17, 68), and in the brainstem of animal models (17, 68, 69), supporting the evidence that COVID-19 affects the CNS (22), and also a possible bidirectional communication with the immune system (63). Moreover, other short-term neurological symptoms observed in COVID-19 patients could also be a manifestation of CNS invasion, such as high-grade fever, hypoxia, respiratory, and metabolic acidosis at an advanced stage of the disease (16).

However, a recent study reported inconsistent results on SARS-CoV-2 invasion of the CNS, and one cannot rule out that all the above-described neurological symptoms could be secondary to a non-neurological process (e.g., general inflammation, cytokine storm, hemodynamic shock, systemic thrombotic phenomena). Characterizing the symptoms and etiology of COVID-19 neurological manifestation is complex and subject to ongoing studies, including post-pandemic consequences of the infection, such as encephalitis (70, 71), acute flaccid paralysis (72), acute disseminated encephalomyelitis (19, 73, 74), neuropsychiatric and cognitive impairments consequent of neuroinflammation together with prolonged hypoxia (18). A recent report suggests that neurological manifestations in COVID-19 patients should be classified as confirmed, probable or possible/suspected based in a WHO classification (6). This effort will probably be useful to shed light into the clarification of the involvement of the nervous system pathology into COVID-19. Non-invasive neuromodulation techniques are currently used and trialed for the management of a broad range neurological diseases (7, 8), and are thus candidates in the management of neurological manifestations of COVID-19—as considered later in this article.

Immune Response to COVID-19

The innate immune system can recognize lipopolysaccharides, viral antigens, and viral genomes through pattern recognition receptors (PRRs), leading to the activation of intrinsic signaling pathways and the production of pro-inflammatory and anti-inflammatory cytokines (75–78). An immune response initiates after a virus invading the body (host) is recognized by the host innate immune system through PRRs (79, 80). The expression of inflammatory factors, maturation of dendritic cells, and synthesis of type I interferons (IFNs) are induced by the virus, limiting the spreading of the virus while stimulating macrophages (81).

Notwithstanding this innate immune response to the virus, Lu et al. (82) argued that the N protein of SARS-CoV could aid the virus in "escaping" from the expected immune responses. After the initial activation of the innate immunity, the adaptive immune response is involved in a battle against the virus (82). The T lymphocytes (T-cells; CD3+, CD4+, and CD8+) and B-cells (CD19+, CD20+, CD22+), the cellular adaptive components, play an important and complex role in the body defense. For example, CD4+ T-cells stimulate B-cells to produce virus-specific antibodies, and CD8+ T-cells have the function to kill the virus-infected cells. Moreover, the helper cells will produce pro-inflammatory cytokines to aid in the defense. Indeed, humoral immunity is also essential in fighting against the virus in order to combat the viral infection (82, 83). However, SARS-CoV-2 can inhibit T cell functions by inducing apoptosis of T-cells, and an overreaction of the immune system could exaggerate elevating the number of free radicals locally that in turn could lead to damages to the lungs, organs, and. to multi-organ failure and even death (84).

A cytokine storm results from an overreaction of the immune system in SARS and MERS patients (84–86), which releases excessively free radicals and causes acute respiratory distress syndrome and multiple organ failure (87). Therefore, a cytokine storm is a systemic inflammatory response due to a release of cytokines such as TNFα, IL-1β, IL-2, IL-6, IFNα, IFNβ, IFNγ, and MCP-1 (80), and activated macrophages responsible for pro-inflammatory mediators such as cyclooxygenase and nuclear factor-kappa B (88). Sustained inflammatory responses may be related to the critical conditions of COVID-19 patients, whereas those patients admitted in the intensive care unit had higher plasma levels of TNFα, IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, and MIP1A, indicating that the cytokine storm is related to disease severity (84, 85, 89).

Therapeutic immunosuppression is fundamental and critical in the treatment of cytokine storms, notably, in COVID-19 severe conditions. Mehta et al. (12) reported a subgroup of patients with severe COVID-19 that might have cytokine storm syndrome. Huang et al. described patients with COVID-19 in Wuhan (China), presenting high amounts of IL-1β, IFNγ, IP10, and MCP-1, probably leading to activated Th1 cell responses (12, 89). Huang et al. (89) also described that SARS-CoV-2 induces an increased secretion of Th2 cytokines (e.g., IL-4 and IL-10) that suppress inflammation, differently to those observed from SARS-CoV infection. These mechanisms may also be related to the genesis of acute cerebrovascular disease and acute hemorrhagic necrotizing encephalopathy (90), resulting from blood-brain-barrier damage (91). Indeed, data from mouse models suggest that the influenza virus can aggravate ischemic brain injury by triggering a cytokine cascade (92). As all the above mentioned immune responses are linked to peripheral nervous system (PNS) and CNS activity through autonomic responses, nervous system activity may be a key factor in the response to infection, which could in turn be modulated by non-invasive neuromodulation techniques especially through vagus nerve stimulation.

Autonomic Response in COVID-19 Infection

The vagus nerve releases acetylcholine (ACh) in the periphery to activate parasympathetic responses in target organs throughout the body such as lowering heart rate HR) and myocardial contractility in the heart (93). There are numerous downstream effects of ACh release in the periphery, such as activating α7 nicotinic ACh receptors (α7nAChR) on macrophages (94–99), inhibiting the production of IL-1, IL-6, IL-18, and HMBG1 (100–102) in several tissues and organs, such as the spleen, intestine, liver, heart, and lung (20, 103). The α7nAChR has an important role in the control of inflammation since α7nAChR-deficient mice show higher levels of pro-inflammatory cytokines in blood, spleen, and liver after endotoxin when compared to wild-type mice (104). In addition to that, ACh is also released by T and B cells with autocrine responses such as IL-2 release and T cell proliferation (105, 106), corroborating its importance in the inflammatory modulation.

Vagal activity is correlated with decreased inflammatory markers (e.g., IL-6, C-reactive protein) (107, 108). In experimental models, lesioning the vagus nerve (vagotomy) exacerbates the inflammatory response in colitis, pancreatitis, viral myocarditis, and sepsis (109–111). It also increases the synthesis of pro-inflammatory lipid mediators, while decreasing pro-resolving mediators such as netrin-1 and specialized pro-resolving mediators (SPMs) (112), which decrease the resolution

of bacteria inflammation (113, 114). In addition, vagotomy not only decreases ACh release but also catecholamines (113, 114), which likewise have an important role in controlling inflammation (115). Deficiency in T- and B-cells related to increasing in alternatively activated immune cells lead to exacerbated viral replication, prolonged inflammatory responses both systemic and locally, induction of procoagulant factors, hemodynamic changes, ischemia and thrombosis leading to poor outcomes (116–118). The presence of SARS-CoV-2 in the brainstem, independently of the infection detected in the lungs, induces neuronal loss and dysfunction (119), which may be associated with an autonomic imbalance with a decrease of ACh and catecholamine release in the periphery. It is noteworthy that cardiovascular disease and diabetes, risk factors for worse prognostic and death by the COVID-19 (120–122), are characterized by decreased autonomic function. This condition may be relevant in some COVID-19 patients who present a high inflammatory profile and could be targeted by strategies to increase vagus activity, which have already been shown to regulate autonomic function in patients with cardiovascular diseases and diabetes.

Musculoskeletal Symptoms and Fatigue in COVID-19

Musculoskeletal symptoms and fatigue in COVID-19 may also represent the affection of nervous and/or immune function. Skeletal muscle symptoms were shown to be common in individuals with COVID-19 (67). Different meta-analyses of COVID-19 clinical characteristics have reported an incidence of generalized myalgia and/or fatigue that ranges from 35.5 to 42.5% (33, 34, 123). Muscular symptoms are the third or fourth more frequent manifestation reported by individuals. Also, these symptoms should be taken into account for diagnostic criteria, since individuals with severe infection are more likely to present non-typical symptoms first (67). Individuals with muscular symptoms presented an increased inflammatory response, including higher levels of C-reactive protein (67). These findings are indicative of muscle injury, although the lysis of striated muscle is considered as a rare complication of COVID-19 (34).

There are two proposed mechanisms to explain myalgia and fatigue. The first is that the inflammatory response is not only the consequence of muscle injury but also the cause. Not only individuals with a more severe infection have more incidence of muscle symptoms, but also those who present muscle symptoms usually have multiple organ lesions (67). Altogether, there is some evidence that systemic inflammation can lead to muscle fiber necrosis (124). The second mechanism is related to the ACE2 receptor targeted by the virus and also found in muscle cells (67, 124). It is hypothesized that COVID-19 could injure directly the muscle tissue, but there is no evidence to substantiate this theory, and it comes from studies of SARS. Two studies conducted an analysis of post mortem muscle tissue of patients who died with SARS (68, 125). One of them did not find any evidence of the virus in muscle tissue (68). The other found focal myofiber necrosis but with small quantities of inflammatory infiltration (125). Authors of the second study argue about not being able to remove the confounding influence of mechanical ventilation used by these patients, and its side effects on their findings. Probably, the systemic inflammatory response is the main cause of muscle symptoms in individuals with COVID-19. Muscle fatigue and weakness could hamper respiratory function and become a vicious cycle with the aid of mechanical ventilation devices, which *per se*, can cause more weakness (125).

Psychiatric Symptoms and the Mental Health Outbreak Related to COVID-19

The evidence of the impact of this pandemic on mental health is evolving. An online survey of 714 Chinese patients with stable COVID-19 disease reported a 96.2% prevalence of significant post-traumatic stress symptoms (126). As for the general population, a survey of residents of Wuhan and surrounding cities, the epicenter of the China outbreak, the prevalence of post-traumatic stress symptoms was 7% as assessed up to 2 weeks after mandatory quarantine for all citizens was implemented. Women and those with sleep complaints were reported to be at increased risk (127). As for protective factors of anxiety symptoms, family income stability, and living with parents were protective (128). Among healthcare professionals, 28% of nurses and physicians working in Wuhan were found to have either moderate or severe symptoms in the domains of depression, anxiety, insomnia, and distress (129).

Potential Use of Non-invasive Neuromodulation on COVID-19 Related Disorders

In the previous section we described how COVID-19 may affect or be mediated by the nervous system and immune activity, aspects that can be targeted by non-invasive neuromodulation techniques in order to manage the disease. We now present the rationale specific uses of these techniques in the management of COVID-19 patients, relying largely on evidence from relevant non-COVID-19 populations, as direct trials of non-invasive neuromodulation in COVID-19 patients remain limited or are ongoing.

The possible presence of an autonomic imbalance in COVID-19 and the importance of vagus nerve activity in the control of inflammation may represent key features to the use of NiN in the treatment of COVID-19 patients, markedly those with high levels of inflammatory profile. Vagus nerve activity can be increased via the cerebral cortex through areas that modulate it indirectly such as the left dorsolateral prefrontal cortex (DLPFC) (130), corresponding to the F3 position of the 10–20 International EEG System, or temporal cortices. Also, the vagus nerve innervates the ear, mainly the pinna of the outer ear (131), making it possible to stimulate these areas transcutaneously to influence vagus activity (9, 10). In this section, we will review the most promising, readily available NiN approaches that modulate the central and peripheral immune response. At the same, NiN may be useful in the control of musculoskeletal psychiatric symptoms and through the same or even different cortical targets as those used in the control of inflammation. The subsequent sections will present the basis for the use of NiN in the treatment of COVID-19 patients using techniques such as rTMS, tDCS, and

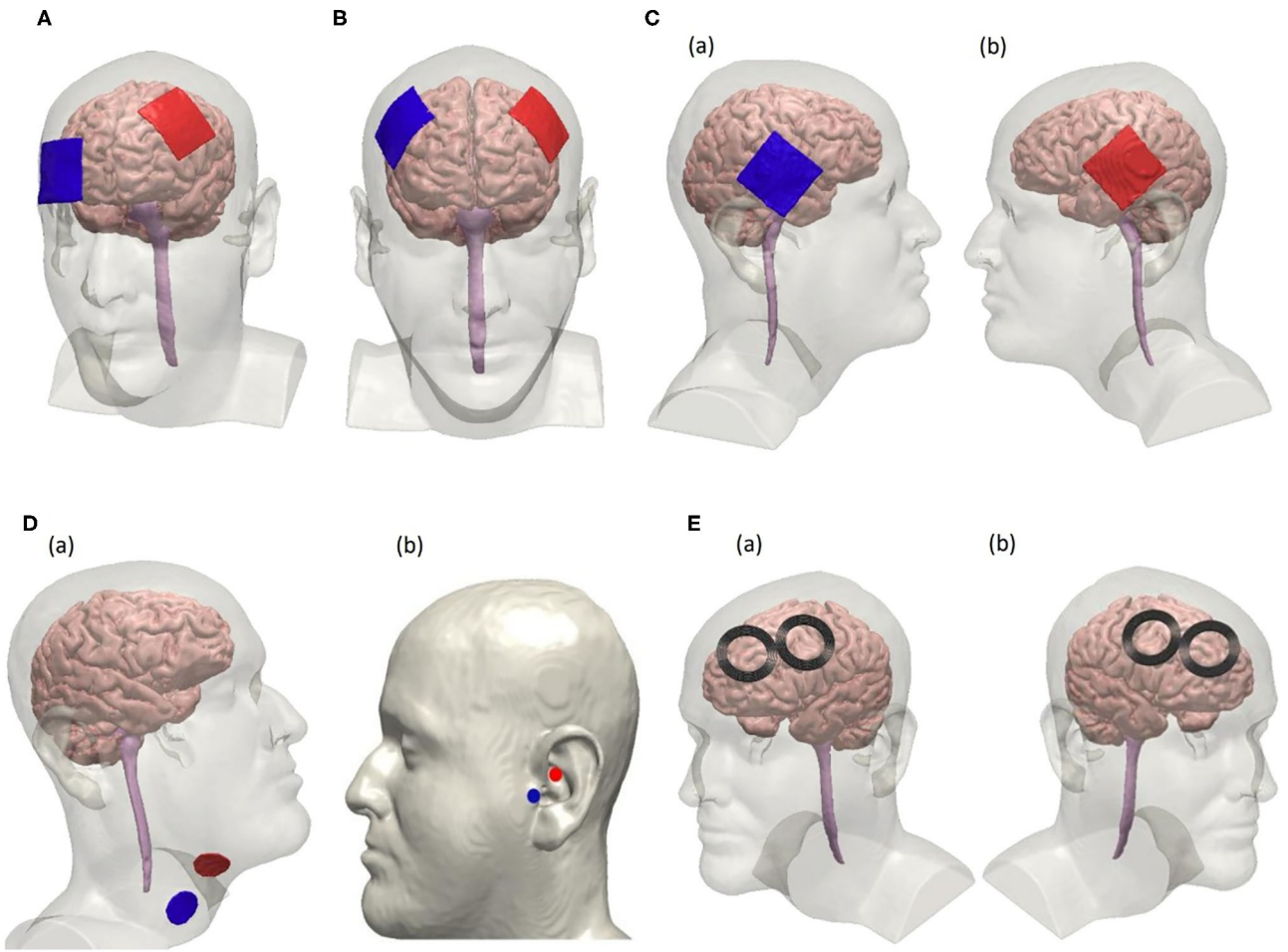


FIGURE 2 | Electrode configurations for non-invasive tDCS, VNS, and rTMS following the 10–20 EEG system. **(A)** Unilateral tDCS with anode positioned over F3 and cathode over Fp2 on the scalp to modulate the left dorsolateral prefrontal cortex (DLPFC). **(B)** tDCS using a bifrontal montage to perform anodal stimulation on left DLPFC where the anode is positioned over F3 and cathode is positioned over F4. **(C)** Anodal tDCS to stimulate the temporal cortex using a bifrontal configuration where the cathode is positioned over T4 and the anode over T3 as seen in (a,b), respectively. **(D)** Non-invasive vagus nerve stimulation by modulating the cervical branch of the vagus nerve in (a) and the ear in (b). Electrode placement for cervical vagus nerve stimulation is shown in (a). Electrodes are placed at the tragus and the cymba conchae of the left ear to perform unilateral taVNS as shown in (b). **(E)** rTMS using a figure-8 coil positioned over F3 to stimulate the left DLPFC suggested for high-frequency protocol is shown in (a). Right DLPFC is stimulated using the low-frequency rTMS protocol by placing the coils over F4 as shown in (b).

vagus nerve stimulation directed to the DLPFC, motor cortex, and where the vagus nerve is superficially accessible (**Figure 2**).

Left Dorsolateral Prefrontal Cortex Neuroimmune Modulation With TMS or tDCS

The vagus nerve is responsible for the parasympathetic innervation of the heart; its stimulation decreases heart rate (HR), and interferes with heart rate variability (HRV) (132, 133). This phenomenon was also observed when stimulating other areas of the CNS, such as the DLPFC (134), perigenual, and mid-anterior cingulate cortex (pgCC and maCC) (135, 136), which lead researchers to suggest that those cortical areas modulate vagal activity.

Studies with transcranial magnetic stimulation (TMS) have helped elucidate the relationship between the DLPFC and vagus nerve activity. Iseger et al. (134) applied trains of high-frequency 10 Hz rTMS over 10 cortical regions aiming to identify which regions would affect HR. They found that 20–40% of the participants presented decreased HR and heart rate variability (HRV) with stimulation of the DLPFC, either left (F3, FC3; 10–20 EEG System) or right (F4, FC4; 10–20 EEG System). Interestingly, stimulation of the motor (C3, C4–10-20 EEG System) and parietal (Pz–10–20 EEG System) cortices showed opposite effects. Effects were more pronounced in the right DLPFC, which is contrary to other studies showing that stimulation of the left, but not the right DLPFC changes HRV (137). The variability found in these studies is probably because of individual patterns of connectivity between the DLPFC and

other cortical and subcortical structures. As an example, in a TMS/fMRI, Iseger et al. (134) and Vink et al. (138) found that only four under 10 participants had the subgenual cingulate cortex activated by stimulation of the DLPFC.

The anti-inflammatory effects of DLPFC stimulation support the idea of DLPFC/vagus connectivity. Aftanas et al. (139) applied dual-target rTMS to the motor cortex (bilaterally; 10 Hz; 100% of resting motor threshold; 4,000 pulses) and to the left prefrontal cortex (DLPFC; 10 Hz, 110% of resting motor threshold; 3,000 pulses) for 20 days in patients with Parkinson disease. They reported significant down-regulation of the spontaneous production of pro-inflammatory cytokines. Although not tested in this study, the effect may be related to increased vagal activity and suggests that the DLPFC would be a potential target in the control of inflammatory cascade in patients with COVID-19.

Transcranial direct current stimulation (tDCS) has also been used to probe HRV and vagal activity. Carvenali et al. stimulated the left DLPFC with anodal tDCS immediately before and during exposure to stress and showed decreased HRV only in the period prior to stress exposure (140). Similar results were found with bifrontal tDCS (141), which raises again the question about the effect of laterality when stimulating the DLPFC with the aim to increase vagus nerve activity.

Taking together, those studies suggest that stimulation of the DLPFC with rTMS or tDCS could be useful to increase vagal activity. The consequent decrease in inflammation with those strategies is speculative. However, as patients with COVID-19 also present mood disturbances such as stress and anxiety, targeting the DLPFC would be useful in the control of inflammation and neuropsychiatric problems associated with the infection (see below for neuropsychiatric effects). Unilateral tDCS protocols would target the left DLPFC with the anode positioned over the F3 scalp position (10–20 EEG System), and cathode over the Fp2 scalp position (10–20 EEG System) or another distant location. Typical current intensities of 1–2 mA, for 20–30 min, and electrodes' sizes ranging from 5 × 5 cm or 7 × 5 cm. Bifrontal protocols would position the anode over F2, and cathode over the F4 scalp position (10–20 EEG System) or in the bifrontal "OLE" montage which can optimize current delivery to DLPFC (11–13). Targeted tDCS of DLPFC can be achieved using 4x1-tDCS centered over DLPFC (142, 143). High-frequency rTMS protocols would target the left DLPFC with 10 Hz, trains of 50 pulses, with intertrain intervals of 25–50 s, at 90–120% of the resting motor threshold, until 3,000 pulses per session, with figure-of-eight coils positioned at the F3 scalp position or using neuronavigation (14). The right DLPFC may be targeted with low-frequency 1 Hz rTMS, maintaining the same intensity and number of pulses of high-frequency rTMS. More details for rTMS treatment can be found in the study of Pereira et al. (144).

Temporal Cortex Autonomic Modulation With tDCS

The use of tDCS over the temporal cortex aims to reach the insular cortex, an area beneath the temporal cortex with profuse autonomic and limbic connectivity. Intraoperative electrical stimulation of the left insular cortex increased blood pressure and HR and stimulation of the right insular cortex resulted in opposite effects (145). In addition, left insular cortex lesion resulted in perturbations of the cardiac autonomic function in humans (increased cardiac sympathetic tone and decreased parasympathetic tone) and predisposed individuals toward a pro-arrhythmic state (145). Furthermore, neuroimaging studies have shown the relation between the insular cortex and cardiac autonomic control (146, 147), and acute ischemia of the insular cortex was independently associated with poststroke hyperglycemia, which may reflect sympathoadrenal dysregulation, although no evidence of lateralization was found (148). Other studies have suggested a role played by the insular cortex in a phenomenon called post-exercise hypotension (e.g., temporary decrease in blood pressure below pre-exercise values) (149, 150). Hence, the temporal cortex has been the target in several studies aiming to modulate cardiac autonomic control or other functions associated with the insular cortex (151–155).

Montenegro et al. (155) assessed the effects of anodal tDCS (2 mA for 20 min) over the left temporal cortex on measures of cardiac autonomic control at rest in two groups of healthy adults, a group of athletes and a group of non-athletes. The stimulation improved cardiac autonomic control in athletes but not in untrained individuals, namely parasympathetic activity, increased whereas the sympathetic activity decreased. The authors attributed the specific results to neuroanatomical and functional changes in the brain induced by long-term exercise training (155). Furthermore, Piccirillo et al. (154) demonstrated that anodal tDCS over T3 scalp position (10–20 International EEG System), 2 mA for 15 min, improved temporal ventricular repolarization dispersion, reduced sinus sympathetic activity and systemic peripheral resistance, and increased vagal sinus activity and baroreflex sensitivity in older (>60 years old; mean age 70 ± 6 years), but not younger (<60 years old; mean age 36 ± 11 years) individuals. It should be noted that older individuals are at increased risk for worse prognosis and death (120, 121, 156).

Interestingly, besides modulating cardiac autonomic control at rest, tDCS over the left temporal cortex may also modulate autonomic control during exercise (151, 152). Okano et al. (152) applied anodal tDCS over T3 scalp position (2 mA for 20 min) in a sample of elite cyclists before submitting them to a maximal graded cycling exercise test (e.g., stress test) and found that the stimulation decreased heart rate at submaximal intensities for roughly half of the exercise test duration. These results were also replicated by Kamali et al. (151) who found decreased HR during fatiguing knee extension exercise after concomitant anodal tDCS over T3 and primary motor cortex (M1) (2 mA for 13 min) in trained bodybuilders.

Taken together, these results demonstrate that anodal tDCS applied over the temporal cortex may improve autonomic function in healthy individuals at rest and during stressful stimuli (e.g., exercise). Respiratory exercises are being used in patients with COVID-19, and temporal cortex tDCS may be used to increase their effectiveness in restoring respiratory function in these patients. It is suggested that tDCS may be used with the anode positioned at the T3 scalp position, and cathode at the T4 scalp position, with 2 mA for 20 min, using 5 × 5 cm or 5 × 7 cm electrodes, together with exercises directed to respiratory

function. For targeted temporal cortex tDCS the 4x1 HD-tDCS can be used (142, 143).

Neuroimmune Modulation Through Transcutaneous Vagus Nerve Stimulation

The vagus nerve plays a central role in the autonomic nervous system. It mediates major visceral functions such as heart rate, gastrointestinal motility and secretion, pancreatic endocrine and exocrine secretion, hepatic glucose production, and other visceral functions. Furthermore, and most relevant to the current pandemic is that activation of the vagus nerve suppresses immune and inflammatory responses to pathogen invasion and tissue injury (157). Modulating the vagus nerve has been demonstrated to suppress inflammation is being explored as a treatment for pulmonary arterial hypertension and COPD-related bronchoconstriction (ClinicalTrials.gov: NCT01612793).

The vagus nerve may be stimulated invasively and non-invasively. Cervically-implanted vagus nerve stimulation (VNS) activates the parasympathetic system and mediates lymphocytes and macrophages inhibiting pro-inflammatory production (113, 158–160), improving survival in experimental sepsis, hemorrhagic shock, ischemia-reperfusion injury, and other conditions of cytokine excess (161). Interestingly, VNS increases dopamine levels, and similarly to ACh, dopamine also shows anti-inflammatory mechanisms by decreasing TNF-α and inflammasome after endotoxins (113, 114). VNS not only inhibits the inflammation but also induces the expression of the SPMs, including the lipoxins, resolvins, protectins, and maresins (162). VNS also regulates the SPMs expression, polymorphonuclear infiltration, and the chemokines and cytokines release, which are directly involved in the inflammatory inhibition within the nervous system (162). Hence, the so-called pro-resolution vagal reflex (163), may induce a more efficient resolution of the inflammatory storm in COVID-19 patients, helping also to improve the quality of life and survival expectancy in these patients.

Recently, a non-invasive form of VNS known as transcutaneous VNS (taVNS) has emerged as a promising, non-invasive alternative to its surgically-implanted predecessor. taVNS activates the vagal system by delivering electrical pulses to the auricular branch of the vagus nerve (ABVN) that innervates both left and right ears (164). taVNS is simple and inexpensive to administer, requiring only bipolar electrodes attached to the skin mainly in the tragus and cymba conchae (131, 165). A consensus on optimal stimulation parameters is yet to be determined, however, taVNS is generally administered using the following range of waveforms: monophasic or biphasic pulses delivered at 5–25 Hz pulsed, $\leq$ 500 μS pulse width, $\leq$ 10 mA (166). taVNS can be administered either unilaterally (left ear) or bilaterally (left and right ears) at either the left tragus or cymba conchae, for 1 h sessions (166). The safety and tolerability of this method were assessed in several studies which showed minimal side effects (165, 167–170). It is important however to consider parasympathetic activation *via* taVNS and monitor for cardiac effects (171).

Transcutaneous cervical VNS (tcVNS) is another form of non-invasive VNS that delivers electrical stimulation to the cervical vagus nerve transcutaneously through the neck. Electrodes are placed over the carotid sheath and stimulation is applied with devices that activate the underlying nerve and tissue. tcVNS frequencies range from 5 Hz to 5 KHz (172, 173). A recent paper has proposed, based on two case studies, the use of tcVNS to manage respiratory symptoms in COVID-19 patients (174). They showed that tcVNS decreased the use of opioids and cough suppressant medication, and promoted relief from chest tightness and shortness of breath, improving lung clearance. As both taVNS and tcVNS are very easy to administer and studies have shown they can increase vagus nerve activity, they both are suggested as potential techniques in the treatment of COVID-19 patients to control inflammation and decreased respiratory discomfort associated with respiratory symptoms.

Non-invasive Neuromodulation to Target Musculoskeletal Symptoms, Restore Normal Respiration, and Function and to Accelerate Patient Discharge

Musculoskeletal symptoms in COVID-19 are probably a consequence of systemic inflammation, but a key factor to be addressed, as the musculoskeletal system is strongly related to the capacity to move and perform daily life activities, and probably should be addressed early in the treatment of infected patients. Non-invasive neuromodulation techniques could not only reduce the muscle symptoms present in this population but also improve respiratory muscle function (175–178), training (44, 179–181), and fatigue (182), increasing their motivation, and likely positively affecting the cognitive process, which could aid them in the recovery from the illness.

Respiratory dysfunction is a major concern in COVID-19 (183), with many patients submitted to oxygen support and mechanical ventilation (184, 185). It is already known that respiratory dysfunction has a neural correlate which has in part to do with the potential role of the supplementary motor cortex (SMA) in the control of the diaphragm muscle, what has been recently evidenced by the use of TMS (186) and functional magnetic resonance imaging (187). Conditions such as diaphragm loading, and changes in hypoxia and hypercapnia, change transiently diaphragmatic motor-evoked potentials, but these changes may be the source of difficulties in mechanical ventilation weaning.

At present, only one study investigated the effects of mechanical ventilation on cortical excitability and showed that motor-evoked potentials were depressed; one mechanical ventilation was performed non-invasively *via* nasal mask (188). This result highlights the potential role of mechanical ventilation in depressing CNS excitability and raises the question if failure in weaning from mechanical ventilation has a CNS component. Reports from hospitals struggling with the COVID-19 infection have shown that patients stay ∼15–20 days intubated and in mechanical ventilation and that weaning off is slow (189). It is possible that this exquisite pattern may be due to the invasion of the CNS by the virus, as previously shown. Non-invasive neuromodulation techniques such as tDCS or rTMS

could be used to help the re-establishment of diaphragmatic drive, but there is still not sufficient evidence to support this use. However, one study has shown that tDCS reduced diaphragmatic motor-evoked potentials (190), which would suggest that stimulation of the motor cortex would not help in mechanical ventilation weaning.

Non-invasive Neuromodulation on Outbreak-Related Mental Distress

Infectious disease outbreaks pose many challenges to society. As a consequence of fear, stress, social isolation, reduced income, and other factors, psychiatric symptoms may worsen or emerge in those previously asymptomatic people (191). Patients with prior mental illness and frontline healthcare personnel are at an increased risk of psychiatric symptoms during outbreaks (192). Moreover, the impact on mental health on survivors occurs in the long-term, outlasting the pandemic for months to years (193). Non-invasive neuromodulation strategies have been increasingly used as effective clinical interventions in the treatment of diverse neuropsychiatric disorders (194, 195). Amongst non-invasive neuromodulation techniques, the most established on clinical grounds is rTMS, an intervention already approved by regulatory agencies for the treatment of major depression in many countries, such as the United States, across the European Union, Israel, Australia, and Brazil (196). Furthermore, rTMS may also be an effective treatment for anxiety and trauma-related disorders, as shown in a recent meta-analysis (PMID: 31066227). One of the major barriers of the broad use of rTMS as mental health interventions is the non-portability of devices. As such, patients need to move to health care facilities, which can be located either in small clinics or in hospitals, to have access to this therapy. Usually, the acute treatment is performed in daily sessions five times a week for some weeks, while the maintenance treatment is more spaced out, with fewer weekly, biweekly, or monthly sessions (197). Since a relevant number of patients that receive rTMS comprise risk groups for COVID-19 severe outcomes (e.g., elderly, smokers, chronic cardiopulmonary diseases), there is a need for session frequency reduction or postponement in those with relatively controlled symptoms, which should be addressed in a case-by-case approach. On the other hand, for hospitals with non-invasive neuromodulation services, rTMS treatment could be offered both for stable COVID-19 inpatients and healthcare personnel, assuring proper measures to control viral transmission are implemented. For inpatients with COVID-19 and psychiatric symptoms requiring medical intervention, care must be taken in the prescription of psychotropic drugs if antiviral medications are concomitantly administered, in order to avoid harmful drug-drug interactions (198). Antipsychotics such as risperidone, aripiprazole, and haloperidol (199) and antidepressants such as fluoxetine, paroxetine, sertraline, and duloxetine (200) are metabolized by CYP2D6, the same enzyme that metabolizes chloroquine, a current investigational drug for the management of COVID-19 (201). In this context, the use of NiN would be a safer option.

Standard rTMS protocols for the treatment of psychiatric disorders include high ("excitatory") and low ("inhibitory") frequency trains with coil positioned in the scalp usually over either the right or left DLPFC, according to the indication (195, 198, 202). Stimulation of the DLPFC can transynaptically enhance activity in the ventromedial prefrontal cortex, which is hypoactive in trauma-related disorders and possibly related to impaired fear responses, a hallmark of these conditions (203). High-frequency rTMS delivered over the right DLPFC has been deemed efficacious for post-traumatic stress disorder (PTSD) in some clinical trials (195, 198, 202) and would be a reasonable approach to treat patients with trauma-related symptoms. However, in the presence of signs or symptoms that suggest CNS organic compromise, "inhibitory" protocols should be preferred in favor of minimizing the theoretical risk of induced seizures. Low-frequency stimulation of the right DLPFC would be an alternative since one trial that compared both high and low-frequency protocols found no superiority of one intervention over the other in the improvement of PTSD symptoms (204). Furthermore, low-frequency pulses delivered to the right DLPFC may also be effective for the treatment of generalized anxiety disorder (205). Hence, the choice of the ideal strategy should be guided individually after a careful psychiatric assessment. Since the length of hospital stay for recovered COVID-19 patients is around 21 days (156), rTMS treatment might be continued after discharge in some cases. As neither the immunization (206) nor transmitter status (207) after COVID-19 symptom resolution is clear yet, hygienization procedures and personal protective equipment use should be maintained during further rTMS sessions.

As for the treatment hospital staff, a small sham-controlled trial delivered high-frequency rTMS stimulation over the left DLPFC in healthcare workers diagnosed with occupational stress. Sessions were performed three times a week for 4 weeks, with significant improvement of symptoms at follow-up (208). Another expedite strategy would be to administer intermittent theta-burst stimulation (iTBS) over the right DLPFC, an approach effective for PTSD (209). TBS is a particular type of rTMS that can be performed in shorter sessions (maximum of 10 min), minimizing the time that healthcare personnel would need to spend in the NiN sector.

As opposed to rTMS, tDCS could safely be instituted in different environments, including the domestic or ICU setting. However, evidence of tDCS efficacy in anxiety and stress disorders is evolving (194, 210). Bifrontal 2 mA stimulation with cathode over the right and anode over the left DLPFC was performed on a recently published controlled randomized trial, supporting the efficacy of tDCS in the treatment of PTSD (211). In contrast, evidence for tDCS in the treatment of generalized anxiety disorder is less robust (212). A randomized controlled trial showed improvement in physical stress symptoms but not in the primary outcome measure (Hamilton Anxiety Rating Scale) in the active group in comparison to sham (213). Therefore, should tDCS be prescribed, the anode should overlie the left DLPFC with cathode either on the right DLPFC (preferably) or over the right supraorbital area. The current intensity should be set at 2 mA for 20 min, with 5 or 10 (preferably) daily sessions.

Home Use of Non-invasive Neuromodulation

Prior to the COVID-19 pandemic, the availability of home-based non-invasive neuromodulation was already compelling and developed (214–218), especially noting the inconvenience for patients already struggling with debilitating disorders to travel daily for brief non-invasive neuromodulation treatment. Home-use tDCS could also offer an advantage in the context of limited outpatient resources for people living in remote areas (219). Home-base treatment is taken on increasing importance with travel and in-patient treatment severely constrained by the COVID-19 pandemic (e.g., many ill patients confined to the domestic environment).

In the context of clinical care, recommendations for home-based non-invasive neuromodulation involve intervention (device, patient) specific levels of oversight to ensure compliance and tolerability. The remote-supervised tDCS rubric provides specific guidance (16), that is directly applied through the COVID-19 pandemic (218). The need for devices that can be reprogrammed remotely, video-conferencing, and accessories to support reproducible stimulation are all intervention specific considerations. For example, online monitoring with a video conference, so that the supervisor can check the correct positioning of electrodes may be deemed important only a first on-boarding session, for only a few sessions until subject competence is confirmed, or every session (214, 216, 220, 221).

Candidates for home use should receive the device from care providers, along with appropriate training on a physical encounter, to minimize the risk of misuse and overuse (194). Training should cover sponge preparation, electrode placement, stimulation initiation with ramp up until the target intensity, and standard operating procedures for troubleshooting common problems. Customized head-bands that facilitate electrode positioning and improve compliance could also be provided (142, 220, 222). Parameters used in most clinical trials are similar to what is usually employed in care facility settings (220). Therefore, tDCS interventions outlined previously could be recommended for home use (216).

Practical Aspects and Devices Hygienization

As with all COVID-19 safety procedures, regional and institutional guidance, applied judiciously to specific protocols considering changing conditions, will determine which procedures should be implemented and which should be abbreviated (143). Social/physical distancing parameters as defined by governments and regional regulatory authorities vary and change over time as regional COVID-19 situations evolve. Any recommendations, including the following discussion, is, therefore, region and institute specific, and subject to ongoing risk-burden evaluation. Frequent and adequate hand hygiene is one of the most important measures that should be used to prevent infection by the COVID-19 virus (223). Professionals should perform more frequent and regular hand hygiene, with appropriate techniques (224), including before and after NiN sessions. In addition, the use of personal protective equipment (PPE) is recommended for the provision of health care with direct contact with infected patients, and include gloves, medical masks, goggles or face shields and gowns, and for specific procedures, respirators and aprons (225).

In inpatient units, the use of an apron is recommended for each suspected case. However, considering that overuse of PPE may impact supplies in situations of shortages (225). Following this rationale, in relation to non-invasive neuromodulation, appropriate protocols should be implemented for the single-use or cleaning or components—this applies not only to accessories that both contact patients (e.g., headgear) but to all surfaces, equipment, and cables (e.g., lead wires from the device). Still, additional precautions should be taken in patients under isolation because of COVID-19 and other infections (e.g., acinetobacter, clostridium), to avoid the risk of cross-infection.

Some essential aspects must be pointed out in relation to the hygiene of non-invasive neuromodulation equipment[1]. The recommended cleaning and disinfection procedures for healthcare equipment must be followed consistently and correctly. In particular, for the disinfection of small surfaces between uses (reusable equipment), the use of 70% ethyl alcohol is recommended (223). In cases of application of TMS, it may be important to use support for fixing the coil. If another associated intervention is not necessary, the therapist must maintain a distance of at least one meter, always monitoring the session and the patients' signals. We emphasize, as with any COVID-19 safety protocols, the appropriateness of googles, visors, protective visors, and other PPE, and relevant distancing protocols, for specific social and clinical environments, will ultimately be guided by on the current regional and institutional rules.

CONCLUSIONS

This paper presents empirical evidence, theoretical foundations, and rationale for the potential use of non-invasive neuromodulation techniques such as tDCS, rTMS, taVNS, and tcVNS in the management of COVID-19 related disorders. These techniques may be useful to modulate peripheral and central inflammation response, musculoskeletal and respiratory symptoms, and mental distress associated with COVID-19, even though neuroinvasiveness is still unclear. Thus, the potential benefits of non-invasive neuromodulation should be an important component of ongoing COVID-19 treatment research. Contributing with these international efforts, we made a web-based open-access guideline resource that centralizes all available information related to the use of non-invasive neuromodulation techniques in the management of COVID-19 symptons, including research results and treatment protocols.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

[1]https://psyarxiv.com/82bmu/ (accessed May 12, 2020).

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Active Video Games and Low-Cost Virtual Reality: An Ideal Therapeutic Modality for Children With Physical Disabilities During a Global Pandemic

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Current guidelines against spread of coronavirus (COVID-19) interrupt non-essential rehabilitation services. Thus, individuals with physical disabilities such as children with cerebral palsy can no longer benefit from physical rehabilitation during this undetermined period. Using either a synchronous or asynchronous format, in collaboration with a therapist via telerehabilitation, we suggest that active video games and low-cost virtual reality are a promising delivery mode for at-home rehabilitation in the context of a global pandemic. This therapeutic modality, incorporated into an at-home individualized treatment plan, provides a means to lessen the impact of an interruption in rehabilitation services while not loosing the pre-pandemic, in-person physical activity gains. Growing evidence supports active video games and low-cost virtual reality as viable therapeutic interventions for children with physical disabilities. These technologies are especially well-accepted by pediatric populations for the ludic and motivating features that lend themselves to nearly seamless incorporation into telerehabilitation. Advantages for rehabilitation of active video games and low-cost virtual reality include a rich, challenging, multi-modal training environment in which high numbers of movement repetitions can be accomplished, and a unique opportunity to foster engaged practice actions that go beyond household activities. We offer suggestions for the clinician about how to adopt active video games and low-cost virtual reality into your practice during a global pandemic.

Keywords: COVID-19, active video game, virtual rehabilitation, cerebral palsy, telerehabilitation

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INTRODUCTION

Current strategies to combat the Coronavirus (COVID-19) involve flattening the incidence curve and reducing the rate of spread, such as social distancing, school closures, and confinement of the population (1–3). While these preventives measure effectively reduce the rate of COVID-19 on a population scale, individuals with physical disabilities and their families are facing unique challenges, including disruption of daily routines, and limited access to rehabilitation programs (4). The World Confederation for Physical Therapy among several other professional associations worldwide recommends to either stop or post-pone rehabilitation services that are considered non-essential (5). In a recent survey of health professionals across 35 European countries (6),

rehabilitation outpatients' activities were stopped in 83% of countries, with an estimated range of 1.3–2.2 million Europeans deprived of rehabilitation services. The negative consequences of such an interruption is especially high for children with physical disabilities; a vulnerable population for which these critical services bring access to valuable resources that are essential to maintain physical abilities during natural development and prevent secondary complications. There are some important parallels to the global trends in aging and the increased prevalence of multiple chronic conditions that sparked development of a subfield in rehabilitation science at the nexus of new technologies, aging and disability (7). This perspective focuses directly on the impact of the COVID-19 response for children with physical disabilities. We propose that in-home therapy which enlists engaging technologies such as active video gaming and low-cost virtual reality, offers a promising solution to minimize the impact of long-term interruptions in rehabilitation services. Active video gaming is defined as video games that require interactive physical activity beyond being controlled passively through conventional hand controller (8). Virtual reality in the context of a rehabilitation program is described as an intervention delivered through virtual reality platforms that involves real-time simulation of an engaging environment and allows the user to interact via multiple sensory channels (9). These possible therapeutic modalities may be an ideal means to maintain and even advance gains achieved through in-person therapy and thereby prevent further functional decline likely to ensue as a consequence of interruptions in rehabilitation services.

Among children with physical disabilities typically followed by rehabilitation specialists, cerebral palsy (CP) is the most common neuromotor disorder in children (10) with a prevalence ranging from 1.5 to 2.5 per 1,000 live births (11–13) and an estimated lifetime cost of 1 million dollars (14). Children with CP and other pediatric populations with physical disabilities have a wide range of impairments, including muscle tone disorders (15), reduced sensation (16, 17), reduced aerobic capacities (18), and cognitive deficits (19, 20). Ultimately, these physical and mental impairments negatively affect most activities of daily living; this inevitably leads to reduced levels of participation in both leisure and physical activities (21, 22). Unfortunately, sensorimotor impairments very often perpetuate a lifetime cycle of degeneration of health status (18).

Aside from sensorimotor impairments, limited participation is attributed to a number of obstacles including: personal, socioeconomic status and environmental factors (23). Other hindrances include lack of community programs that cater to children with disabilities (24, 25), limited resources to adapt the environment (26) and lack of accessibility to resources for the parents (27). In the current global pandemic, confinement can accentuate these obstacles, thereby reducing opportunities to socialize with peers and to engage in adapted physical activities. These lost opportunities can further generate a vicious cycle of functional decline. Traditional, face-to-face rehabilitation interventions aim to reduce the impact of sensorimotor impairments and provide a means to circumvent these obstacles and assuage the effects of deconditioning to some extent, with some interventions being more effective than others (28). However, given that accessibility to face-to-face programs is greatly limited by the global pandemic, there is an urgent need for a creative solution to the interrupted services, but with full recognition that deferral of the rehabilitation specialists' role to that of a parent is not a desirable solution.

Recently, an expert group of clinicians, researchers and outpatient health program leaders proposed telerehabilitation as a promising strategy to maintain rehabilitation services during this unprecedented time (5). Telerehabilitation is defined as the provision of rehabilitation services via telemedicine methods and techniques (29). This is an ideal strategy to address health issues in low and middle-income countries and remote areas with perpetual restricted access to rehabilitation services (30, 31). This will not only benefit the children with physical disabilities to preserve social contact with their therapist, and maintain improvements already realized, but it could simultaneously reduce the burden on parents. However, telerehabilitation also presents several challenges including: limited training, knowledge and technology/equipment needed for both clinicians and parents as well as a structured therapy intervention (5). Telerehabilitation could be used to facilitate the delivery of rehabilitation services remotely, and the inclusion of active video games and/or low-cost virtual reality, that uses either a synchronous or asynchronous format, in collaboration with a therapist could provide a unique and engaging substitute for in-person services in the current global pandemic.

ACTIVE VIDEO GAMES AND LOW-COST VIRTUAL REALITY: A POTENTIAL SOLUTION FOR IN-HOME REHABILITATION

Active video games and low-cost virtual reality have the potential to engage school-age children and adolescents afflicted by physical disabilities to be physically active while sheltered at home and to continue their engagement with rehabilitation using technology-enhanced game-like interventions. Video games has a large penetration rate in the general population, with over 70% of U.S. families including a child who plays video games (32). Virtual reality, often delivered through low-cost systems, and active video games have increasingly been adopted in rehabilitation practices to mitigate sensorimotor impairments especially for children with CP (28, 33–35). The range of virtual reality technology used for rehabilitation purposes is wide and encompasses video games available commercially to custom-made virtual reality applications specifically designed for rehabilitation applications and with varying degrees of immersion. To demonstrate how rehabilitation services can be offered at home using a virtual reality platform, we focus on systems and applications easily adapted to the home context, including commercially available active video games and low-cost virtual reality applications (AVG/VR). We acknowledge that expensive and research-only virtual reality system may not be a suitable option to reach a large population of children with physical disabilities.

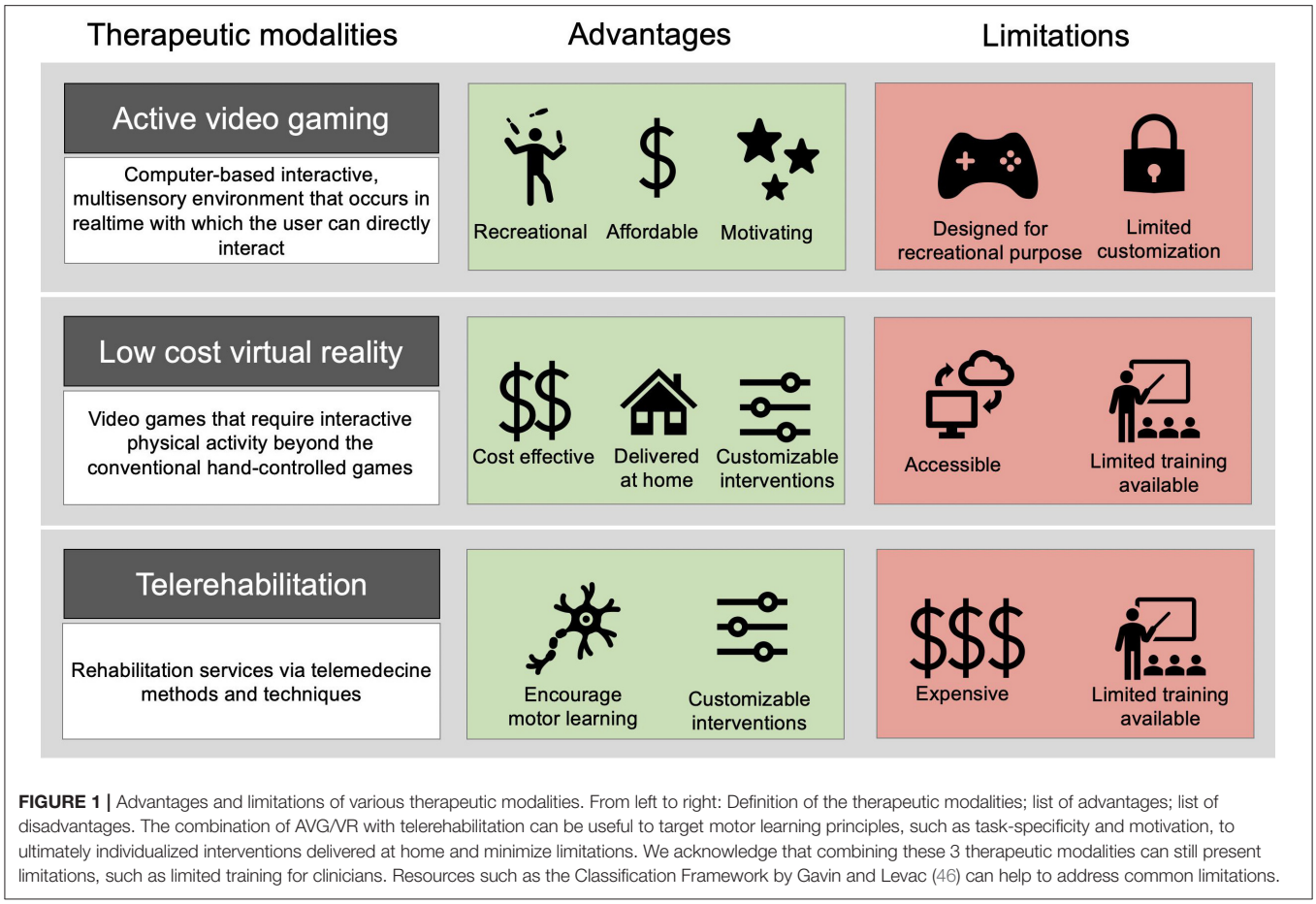


FIGURE 1 | Advantages and limitations of various therapeutic modalities. From left to right: Definition of the therapeutic modalities; list of advantages; list of disadvantages. The combination of AVG/VR with telerehabilitation can be useful to target motor learning principles, such as task-specificity and motivation, to ultimately individualized interventions delivered at home and minimize limitations. We acknowledge that combining these 3 therapeutic modalities can still present limitations, such as limited training for clinicians. Resources such as the Classification Framework by Gavin and Levac (46) can help to address common limitations.

How Can Active Video Games and Low-Cost Virtual Reality Applications Drive Retention of Motor Skills?

AVG/VR, grounded in principles of experience-dependent neural plasticity and motor learning, offers many advantages to deliver rehabilitation interventions at home. These include: intrinsic motivation, task salience, number of repetitions, intensity and duration, and challenging practice along with the provision of augmented feedback (36). Amidst the current confinement, AVG/VR enables a unique opportunity for skills practice that goes beyond simple household activities; these are engaging skills such as running on the beach, sword fighting or various outdoor sports. A recent study showed that children with physical disabilities are most likely to demonstrate improvements when participating in interventions that are structured, motivating and incorporate various recreation activities (37). Gamification elements, known to drive interest and engagement, are important features of AVG/VR. These very features are more likely to encourage children to be physically active, maintain attention and actively participate in play that is disguised as a rehabilitation program, performed at home and without the formal structure imposed by the rehabilitation setting itself (38–40). Empirical evidence supports progressive practice, that is engaging for the learner and optimally adapted to the individual's capability and the environmental context (41–43). AVG/VR provides the opportunity to customize progressions in task difficulty by incorporating spatial and temporal constraints (40) and to encourage sufficient movement repetitions to drive positive experience-dependent neuroplastic changes (36, 44, 45). Furthermore, meaningful performance feedback can be provided in the form of augmented information about the outcome of the movement and/or the elements of motor performance (17). Feedback type and delivery schedule can be manipulated with AVG/VR. Unlike most tasks performed in the real-world, feedback can be amplified to highlight components of movement performance and quality (44). The numerous benefits of AVG/VR can help clinicians to offer motivating and challenging in-home rehabilitation interventions using a technology often familiar to children and their families.

Despite the advantages of AVG/VR for rehabilitation, commercially available active video games are primarily designed for the general population and have limitations that should be acknowledged (**Figure 1**). Foremost, despite the popularity of these commercial video games, some consoles were discontinued (i.e., Wii™ and Kinect) by gaming companies over the last few years. While the consequences for clinicians remains unclear, this may have an important impact on the sustainability of this technology in rehabilitation (47). Nonetheless, the large

penetration rate of commercial video games consoles such as the Wii™ facilitates its accessibility. Another limitation is that many active video games do not all offer sufficient control over the difficulty progression and the task difficulty level may not be suitable for children with more severe motor impairments (48). This stresses the importance of rehabilitation specialists, such as occupational and physical therapists, in the selection of appropriate platforms to best accomplish the individualized treatment goals and for implementing an appropriate level of progression in task difficulty and specification of constraints. When incorporated into a comprehensive treatment plan that includes individualized goals, interventions using AVG/VR can promote the consolidation and retention of motor skills acquired through in-person therapy and in so doing, prevent functional decline mediated by the interruption of vital therapy services.

Evidence of the Effectiveness of Active Video Games and Low-Cost Virtual Reality in Children With Physical Disabilities

There is growing evidence that supports the use of AVG/VR in children with physical disabilities to achieve improvements across the domains of the International Classification of Functioning, with the bulk of evidence coming from studies of children with CP (28, 33, 40, 46, 49–52). Several studies report the possibility to attain light to moderate levels of physical activity while playing various active video games such as boxing and dancing (53, 54). Active video game practice has been shown to improve voluntary weight shift control while standing for children with CP during a skiing game and standing balance following a short intervention (55, 56). Some preliminary evidence supports the use of AVG/VR to improve upper limb function in children with CP as demonstrated by either kinematic analyses (54, 57) or clinical measures (46, 49, 58–60). Lastly, interventions using AVG/VR can facilitate the transfer of motor skills to the real-life situation, as evidenced by completion of activities of daily living (54, 61, 62). AVG/VR has potential to preserve prior functional improvement and prevent an inevitable decline that will likely occur after a prolonged period in which physical activity is limited (63). While the results are encouraging, the level of evidence is still limited and cannot be generalized across conditions and to all severity of physical disabilities. Moreover, these results were done in a controlled environment with supervision of a clinician ensuring a high adherence and motivation. To reduce the impact of these limitations, the combination of telerehabilitation and AVG/VR, which may facilitate improvements beyond simple maintenance by providing a means to deliver challenging and motivating task-oriented practice and allow the clinician to track progress. To date, many studies from different research groups demonstrate the feasibility to deliver in-home rehabilitation using AVG/VR (either with or without telerehabilitation) for children and adolescents with physical disabilities (64–68). These studies, along with the increasing evidence to support the use of AVG/VR for pediatric physical rehabilitation highlight the potential that this emergent technology has if delivered in participants' home to improve task outcomes and motor function in the current global pandemic.

DISCUSSION AND RECOMMENDATIONS FOR CLINICAL PRACTICE

More than ever, children with physical disabilities whose accessibility to rehabilitation services is limited, are more likely to adopt sedentary behaviors (69). Sedentary behavior, physical inactivity and health deconditioning are also likely to be exacerbated due to the confinement and school closures. We propose to leverage AVG/VR to deliver in-home rehabilitation to: (1) minimize the impact of limited rehabilitation services, (2) encourage children with physical disabilities to be physically active within their home environment, and (3) maintain a level of function during this unprecedented global pandemic. With a growing evidence-base in support if AVG/VR in children with physical disabilities, in-home rehabilitation using AVG/VR offers new opportunities to integrate key principles of experience-dependent neuroplasticity and motor learning in the home environment to drive retention of motor skills (i.e., intrinsic motivation, task salience, number of repetitions, intensive and challenging practice, provision of augmented feedback).

Clinicians play a crucial role in selection of an appropriate platform and games to meet individual rehabilitation needs and goals. Clinicians can work with parents and children to explore suitability of various games and consoles already available to the home environment. While frequent follow-up may not be possible, clinicians can offer guidelines on intensity of physical activity, the nature of movement, amount and frequency of active movement and adjustment to the therapeutic goals for each child (70). Results from a recent cross-sectional survey suggests that only ∼50% of clinicians have clinical experience using active video games or virtual reality, with lack of knowledge about virtual reality systems, and time to implement them into practice, identified as important barriers to address (71). Resources and knowledge tools can be used to support clinical decision-making about AVG/VR and facilitate the integration into clinical practice. Among already available resources, the "Kinecting with Clinicians" resource (72) and the Nintendo Wii™ game analysis (73) can be used for clinicians to weight the pros and cons of two commercially available active video games. It is also important to note that while the Wii™ and the Kinect are discontinued, other platforms and devices, such as the PlayStation®VR and SteamVR platforms, are currently available, which offer a wide range of active video games that could also be used for rehabilitation purposes. The evolution in AVG/VR technology is rapid and progresses faster than the evidence, which remains a challenge for clinical practice. Two frameworks could help to guide clinical decision-making in gaming choices for therapeutic use: the Classification Framework of pediatric virtual reality systems (46), and the systematic framework (74). As an example, we use the Classification Framework (50) to illustrate how frameworks can be used to guide clinical practice, once AVG/VR systems available in the home environment have been identified. Clinicians can use this framework to identify and select systems and games that

can provide multisensory feedback, the opportunity to perform 3D movement to interact with the virtual environment and consistent practice repetitions. As a second step, clinicians can use the seven categories of the framework, such as the ability to manipulate and measure therapeutically relevant variables or the specific movement capacities required, to quickly identify which system meets the needs of the child they are working with or of their current settings. We encourage clinicians to become familiar with AVG/VR prior to adopt it with a child to minimize technical difficulties. When available, the use of clinical champions can also help to foster the development of knowledge and skills of clinicians and facilitate implementation of AVG/VR (75). The choice of platforms and systems often relies of the game consoles available at home. Nonetheless, games incorporating physical activity available on popular gaming consoles (e.g., Nintendo Wii™, PlayStation®VR) should be prioritized since they are user-friendly, interactice and were developed specifically to entice children and adolescents for continuous usage. Guidelines about telerehabilitation from professional associations can be valuable resources help address common barriers to telerehabilitation and facilitate the delivery of remote rehabilitation services (76, 77). To better support clinicians who wish to integrate VR into their practice, our ongoing work includes a systematic review to describe different platforms and active video games in relation to the principles of motor learning (Prospero registration: CRD42020151982).

The past few months taught us that people around the world can develop creative solutions to adapt to the COVID-19 pandemic. The use of AVG/VR could be one creative and evidence-based solution to guide clinicians in the delivery of challenging and motivating in-home physical rehabilitation activities to drive a positive impact on the lives of children with physical disabilities.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MD and MR conceived the presented idea. MD, OM, and MR critically reviewed the literature. All authors discussed the results and contributed to the final manuscript.

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REVIEW
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Acute Ischemic Stroke in SARS-CoV, MERS-CoV, SARS-CoV-2: Neurorehabilitation Implications of Inflammation Induced Immunological Responses Affecting Vascular Systems

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Coronaviruses (CoVs) are enveloped RNA viruses and have been shown to cause mild to severe respiratory infections in humans, with some severe cases inducing neurological manifestations. The lethality and Neurological effects of the Severe Acute Respiratory Syndrome (SARS-CoV), Middle-East Respiratory Syndrome (MERS-CoV), and recently the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) have been well documented though currently there is little literature regarding long term effects and the implications for neurorehabilitation. SARS-CoV-2 and MERS-CoV have been linked to the infection associated inflammatory cytokine storms and induced hypercoagulopathic states that affect the entire vascular system including that of the brain. This mini-review provides an overview of the commonalities among studies published on all three types of the coronavirus related to acute ischemic stroke (AIS). The aim was to elucidate the physiological mechanisms underpinning COVID-2 and to reflect the similarities with the chronic inflammation induced symptoms of AIS that are likely to prove a further challenge for neurorehabilitation clinicians post COVID. In terms of increased incidence of COVID and AIS, it is likely that in depth knowledge of increased thrombotic risk in this population will require appropriate anticoagulation treatment, and other therapeutic interventions as well as neurorehabilitation interventions. Lastly the risk of spreading the virus requires further balancing of the provision of neurorehabiliatation services useful to the patient.

Keywords: COVID-19, hypercoaguability, ACE—angiotensin-converting enzyme, rehabilitation, SARS, MERS, SARS-CoV2, inflammation

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INTRODUCTION

Currently, four genera of *Coronavirina* have been identified, three of which can infect mammals (1). Alpha and beta coronaviruses include the Severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (2, 3). Extensive research in the last two decades has traced the evolutionary

origins of these organisms to warm-blooded flying vertebrates where they are non-pathogenic (4). Indeed, a molecular epidemiological study conducted by Woo et al. in 2012 suggests that bats are the most likely sources of coronaviruses and that bats have been instrumental in its widespread dissemination and evolution since 8100 BC (5). The primary entry point of the coronavirus family is the angiotensin-converting enzyme 2 (ACE2) receptor which is ubiquitous across human tissues, especially on epithelial and endothelial cell surfaces. ACE2 plays a vital role in the transmission of the virus as the targeted receptor of the SARS-CoV-2, virus, especially on the epithelia of the respiratory system. Impairment of normal functioning of the ACE2 receptors following the invasion of the virus leads to down regulation of the Renin Angiotensin Aldosterone system (RAAS) and cascade of inflammatory events culminating in pneumonia, severe acute respiratory distress syndrome, multi-organ failure and has led to numerous fatalities during earlier regional outbreaks in China (SARS-CoV), Saudi Arabia (MERS-CoV), and globally SARS-CoV-2 (6). The presence of the ACE2 receptor in other tissues such as the gut, cardiac muscles, and the glial cells of the nervous system contributes to its myriad of manifestations (7–9). Neurological manifestations of coronaviruses were first described during the SARS CoV epidemic in 2002 (10). Tsai et al. reported cases of neuropathies, myopathies, and strokes during the SARS I epidemic while encephalitis and acute inflammatory demyelinating polyneuropathy (AIDP), and Gullian-Barre syndrome (GBS) have also been described in patients with MERS-CoV by Kim et al. (10, 11). Currently, during the SARS-CoV-2 pandemic, an increasing number of patients have presented with stroke and other neurovascular complications as well as the aforementioned manifestations (9, 12).

The following research questions guided this mini review:

a. What is the incidence of stroke among patients with SARS, MERS, and SARS-CoV-2?
b. What are the main pathophysiological mechanisms of acute ischemic stroke in patients with SARS, MERS, and SARS-CoV-2?
c. What are the potential/best treatment options for best clinical outcomes of stroke patients with SARS, MERS, and SARS-CoV-2?
d. What is the balance between treating patients while maintaining the case management tailored to avoid the diffusion of infection?

METHODS

Search Strategy

The concepts of this mini review included studies reporting on the incidence, treatment options, and challenges of ischemic stroke patients with confirmed SARS, MERS, and SARS-CoV-2 infection.

The following search strategy was followed (13):

1. In the first step MEDLINE, Cochrane, and CINAHL databases were searched, followed by title and abstract search.
2. In the second step, the keywords were used when searching on Ovid MEDLINE, Cochrane, PubMed, CINAHL, and EMBASE databases.
3. In the last step, a manual search was carried out to ensure no study was inadvertently left out.

The keywords used to conduct the search were: Stroke, thrombosis, coronavirus, neurorehabilitation, neurological complication, SARS-CoV, MERS-CoV, coronavirus, COVID19, SARS-CoV-2, and autopsy.

Study Methodologies

Most of the studies included were case reports and case series. Six of the publications were retrospective cohorts while the rest were systematic reviews and commentaries; See **Table 1** for key papers.

RESULTS

The Incidence of Stroke With SARS, MERS, and SARS-COV2

The occurrence of stroke in patients with coronavirus infection was first detailed by Umapathi et al. in four out of the 206 patients with SARS infection in Singapore in 2002. All patients presented with large vessel occlusion (14). Two patients with ischemic stroke (IS) and intracerebral hemorrhage (ICH) were also described in MERS-CoV-infected patients in Saudi Arabia during the 2002 epidemic (15, 17). Most recently, there has been growing concerns about the occurrence of stroke, predominantly affecting large vessels, among confirmed SARS-CoV-2 cases (25). The World Stroke Organization (WSO) has recently identified that stroke increases the severity of SARS-CoV-2 infection by 2.5-fold (21, 41).

While much of the focus has been on cardiovascular, pulmonary, and hematologic complication, there has been a corresponding increase in morbidity and mortality due to neurological complications. According to Bridwell et al. (42), these include acute cerebrovascular events, encephalitis, Guillain-Barré syndrome, acute necrotizing hemorrhagic encephalopathy, and hemophagocytic lymphohistiocytosis (42). Pre-existing neurological conditions have also been linked to more severe COVID-19 infections. It has been documented that elderly patients with chronic medical conditions who contract COVID-19 can present with acute encephalopathy and altered level of consciousness (43).

According to level 1 evidence, "remdesivir therapy in mild to severe disease, and the triple medication regimen (lopinavir-ritonavir, ribavirin, and interferon beta-1b) in mild to moderate disease are promising agents against SARS-CoV-2 in terms of symptom improvement and time to a negative RT-PCR, while further studies are needed (25). However, many of the recently proposed medications, such as antivirals and antimalarials have significant drug interactions and side effects, especially with patients with prior strokes (42). It is important that medical staff are cognizant of potential neurological complications when treating COVID-19. Because some of the neurological manifestations tend to occur early in the illness, neurologists, and neurorehabilitation teams need to be involved, alert, and prepared during the pandemic period (44).

TABLE 1 | Summary of studies on acute ischemic stroke patients with human SARS, MERS, SARS2 (13).

Author, year, country	Title	Study design	Study population and sample size	Key findings
SARS-CoV studies				
Umapathi et al. (Singapore) 2004 (14)	Large artery ischemic stroke in severe acute respiratory syndrome (SARS)	Retrospective cohort	Two hundred and six patients with confirmed SARS	Age ranges of ischemic stroke patients were 39–68. Vascular risk factors were present in 2/5. Five had large artery cerebral infarctions IVIg and anticoagulation was given in 3/5 of the patients 3/5 died
MERS-CoV studies				
Arabi et al. (Saudi Arabia) 2015 (15)	Severe neurologic syndrome associated with middle east respiratory syndrome corona virus (MERS-CoV)	Case series	Not applicable	Three patients with confirmed MERS-COV and concomitant neurologic manifestations with one presenting as stroke. 65M DM, HPN with bilateral ICA stenosis. Patient died
Al-Hameed et al. (Saudi Arabia) 2017 (16)	Spontaneous intracranial hemorrhage in a patient with middle east respiratory syndrome corona virus	Case report	Not applicable	42F with confirmed MERS-COV presenting with massive ICH with IV extension. Patient died
Alghatani et al. (Saudi Arabia) 2016 (17)	Neurological complications of middle east respiratory syndrome coronavirus: a report of two cases and review of the literature	Case series	Not applicable	Two patients with confirmed MERS-COV and concomitant neurologic. manifestations with one presenting as stroke. 34F, HPN, DM with intracranial hemorrhage. Patient died
SARS-CoV2 studies				
Lodigiania et al. (Italy) 2020 (18)	Venous and arterial thromboembolic complications in COVID-19 patients T admitted to an academic hospital in Milan, Italy	Retrospective cohort	Three hundred and eighty eight consecutive patients with laboratory- proven COVID-19	Eight of the 28 thrombotic complications were acute ischemic stroke. Ages from 64-76. Three of the eight patients had elevated D-dimer. All patients were anticoagulated. 25% of the cases died
Klok et al. (Netherlands) 2020 (19)	Incidence of thrombotic complications in critically ill ICU patients with COVID-19	Retrospective cohort	One hundred and eighty four patients with proven COVID-19 pneumonia	Three of the 31 thrombotic complications were acute ischemic stroke
Mao et al. (China) (9)	Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China	Retrospective cohort	Two hundred and fourteen patients with coronavirus disease	Six patients had ischemic stroke. Among the severe patients, 4 had ischemia while 1 had ICH. In the non-severe group, 1 had ischemia
Meza et al. (Spain) 2020 (20)	Ischemic stroke in the time of coronavirus disease 2019	Retrospective cohort	Three hundred and fifty four patients with ischemic stroke	Six out of 28 stroke patients tested positive for COVID-19
Aggarwal et al. (USA) 2020 (21)	Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature	Systematic review and metanalysis	Four studies with a sample of 1,829 confirmed COVID-19 patients (553, 30.2% being severe cases)	About 2.6% of 49 patients had a history of cerebrovascular disease or stroke. Experiencing severe COVID-19 was a higher among patients with a history of CV disease (OR = 2.5)
Pranata et al. (Indonesia) 2020 (22)	Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19—systematic review, meta-analysis, and meta-regression	Systematic review and metanalysis	A total of 4,448 patients were obtained from 16 studies	CV disease was associated with borderline significant for severe COVID-19 [RR 1.88 [1.00, 3.51], $p = 0.05$; I^2: 87%]
Viguier et al. (France) 2020 (23)	Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection	Case report	Not applicable	73F with SARS-COV 2 symptoms 7 days prior to presenting with acute stroke. Thrombus seen at the L CCA
TUNÇ et al. (Turkey) 2020 (24)	Coexistence of Covid-19 and acute ischemic stroke	Case series	Not applicable	Four stroke patients thatdiagnosis of Covid-19 Ages between 45-77. Hypertension was present in 3/4 cases. They presented with COVID symptoms 1–4 days from diagnosis of stroke. Three patients had elevated D-dimer levels, and two of them with high C-reactive protein (CRP).

(Continued)

TABLE 1 | Continued

Author, year, country	Title	Study design	Study population and sample size	Key findings
Oxley et al. (USA) 2020 (25)	Large-vessel stroke as a presenting feature of Covid-19 in the young	Case series	Not applicable	Five stroke patients with diagnosis of SARS-COV2 from USA. Ages are 33–49. Four of the five are males with risk factors of HPN, DM and Dyslipidemia. Abnormalities in ferritin, fibrinogen, and D-dimer were noted in most of the patients. Large vessel occlusion were noted in all of the patients with 4/5 undergoing clot retrieval. No deaths were documented
Valderrama et al. (USA) 2020 (26)	Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke	Case report	Not applicable	52M with HPN with SARS-COV symptoms 7 days prior to presentation. Fibrinogen and D-dimer were elevated. CTA showed ICA occlusion
Beyrouti et al. (UK) 2020 (27)	Characteristics of ischemic stroke associated with COVID-19	Case series	Not applicable	Six stroke patients with diagnosis of SARS-COV2 from UK. Ages are 53–83. Five of the six are males with risk factors of HPN, DM, AF, and Dyslipidemia. Abnormalities in ferritin, fibrinogen and D-dimer were noted in most of the patients. APAS and anticardiolipin antibodies was present in 1 patient while lupus anticoagulant was positive in 5/6. 5/6 patients had large vessel occlusion and most were treated with anticoagulation
Avula et al. (USA) 2020 (12)	COVID-19 presenting as stroke	Case series	Not applicable	Four stroke patients with diagnosis of SARS-COV2 from USA. Ages are 73–88. Three of the four are females with risk factors of HPN, DM, and Dyslipidemia. Leukocytosis was present in 2/4 patients. D-dimer was elevated in 2/4. Large vessel occlusion was seen in 2/4 while stenosis was present in 1/4. Half of the patients died
Berekashvili et al. (USA) 2020 (28)	Etiologic subtypes of ischemic stroke in SARS-COV-2 virus patients	Case series	Not applicable	Ten ischemic stroke patients with diagnosis of SARS-COV2 from USA. Ages are 30–80 years. Six of the 10 are females with risk factors of HPN, DM and Dyslipidemia. Abnormalities in ferritin, fibrinogen and D-dimer were noted in most of the patients. Large vessel occlusion were noted in 5/10 of the patients with three undergoing clot retrieval. Four of the 10 patients died
Moshayedi et al. (USA) 2020 (29)	Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion associated with coronavirus infection	Case report	Not applicable	80M with HPN diagnosed with stroke 5 days after experiencing SARS-COV2 symptoms. MRA showed M1 occlusion. Patient was anticoagulated with Heparin but died subsequently
Co et al. (Philippines) 2020 (30)	Intravenous thrombolysis for stroke in a COVID-19 positive filipino patient, a case report	Case report	Not applicable	62F with HPN, DM and dyslipidemia presenting with stroke symptoms 14 days after onset of SARS-COV2 symptoms. Ferritin, D-dimer and CRP were elevated. CTA showed left M1 stenosis. Patient was thrombolysed and discharged with good outcomes
Deliwala et al. (USA) 2020 (31)	Encephalopathy as the sentinel sign of a cortical stroke in a patient infected with coronavirus disease-19 (COVID-19)	Case report	Not applicable	31F with no known vascular risk factors presenting with encephalopathy 5 days prior to experiencing SARS-COV 2 symptoms. CTB showed acute infarct in the right frontal region. She received therapeutic anticoagulation and discharged to rehab subsequently.

(Continued)

TABLE 1 | Continued

Author, year, country	Title	Study design	Study population and sample size	Key findings
Hess et al. (USA) 2020 (32)	COVID-19-related stroke	Commentary	Not applicable	SARS-CoV-1 & 2 deplete ACE2 via receptor endocytosis upon viral entry, leaving ACE1 unopposed with generation of angiotensin II. Angiotensin II worsens lung in- jury and also worsens endothelial function in organs like the heart and brain
Schulman et al. (Canada) 2020 (33)	Coronavirus disease 2019, prothrombotic factors, and venous thromboembolism	Review	Not applicable	Evidence of increased expression in the urokinase pathway involving pro- and antifibrinolytic genes, resulted in increase in plasminogen peptides associated with increased urokinase activity
Amiral et al. (France) 2020 (34)	Covid-19, induced activation of hemostasis, and immune reactions: can an auto-immune reaction contribute to the delayed severe complications observed in some patients?	Review	Not applicable	The delayed autoimmune response contributes to the cytokine storm and generate tissue injury and destruction
Calcagno et al. (Italy) 2020 (35)	Rising evidence for neurological involvement in COVID-19 pandemic	Review	Not applicable	SARS-CoV- binds to the ACE2 receptor on vascular endothelial cells, resulting in abnormally increased blood pressure. Along with platelet and coagulation dysfunctions, the abnormally high blood pressure contributes to the increased risk of intracranial hemorrhage in COVID-19 patients.
Debuc et al. (France) 2020 (36)	Is COVID-19 a new hematologic disease?	Review	Not applicable	The resultant cytokine storm may also cause a surge in interleukin (IL)-2, IL-7, interferon-γ, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α leading to hyperinflamation. This systemic inflammation causes severe encephalopathy in the patient, and that may lead even to stroke.
Varga et al. (Switzerland) 2020 (37)	Endothelial cell infection and endotheliitis in COVID-19	Case series	Not applicable	Endothelial dysfunction was a main determinant of microvascular dysfunction.
Escalard et al. (France) 2020 (38)	Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19	Case series	Ten patients with confirmed COVID-19 treated for an acute ischemic stroke due to LVO	Best medical care including early intravenous thrombolysis, and successful and prompt recanalization achieved with mechanical thrombectomy, resulted in poor outcomes in patients with COVID-19. 6 patients (60%) died during hospitalization. Despite high angiographic recanalization rates and timeframes, none of our patients had dramatic neurological improvement 24 h after MT.
Zubair et al. (global) 2020 (39)	Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review	Review	Not applicable	The pathophysiology of increased risk of cerebrovascular disease during COVID-19 infection is likely multifactorial. Common abnormal laboratory test results in patients include elevated leukocyte count, C-reactive protein level, D-dimer level, ferritin level, and lactate dehydrogenase level. 81 Severe cases are characterized by elevated inflammatory markers and hypercoagulability compared with moderate cases and with increased likelihood of stroke.
Benussi et al. (Italy) 2020 (40)	Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy	Retrospective, single-center cohort study	Fifty six were positive and 117 were negative for COVID-19	Patients with COVID-19 admitted with neurological disease, including stroke, have a significantly higher in-hospital mortality and incident delirium and higher disability than patients without COVID-19

A literature review of neurological manifestations and complications of COVID-19 suggests that most commonly reported symptoms include headache, dizziness, hypogeusia, and neuralgia, followed by stroke, seizures, encephalopathy, and delirium (45, 46). It also highlights that some of the neurological manifestations can precede the typical manifestations such as fever, cough, sore throat, and headaches. The neurological damage caused by COVID-19 can be divided into central and peripheral effects and is likely due to hypoxic brain injury and immune mediated damage to the central nervous system. Currently, the proportion of patients with neurological manifestations is much smaller compared to those with respiratory disease. However, as the pandemic progresses, it is expected that the overall number of patients with neurological symptoms will increase. Neurological complications such as stroke and encephalitis can cause lifelong disability, resulting in long term care needs, associated rehabilitation needs and large health, social and long-term care needs and large health, social, and economic costs (47).

While the incidence of stroke among hospitalized patients with Covid-19 is relatively low, patients in their 30s, 40s, and 50s diagnosed with COVID-19 have presented with large-vessel occlusion stroke (25). Social distancing and isolation are important preventive measures; however, patients with acute neurological symptoms delaying calling an ambulance because of concerns about going to a hospital during the pandemic may contribute to poor outcomes. While strokes occurring in younger, asymptomatic patients with COVID-19 are concerning, patients not seeking care for symptoms of stroke are equally worrying. The overall incidence is low; however, the prognosis of acute ischemic stroke among young adults with COVID-19 is grim. There is evidence that young asymptomatic people are developing clots that cause major stroke. In a small sample, the mortality rate among the COVID-19 patients was 42.8%; the typical mortality from stroke varies between 5 and 10% (45).

Three cases of stroke were also reported during the MERS-CoV epidemic affecting more than 2,500 patients globally so far (48). Majority of the patients were males (66%) older than 45 years (66%). Only one patient was younger than 45 (33%). The average age was 54 years old. The majority had a previous history of HPN (66%), and all suffered from DM (100%). Only one (33%) had a prior history of stroke. All three patients died.

In the most recent SARS-CoV2 pandemic, stroke has been one of the main vascular complications documented. Of the total SARS-CoV2 patients identified in the reported studies, number of males and females are quite comparable; A quarter younger than 45 years, and around half older than 65.

In a university hospital in Italy, among 388 symptomatic and laboratory-confirmed SARS-CoV-2 patients, eight (2%) were diagnosed (after testing positive for COVID) to have ischemic stroke (18). Klok et al. also recorded the occurrence of ischemic stroke in 1.6% (3/188) of all SARS-CoV-2 pneumonia patients admitted in the intensive care unit (ICU) Netherland (19). Neurologic manifestations were also reported in 214 cases in Wuhan, China and among these, five (2.3%) patients presented with ischemic stroke (9). Conversely, Meza et al. reviewed 354 ischemic stroke patients admitted in a local hospital in Italy from December to April and 0.8% of them tested positive for SARS-CoV-2 (20).

While there is increasing evidence of the comorbid occurrence of strokes among patients with coronavirus infection, there is also substantial evidence that pre-existing cerebrovascular disease led to worse clinical outcomes (21, 22). A pooled analysis involving four studies has been performed by Agarwal et al. and has shown that a previous history of stroke increases the severity of SARS-CoV-2 disease by 2.5 times (21). The same trend was observed in another study concluding that cerebrovascular disease among SARS-CoV-2 patients increased the risk of poor outcome and mortality with a relative risk of 2.04 and 2.38, respectively (22).

The Immunological and Thrombotic Mechanisms

Preliminary evidence shows a pro-coagulatory state associated with COVID-19 infection and development of ischemic stroke (40). There is also evidence that COVID-19 patients admitted with neurological disease, including stroke, have a significantly higher incidence of in-hospital mortality, incident delirium, and higher disability than patients without COVID-19 (49).

Various theories have been proposed as the putative mechanism leading to the increased occurrence of stroke in patients with coronavirus infection. Schulman et al. describe thrombosis to be associated with over activation of the immunosystem and hypercoagulation of the blood through the body including in the brain (33). Another hypothesis proposed is the imbalance in the expression of ACE1/ACE2 as a result of the preferential affinity of the SARS-CoV-2 to ACE2 receptors causing a disproportionate increase in the ACE1/ACE2 balance which has pro-inflammatory and organ damaging effects (32). Thus this mini- review aimed to report on the incidence of stroke among patients with SARS, MERS, and SARS-CoV2- and to elucidate the role of immunological and hypercoagulable mechanisms in acute stroke patients with SARS-CoV, MERS-CoV, and SARS-CoV-2 infection and its pathogenesis.

Immunological Mechanisms

Various mechanisms have been postulated for the pathogenesis of stroke in patients with coronavirus infection. This includes triggering of the immunological pathways, which results in the activation of the macrophages by the granulocyte–macrophage colony-stimulating factor (GM-CSF) (33). This results in a cytokine surge with a concomitant release of large amounts of Interleukin-6 and other cytokines and chemokines such as interleukin (IL)-2, IL-7, interferon-γ inducible protein 10(IP-10, CXCL10), monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α (33, 36). These phenomena are reported to be responsible for the cytokine storm triggered by the hyperinflammatory state known to affect blood vessels and further cascade of negative effects in hemostasis leading to vasoconstriction and a prothrombotic state (36, 37). This is further supported by autopsy findings of endotheliitis in patients with SARS-CoV-2 (37). Another hypothesized mechanism is the development of allo-antibodies to ACE2, which also generate a delayed immune response which contributes further to the cytokine storm (34). This state also disrupts

the body's physiological capacity to regulate inflammatory and hemostatic processes leading to prothrombotic, pro-inflammatory state and multi-organ damage (34, 50).

Disruption of the ACE1-ACE2 Balance

Direct attack and damage of the SARS-CoV-2 on the ACE2 receptors of the glial cells of the brain is another putative mechanism for the occurrence of cerebral thrombosis among infected patients (32). Normal activation of ACE-2 is known to be neuroprotective and counteracts the ill effects of the ACE1/angiotensin II/AT1 axis (32). Its depletion favors the activity of the latter, which may lead to a hyperinflammatory state and a cascade of damaging effects to target organs. Direct binding of the virus to the receptors on the endothelial cells may also impair blood pressure control mechanism and oxygen and glucose transfer to cells which may further induce neurological damage (35).

The Treatment Options and Outcome

Patients comorbid for coronavirus infection and stroke have usually been treated acutely with standard care regimens such as intravenous thrombolysis and endovascular clot retrieval (ECR) as per standard acute stroke guidelines. Three of the five stroke patients during the SARS-CoV pandemic were treated with intravenous immunolglobulin (IVIg). Three out of four MERS-CoV patients were treated with antibiotic and one with IVIg.

Other therapeutic options are currently being investigated including, recombinant ACE2, which may act primarily by competing with he SARS S protein and prevention of the depletion of the receptors (32). Humanized monoclonal antibodies such as tocilizumab and sarilumab, that block the Il-6 receptor have also shown potential in the treatment of vascular complications of human coronavirus (36).

Neurorehabilitation Challenges

The rapid spread of COVID-19 has become a pandemic emergency departments, choking emergency departments, infectious diseases, and intensive care units. Rehabilitation services have also become affected, causing radical changes both in the organization and in the operating methods (51). Major changes in structure and function of neurorehabilitation and rehabilitation activities during COVID-19 emergency are required, carefully balancing the provision of services useful to the patient and the reduction of the risk of spreading the virus. Stroke in patients with coronavirus infection confers poor clinical outcomes.

DISCUSSION

Current figures indicate that stroke is not unusual in COVID patients and in fact incidence figures are likely to be a gross underestimation given the novelty of the virus and the fact that imaging is not often undertaken to ascertain cerebro-vascular events. Indeed, confirmatory brain imaging is unusual in COVID-19 patients as they usually require sedation and ventilation.

Eight thousand and ninety-eight cases of SARS infections were reported by WHO during the 2003 outbreak with 10% (774) mortality rate (48). Of these, five patients with an average age of 58 were further identified as suffering a stroke associated with SARS-CoV. Out of these five, three died for a 60% mortality. The high rate of thrombotic complications and the uniform pattern of large vessel ischemic strokes suggested a pro-coagulant state among patients infected with SARS-CoV (14).

While the confirmed cases of MERS-CoV were less than SARS-CoV with around 2,495 cases confirmed worldwide, the reported mortality rate was more than three times higher (585/35%). Three cases of stroke related MERS-CoV were reported. The average age was 54 years and mortality rate of 100% (i.e., 3 out of 3).

To date, COVID-19 has been associated with published cases of stroke among individuals with a mean age of around 65. A quarter of patients were younger than 65 years of age. Hypertension, diabetes, smoking, dyslipidemia are among the reported risk factors for stroke among these patients through in many of these patients a comprehensive stroke work up is not available.

Owing to the immunological nature of the disease, immunoglobulin supplementation has been used in three SARS CoV-1 patients with stroke (14). Currently, there is no published evidence of immunoglobulin use among MERS and SARS-CoV-2 patients. As of July 2020, the majority of COVID-19 patients who also experienced AIS in the US also showed high cerebrovascular risk factors (52). Furthermore, there is still a large gap in the literature regarding underlying mechanisms of stroke in human patients with coronavirus infection.

Preliminary reports (53) suggest that there are three predominant COVID-19- related mechanisms independent of risk factors. These include the hypercoagulable state, vasculitis, and cardiomyopathy (53). It has been postulated that the affinity of the SARS-CoV-2 for ACE2 receptors in the brain allows the virus to damage intracranial arteries, causing vessel wall rupture. Poyiadji et al. (54) suggesting that it is possible that the cytokine storm that accompanies the wall rupture might be the cause of hemorrhagic strokes. This was evident in a COVID-19 patient who developed an acute necrotizing encephalopathy associated with late parenchymal brain hemorrhages. Examining hospitalized patients with COVID-19.

Franceschi et al. (55) found that a combination of cytokine release syndrome and direct SARS-CoV-2–mediated breakdown of the blood–brain barrier may be responsible for hemorrhagic posterior reversible encephalopathy syndrome. In COVID-19 patients, there has also been secondary hemorrhagic transformation of ischemic strokes which may happen in the setting of endothelial damage or a consumption coagulopathy accompanying COVID-19 (53).

Further research is needed to elucidate the role or roles that the activation of the immunological and hypercoagulable pathways and specific risk factors potentially play in underlying susceptibility to coronavirus infection and associated stroke to facilitate the design of better treatment options in the future.

Currently, the total global data on stroke epidemiology during the COVID-19 pandemic is obviously not available. This review provides comprehensive but preliminary assimilation of anecdotal observations, case reports, single center experiences worldwide to date. Anecdotal reports have confirmed a reduction

in single event stroke admissions to the hospitals during the global pandemic (47, 56) raising questions whether this is causing more collateral damage by keeping definite mild strokes at home and making these patients more vulnerable to post stroke depression, anxiety, poor quality of life? All these possibilities are hypothetical at present. Only well-designed, prospective research studies will be able to answer these speculations.

Implications for Recovery and Rehabilitation

As of this writing, there are almost 30 million global cases of COVID-19, with global deaths quickly approaching one million. Over 20 million people have recovered from the disease (57). However, there seems to be very little constructive evaluation of what recovery means in the context of a pandemic where the number of infections continues to increase daily, and a small number of cases of reinfection, possibly via a more recent mutated version of the virus are beginning to appear. Among those reported in the press as no longer hospitalized, there is also a growing number who claim that although home they are far from fully recovered with ongoing problems of fatigue, continuing chest and breathing difficulties and mental health issues (58). What rehabilitation is available to such dehospitalized patients remains to be rigorously investigated.

Lastly, the nature of the virus means that until an effective generalized vaccine exists, the protocols of rehabilitation must change. Social distancing, masks, and telehealth format mean alternate devices for remote continuous physiological monitoring of a patients' health must be made available and incorporated into design of management regimes. In particular, measures of activity, oximetry, heart rate variability, and blood pressure for monitoring of oxygen availability and cardiac output are required during exercise routines and as physiological measures of sleep efficiency that act as surrogate measures of mental health (59).

Limitations of This Review

This review has been limited to publications in the English language. Most of the publications describe the experience in managing acute stroke patients with SARS-CoV-2, as the far smaller numbers associated with MERS and SARS-CoV necessarily meant there were less comorbid examples of SARS and stroke and hence predominantly case studies. Furthermore, in most cases only patients with ischemic stroke were extensively reviewed, possibly because patients with hemorrhagic strokes died early.

CONCLUSION

Patients with COVID-19 exhibit a higher risk of acute ischemic stroke compared with patients with other respiratory tract infections. It is important that medical staff are cognizant of potential neurological complications when treating COVID-19. Health personnel engaged in acute stroke care are at risk of acquiring COVID-19 infection from stroke patients with COVID-19 infection.

There is an increased number of reported strokes during the current COVID-19 pandemic with far greater incidence and apparent contagion rates. Patients with COVID-19 exhibit a higher risk of acute ischemic stroke compared with patients with other respiratory tract infections. In terms of COVID-19 and stroke, greater incidence has been seen in the young where most strokes are associated with large vessel occlusion, and most patients have no previous history of stroke or traditional stroke risk factors. The immunologic and hypercoagulable nature of the disease is displayed by the disproportionate rise in the laboratory markers such as D-dimer, CRP, and ferritin. Standard of care treatment with systemic thrombolysis and endovascular retrieval and therapeutic anticoagulation is being used as the standard treatment at present. However it is beyond the scope of this review to address this aspect in-depth as the COVID-19 pandemic is still unfolding. It is likely that anticoagulation will play an important role in the management of stroke in COVID-19.

As more recovering COVID-19 patients are transferred to rehabilitation services and support, there is a strong need for UpToDate clinician knowledge of increased thrombo-embolic risk in this population. Clinicians need to educate patients about thrombotic events associated with COVID-19 infection. There is also a need to use neuroimaging in the post-acute setting for COVID-19 patients given the prevalence of neurological findings. As bed availability is at a premium and outpatient facilities limited due to the pandemic, access to effective rehabilitation will become challenging.

Another problem for healthcare providers engaged in acute stroke care is the risk of acquiring COVID-19 infection from infected stroke patients. As the best strategy to avoid transmission involves not being in the same space with suspected or confirmed COVID-19 stroke patient, providers should maximize the use of Telestroke or a commercially available low-cost smartphone application system to perform all aspects of acute stroke evaluation.

AUTHOR CONTRIBUTIONS

TW, LK, and SC conceived of the presented idea. LK developed the idea further and performed the literature search and drafted the manuscript. CS and TW conducted independent literature search and contributed the PRISMA chart as a group. TW, SC, and CS made significant contributions to the manuscript. All authors 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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CASE REPORT
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Case Report: Postacute Rehabilitation of Guillain-Barré Syndrome and Cerebral Vasculitis-Like Pattern Accompanied by SARS-CoV-2 Infection

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Introduction: The main clinical manifestation of the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is respiratory issues. Neurological manifestations are being increasingly recognized, including febrile seizures, headache, dizziness, and myalgia, as well as encephalopathy, encephalitis, stroke, and acute peripheral nerve diseases. Cerebral vasculitis is rarely reported. We describe a case of SARS-CoV-2 interstitial pneumonia complicated by flaccid tetraplegia due to Guillain-Barré Syndrome (GBS) associated with a cerebral vasculitis-like pattern.

Case description: A 62-year-old man was hospitalized for cough, fever, and severe respiratory failure requiring tracheal intubation and invasive ventilation. The chest Computerized Tomography (CT) showed images related to interstitial pneumonia and the subsequent nasopharyngeal swab confirmed the presence of SARS-CoV-2 infection. During the hospitalization, there was a progressive deterioration of the senses associated with areflexic flaccid tetraplegia. The treatment with high doses of immunoglobulin G (IgG) led to the immediate improvement of the general conditions and a partial response in terms of recovery of the upper limb and of the distal lower limb movements. Subsequently the patient was admitted to our Rehabilitation Unit, where he received an intensive rehabilitation treatment consisting of physiotherapy and occupational therapy. Two months later the patient was discharged at home and able to walk independently even for long distances thanks to the use of Ankle-Foot Orthosis (AFO).

Conclusion: In this report, we present the case of a patient with peripheral and central neurological damage occurred later severe pneumonia induced by SARS-CoV-2. The Immunoglobulin G therapy allowed the patient to benefit considerably from early rehabilitation, reaching the walking, increasing the independence in daily living tasks, and enabling safe discharge from hospital to home. Related neurologic complications of SARS-CoV-2 infection suffer a lack of understanding and further investigations should be conducted.

Keywords: SARS-CoV-2, Guillain-Barré syndrome, polyradiculonevritis, cerebral vasculitis, rehabilitation

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INTRODUCTION

Since the appearance of the first case of coronavirus disease 2019 (COVID-19), the spread of infection has quickly affected millions of people worldwide, and was declared a pandemic by the World Health Organization in March 2020 (1). Severely symptomatic patients may present with pneumonia, acute respiratory distress syndrome (ARDS), acute cardiac dysfunction from myocarditis, and multiorgan failure (2). Although the main clinical presentation is respiratory disease, there is emerging evidence that SARS-CoV-2 infection could be associated with neurological complications, including febrile seizures, headache, dizziness, and myalgia, as well with encephalopathy, encephalitis, stroke, and acute peripheral nerve diseases (3). Cerebral vasculitis is rarely reported (2, 4). features appear to be a combination of nonspecific complications of systemic disease, the effects of direct viral infection, or inflammation of the nervous system and vasculature, which can be para-infectious or post-infectious (4). We aim to report a case of COVID-19 complicated by Guillain-Barré Syndrome (GBS) and central nervous system involvement resembling vasculitis.

CASE DESCRIPTION

The patient is a 62-year-old man without significant medical history, suffering from high blood pressure and obesity, who was hospitalized between April 2020 and July 2020 in the Neuroscience department of the ASST Grande Ospedale Metropolitano Niguarda 'Ca Granda in Milan (Italy). On March 17, 2020 the patient was admitted to the Emergency Room of Clinica Polispecialistica in Paderno Dugnano in Italy. He presented with a fever and cough that had been persisting for about a week and that progressively worsened. He was alert and cooperative, without neurological interest. Gastrointestinal symptoms were not recently experienced. At the entrance, hemogasanalysis parameters showed an acute severe respiratory alkalosis: pH: 7.54 – pCO2: 32 mmHg – pO2: 26 mmHg. Chest Computerized Tomography (CT) showed images of interstitial pneumonia with multiple foci in a consolidative evolution and bilateral pleural effusion. Because of this, and considering the clinical suspicion of infection with SARS-CoV-2, a reverse-transcriptase polymerase-chain-reaction (PCR) oropharyngeal swab was performed that confirmed the diagnosis. The patient was transferred to the Intensive Care Unit (ICU) where, at first, he was treated with Continuous Positive Airway Pressure (CPAP), but subsequently intubation was required to improve respiratory gas exchange. He was treated with antibiotic therapy (Piperacillin and Tazobactam 6.75 mg/day for 12 days, Vancomycin 2 g/day for 8 days, Ceftriaxone 2 g/day for 2 days), antiretrovirals (Darunavir/Ritonavir 800/100 mg/day for 12 days), corticosteroid (Methylprednisolone 60 mg for 25 days), and Low-molecular-weight heparin (LMWH – Enoxaparin 2000 IU 2 times for day). Despite concomitant cardiological complications (atrial fibrillation associated with high ventricular response – Heart Rate: 190 beats/min), severe anemia (hemogasanalysis parameters: hemoglobin (Hb): 5.9 g/dl – hematocrit (Ht): 19% on March 30), and acute renal failure (Creatinine level: 4.40 mg/dl – estimated glomerular filtration rate (eGFR): 13.6 mL/min/1.73 m^2 – blood urea nitrogen level: 192 mg/dl on March 31) improvement of clinical condition and respiratory distress was recorded. On March 20 he was extubated and continued the hospital stay in the General Medicine Department of the same hospital. **Figure 1** shows the timeline of symptoms, diagnostic, interventions, and outcomes.

Diagnostic Assessment and Pharmacological Therapies of Neurological Disorder

Starting from April 1, a progressive worsening of neurological involvement characterized by sensory deterioration associated with flaccid quadriplegia areflexic was detected. For this reason, the patient was transferred to the emergency room of another hospital in Legnano, where more diagnostic exams were performed. The Brain Magnetic Resonance Imaging (MRI) showed two subcortical lesions in the parietal and left occipital sites, with restriction in Diffusion-Weighted Imaging (DWI) and without contrast enhancement. Rare point-like microbleeds without restricted diffusion were also detected in the white matter of both the cerebral lobes, interpreted as suggestive of previous ischemic lesions. Cerebrospinal fluid (CSF) assessment revealed an albuminocytologic dissociation with increased glucose (166 mg/dl, normal 45–80 mg/dl), protein level (51 mg/dl, normal 8–43 mg/dl), and no cells. SARS-Cov-2 RNA was not tested in CSF. Electrophysiological studies were performed: the common peroneal nerve showed no excitation on the left and marked lower amplitude of nerve conduction on the right, as well as a conduction block at the popliteal fossa. Significantly prolonged distal motor latencies and temporal dispersion of the compound muscle action potentials (CMAP) at four limbs muscles, absent F-waves, and reduced motor nerve conduction of the tibial, median, and ulnar nerves on both sides were recorded, as well as slightly reduced sensory potential amplitude size. Sensory conduction pathways of the median, ulnar, and sural nerves were normal. Electromyography (EMG) needle electrode showed no denervation signs. Motor unit recruitment was not assessable. The findings described were consistent with the diagnosis of acute inflammatory polyradiculoneuritis. On the basis of these results, the diagnosis of Guillain Barré Syndrome (GBS; Acute Inflammatory Demyelinating Polyneuropathy or AIDP variant) was done. In this context, we hypothesized that AIDP could be the result of an autoimmune reaction in the course of infection with SARS-CoV-2 (5, 6). Once more the patient was intubated then treated with high-dose Intravenous Immunoglobulin (2 g/kg from April 5 to April 10). GBS prognosis can be estimated by applying the modified Erasmus Guillain-Barré Syndrome outcome score (mEGOS) (7, 8). The results were 8/9 at admission and 11/12 at day 7 of hospitalization, pointing to a poor outcome. Negative mood and sometimes depression were reported mainly due to loss of autonomy and complete dependence on ADLs. On April 12, after extubation, the hospital stay continued in the General Medicine Department, where he underwent hemodialysis for acute renal failure on April 15 (Creatinine level 5.50 mg/dL and diuresis of 500 ml in 24 h). On May 6, general

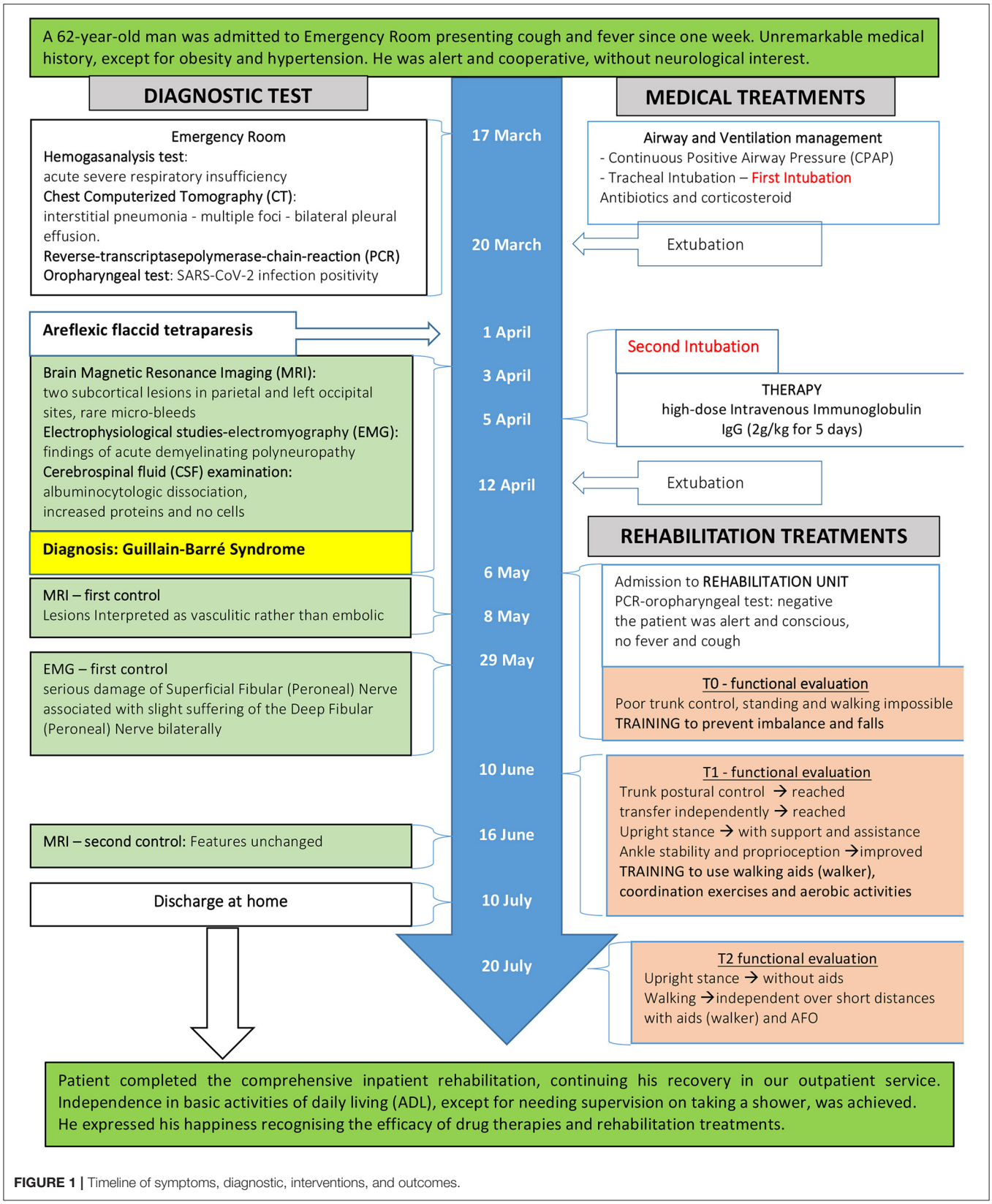


FIGURE 1 | Timeline of symptoms, diagnostic, interventions, and outcomes.

health condition was stable. The muscle strength enhanced, although weakness of the proximal upper limb and of the distal lower limb remained relevant. Consequently, he was admitted to our Rehabilitation Unit (RU) to continue the recovery.

Rehabilitation Assessments and Treatments

At admission the patient was alert and conscious, body temperature was 37.2°C, there was no cough, and the last PCR-oropharyngeal test was negative. Vital signs' measurements were: blood pressure: 125/70 mm Hg, heart rate: 74 beats/min, and oxygen saturation: 95% on room air. Standard laboratory tests detected white blood cells count (17.600), Hb (8 g/dl), c-reactive protein (6.5 mg/dl), creatinine level (4.8 mg/dl), and blood urea nitrogen level (117 mg/dl). Erythropoietin was prescribed to treat anemia. No electrocardiographic changes were visible. At the neurological examination cranial nerves were intact and no speech disorders or swallowing problems were noticeable. All sensations were preserved. Motor clinical assessment was characterized by a marked loss of muscle mass and tetraparesis, evident in the proximal upper and lower limbs (strength muscle was of grade 3/5 at deltoid, biceps, extensor carpi radialis, iliopsoas, and quadriceps) and more intense at ankle dorsiflexor muscles (grade 0/5 at anterior tibial muscles), as measured by the British Medical Research Council muscle strength grading system (9). Deep tendon reflexes were absent; muscle tone was normal in four limbs. Depressive symptoms described during ICU stay were reduced: drug therapy (Citalopram, 20 mg/day), psychological support, and contacts with family members, once a day because of COVID-19 restrictions, gradually had a positive effect on emotions. In order to monitor rehabilitation effectiveness and outcomes, the staff applied the following measurements: Modified Rankin Scale (MRS) (10), Modified Barthel Index (MBI) (11), Trunk Control Test (TCT) (12), Short Physical Performance Battery (SPPB) (13), Berg Balance Scale (BBS) (14), Time-Up and Go (TUG) (15), and 6 Min Walking Test (6MWT) (16). The first evaluation was performed on May 7 (T0) and the final one on July 20 (T2). An intermediate assessment was carried out on June 10 (T1) when it was possible to administer all the tests. The early rehabilitation program consisted of, twice a day, a 45 min' physiotherapy (PT) session alternated with 30 min' occupational therapy (OT) for 6 days a week. At the first stage, the trunk control was poor in a sitting position and the patient needed assistance in transfers, thus a standing position and walking were not possible. Rehabilitation programs were initially aimed to prevent deconditioning and development of skin ulcers, as a result of bed rest and physical inactivity, and muscle shortening and joint contracture, as consequence of motor weakness. Proper bed positioning with frequent postural changes, and sitting posture on the bed through back support and on a wheelchair were provided. Time to sit was gradually increased up to 4 h per day after a week. To reduce fatigue, pulmonary rehabilitation included breathing control, chest-abdominal coordination exercises to stimulate a proper recruitment of the diaphragm muscle, and positive expiratory pressure (PEP) bottle exercise to increase the pulmonary volume. To improve muscle mass and power, initial exercises included gentle strengthening involving isometric manual-resistive exercises, followed by upper and lower limb active exercises and manual progressive resistive mobilization, carefully tailored to the clinical condition of the patient. After 10 days, trunk postural control was achieved and a few days later the ability to transfer independently was also gained. When the upright stance was reached with support and assistance of the PT/OT, more specific training was set up to prevent imbalance and falls. This training involved balance in static and dynamic conditions and active exercises of lower limb and trunk muscles. Due to impaired ankle stability, great care to proprioception (sense of body position and movement) was taken (T1 – 1 month later). In the last month (T2 – 2 months later) the rehabilitation program focused on walking recovery, at the beginning over short distances with supports, assistance, and Ankle-Foot Orthoses (AFO) to contrast bilateral foot drop, then by learning to use walking aids (walker). Coordination exercises and aerobic activities were involved to reach the best performance.

Diagnostic Follow-Up

A first control MRI was checked on May 8 (**Figures 2A–E**). The exam displayed small T2 fluid-attenuated inversion recovery (FLAIR) focal hyperintensities in the subcortical white matter with restricted diffusivity in the left occipital and parietal cortex (IMG); due to the size and location, the multiple lesions were interpreted as vasculitic rather than embolic. On June 16, the neuroimaging features between the first and second MRI were unchanged, showing ischemic lesions in the left parietal and occipital lobes without restricted diffusion and still suggestive for vasculitic-like lesions (**Figures 2F,G**). The EMG of May 29, additionally, corroborated the diagnosis of GBS, defined by serious damage of the Superficial Fibular (Peroneal) Nerve associated with slight bilateral suffering of the Deep Fibular (Peroneal) Nerve (**Table 1**).

Outcomes of Rehabilitation

The rehabilitation process promoted a gradual increase of strength muscle and led to functional recovery. Assessment results are presented in **Table 2.** Walking was initially possible with the support of a four-wheeled walker for medium distances (6MWT: 237 meters) with walking speed of 2.37 Km/h, using two Ankle-Foot Orthoses (AFO), as a consequence of bilateral weakness in the ankle dorsiflexion and plantarflexion. At discharge, 75 days after admittance to our RU, the patient achieved the restoration of strength performance at proximal limb muscles (grade 5/5), however muscle weakness of ankle and toes dorsiflexion persisted (grade 3/5 on the right; grade 1/5 on the left). Balance control was upgraded (BBS: 50/56), as well as walking technique and aerobic endurance. Wearing AFOs, but without assistance or aid, he walked for long distances (6MWT: 345 meters) with a speed of 3.45 Km/h. Independence in basic activities of daily living (ADLs), except for needing supervision on taking a shower, was achieved. After completing the comprehensive inpatient rehabilitation, he continued his recovery in our outpatient service.

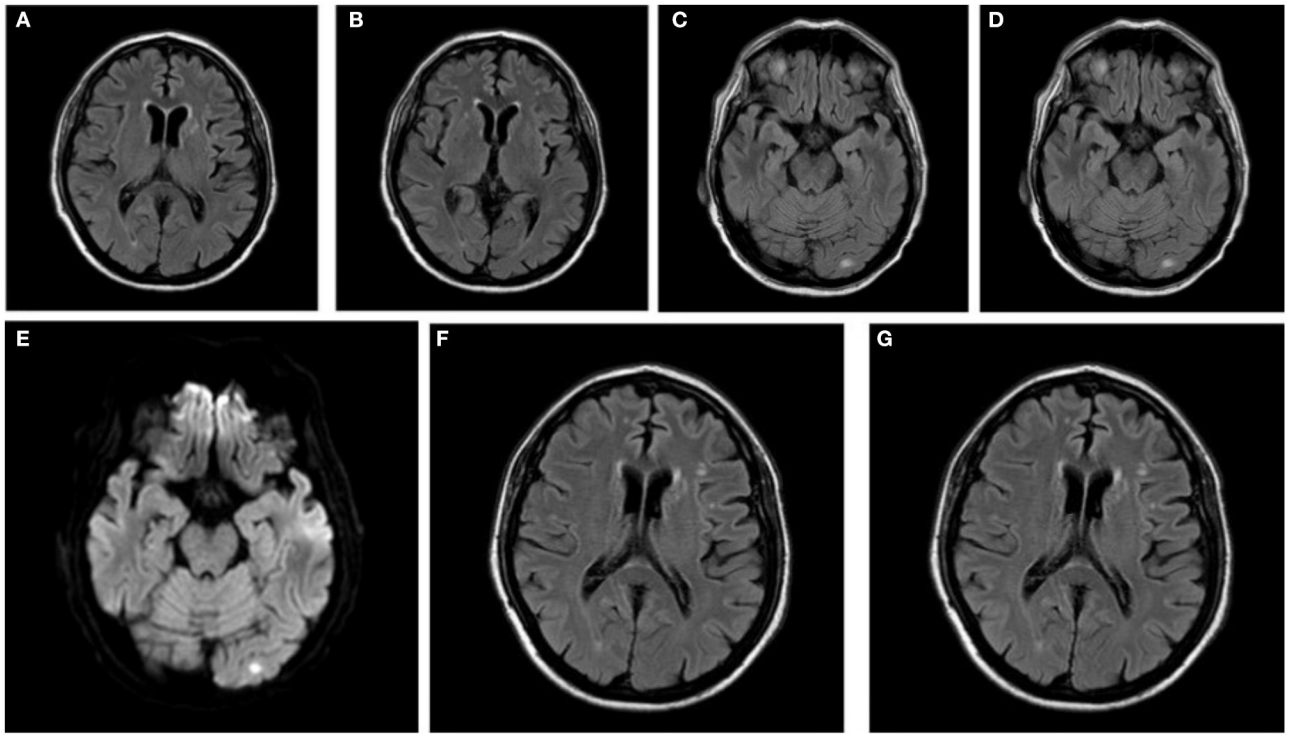


FIGURE 2 | Shoot from brain MRI of May 8 in (**A–E): (A,B)** show T2-FLAIR acquisition. **(C)** Shows occipital lesion in T2-FLAIR acquisition. **(D)** Shows parietal lesion in T2-FLAIR acquisition. **(E)** Shows occipital lesion positive in DWI. Shoot from Brain MRI of June 16: **(F,G)** show T2-FLAIR acquisition.

TABLE 1 | Summary table of results of electromyographic examination of May 29.

	Spontaneous					MUAP			Recruitment
Muscle	**IA**	**Fib.**	**PSW**	**Fasc.**	**H.F.**	**Amp.**	**Dur.**	**PPP**	**Pattern**
L. Tib. Anterior	N	3+	3+	None	None	–	–	–	Absent
L. Ext. Dig. Brevis	N	3+	3+	None	None	–	–	–	Absent
R. Ext. Dig. Brevis	N	3+	3+	None	None	N	N	N	Absent
L. Gastrocn (Med)	N	None	None	None	None	2+	1+	2+	Reduced
R. Gastrocn (Med)	N	None	None	None	None	2+	1+	2+	Reduced
L. Vast. Lateralis	N	None	None	None	None	N	N	N	Sub Interference
R. Vast. Lateralis	N	None	None	None	None	N	N	N	Sub Interference

Abbreviation of Muscles. L. Tib Anterior, Left Tibialis Anterior muscle; L. Ext. Dig. Brevis, Left Extensor Digitorum Brevis muscle; R. Ext. Dig. Brevis, Right Extensor Digitorum Brevis muscle; L. Gastrocn (Med), Left Gastrocnemius muscle medial; R. Gastrocn (Med), Right Gastrocnemius muscle medial; L. Vast. Lateralis, Left Vastus Lateralis muscle; R. Vast. Lateralis, Right Vastus Lateralis muscle. Abbreviation of examination. Spontaneous IA; Spontaneous Fib., Fibrillation; Spontaneous PSW, PolySpike Waves; Spontaneous Fasc., Fasciculations; Spontaneous H.F., High Frequency; MUAP, Motor Unit Action Potential; Amp., Amplitude; Dur., Duration; PPP, PolyPhasic Potential - Recruitment Pattern. Abbreviation Results: N, Normal.

DISCUSSION

The respiratory system is the most commonly affected by SARS-CoV-2, but other organ manifestations have been described involving the heart, kidney, and gastrointestinal system. Previous data indicate that the virus is capable of causing an excessive immune reaction with an increased level of cytokines, such as Interleukin-6 (IL-6) (5, 21). It seems that these immunological processes stimulate an inflammatory cascade, leading to extensive tissue damage, including of the nervous system, with variable clinical implications (3). To date, there is no evidence that SARS-CoV-2 is highly neurovirulent (4), though neurological signs, such as nausea, vomiting, myalgia, dizziness (6), hypogeusia, hyposmia, and impaired consciousness (22), were observed as first symptoms. According to other findings, the body's innate and adaptive immune responses to infection as well as the virus itself could be responsible for both central and peripheral neurological damage (4). With regard to the peripheral nervous system (PNS), GBS is an immune-mediated disease; although mechanisms for coronavirus PNS disease are not

TABLE 2 | Results of motor and functional assessment.

	MRS (points)	MBI (points)	TCT (points)	SPPB (points)	BBS (points)	TUG (seconds)	6MWT (meters)
TIMING							
T0 (May 7, 2020)	5/5	19/100	36/100	0/12	8/56	N.E.	N.E.
T1 (June 10, 2020) (4WW + AFO)	3/5	46/100	100/100	3/12	31/56	22	237
T2 (July 20, 2020) (AFO)	1/5	100/100	100/100	12/12	50/56	10	345
RELIABLE CHANGE							
T0–T1	N.E.	SEM = 1.45 (17) RC = 18.05	N.E.	SEM = 1.42 (18) RC = 5.53	SEM = 2.93 (19) RC = 5.56	N.E.	N.E.
T1–T2	N.E.	SEM = 1.45 RC = 31.22	N.E.	SEM = 1.42 RC = 4.48	SEM = 2.26 RC = 5.94	SEM = 1.14 (20) RC = 7.45	SEM = 22 (18) RC = 3.47

Abbreviations Tests: MRS, Modified Rankin Scale; MBI, Modified Barthel Index; TCT, Trunk Control Test; SPPB, Short Physical Performance Battery SPPB; BBS, Berg Balance Scale; TUG, Time-Up and Go; 6MWT, 6 Minutes Walking Test. Abbreviations Aids: 4WW, four-wheeled walker; AFO, Ankle-Foot Orthoses. Abbreviation Result: N. E., Not Executable. Abbreviation Statistic: RC, Reliable Change method calculated as RC = xt1-xt2/Sdiff; Sdiff = $\sqrt{2}(SEM^2)$ - SEM, standard error measurement. The value is attributed considering: SPPB (Older Adults), 6MWT and MBI (Stroke), BBS (Stroke; T0–T1 individuals who ambulate with assistance; T1–T2 individuals who ambulate independently).

well understood, viral infection is likely to cause an immune response and a pro-inflammatory state that results in dysimmune disorders including GBS. GBS associated with SARS-CoV-2 might follow the pattern of a para-infectious mechanism, instead of the classic post-infectious profile, as reported in GBS associated with the Zika virus (23). The mechanisms of CNS vascular disease related to coronavirus are probably more complex and multifactorial. The main mechanism is linked to a pro-inflammatory state with consequent activation of thrombotic pathways and microvascular damage. Stroke can result from other mechanisms: an acute infection can trigger atrial fibrillation or endothelial dysfunction can lead to vascular complications. An involvement of brain parenchyma by the virus is also possible. Finally, similarly to what happens to other viruses (e.g., varicella zoster), immune response and pro-inflammatory status related to coronavirus-types can result in a vasculitic process (4). Regarding vasculitis lesions, histologic evidence has been reported in many organs such as the lung, liver, kidney, or skin of patients with COVID-19 (24–26), but cerebral vessels have not yet been investigated. To our knowledge, a single case report about COVID-19 and complications with a CNS vasculitis-like pattern was published, showing extensive cerebral small-vessel ischemic lesions resembling cerebral vasculitis (2). On the other hand, it is known that the prevalence and degree of cerebral white matter lesions increased with age (27). What we observed in our case is that brain lesions might have a different pathogenesis. The cerebral ischemic lesions were acute (restricted diffusion in MRI), multiple, and in different vascular territories and in cortical locations; considering the number of acute ischemia it is unlikely that they could originate from an atheromatous mechanism while, conversely, the small size makes an embolic cause unlikely. It might be considered that the pattern may be suggestive of a vasculitic origin: considering the association with both another dysimmune disease and SARS-CoV-2, we could speculate that the viral infection could have caused a dysimmune-response involving the nervous system, as described below. Diagnosis of SARS-CoV-2 infection of our patient was made at admission to the hospital and, primarily, he was treated with respiratory support and drugs, as referenced above. Neurological involvement appeared 14 days later and it was revealed by an acute and severe onset with cognitive impairment and flaccid, areflexic quadriplegia. Considering the temporal association, we can conjecture that SARS-CoV-2 may have contributed to the development of GBS in this patient. One article reported the interval of 5–10 days between the onset of viral illness and the first symptoms of GBS for five patients (28). This time is similar to the interval seen with GBS that occurs during or after other infections (29). Many case report series described increased GBS incidences (up to more than 5 times higher than expected) in COVID-19 affected areas (28). However, some limitations are worth noting. This syndrome was difficult to explore, probably because of the rarity of clinical manifestations. Furthermore, the alternative explanation that the patient coincidentally developed GBS of an unknown cause should be considered. The assumption is that the viral infection might have caused a dysimmune response involving both the PNS and CNS. Indeed, CNS involvement may also be determined by a dysimmune mechanism, with ischemic lesions of possible vasculitic origin, with a monophasic course. Excellent response to Intravenous Immunoglobulin (IgG) is consistent, although not conclusive with the hypothesis. A quick recovery of clinical status was stimulated with early rehabilitation. We applied several measurements for different skills. More specifically, MRS was used to evaluate general motor improvement; TCT, SPPB, and BBS was used for balance ability. TUG and 6MWT was used to assess walking speed, MBI was used for independence in ADLs. In particular, we observed a progressive strength recovery, primarily in upper limbs, hand grip, and manual skills. Upright position was restored in about 30 days. As expected, the clinically significant improvement of lower-limb muscle strength, as well as walking ability, occurred during the rehabilitation time. At the same time, this better clinical status led to significant

improvements in mood and well-being, as well as a significant reduction in anxiety.

Because measuring change in outcome evaluations in an individual can be used to address both statistical and clinical significance, we applied the Reliable Change (RC) index, proposed by Jacobson and Truax in 1991 (30, 31). RC index indicates whether an individual change score is statistically significantly greater than a difference that could have occurred due to random measurement error alone (32). It is computed by dividing the difference between the pre-treatment (Xt1) and post-treatment (Xt2) scores by the standard error of the difference (Sdiff) between the two scores.

$$\mathbf{RC = xt1 - xt2/Sdiff \quad Sdiff = \sqrt{2}(SEM^2)}$$

If the RC is >1.96, then the difference is reliable; a change of that magnitude would not be expected due to the unreliability of the measure? Conversely, if the RC score is 1.96 or less then the change is not considered to be reliable, it could have occurred just due to the unreliability of the measurement. RC index requires knowledge of distribution scores for the normal and disordered populations under scrutiny (33, 34), and, unfortunately, in the case of GBS these data are not known. Nonetheless, considering similar populations affected by neurological disease (e.g., stroke), the standard error measurement (SEM) is calculated for some of the scales we administered. As shown in **Table 2**, RC was calculated for 6MWT, TUG, BBS, SPPB, and MBI. These results are clinically and statistically significant. For TCT and MRS a 30% change from baseline might be considered as a clinically meaningful improvement for individual patients, comparing measurements at different follow-ups (35).

An additional consideration is about walking speed at discharge (3.45 Km/h). It was higher compared to one other reported by Novak et al. (36) in GBS (2.8 km/h), but lower considering the normal walking speed for men aged between 60 and 69 years (4.82–5.16 Km/h) (37).

In summary, in this case report we have reported the clinical history of a patient who suffered from peripheral (GBS) and central (vasculitis) neurological involvement at one time, and then later from SARS-CoV-2 infection. We have only hypothesized a possible association between infection and neurological symptoms. Further studies should be conducted to support a causal relationship and better understand this possible link. Quick detection of neurological symptoms and diagnosis are fundamental to set up the appropriate therapy. IgG infusion allowed the patient to benefit considerably from early rehabilitation, achieving walking, increasing independence in daily living tasks, and enabling safe discharge from hospital to home. The patient was fully aware of the seriousness of his illnesses, especially in the early stages, characterized by a long time spent in the ICU due to severe pneumonia then was made even worse by the tetraplegia. Loss of autonomy (poorly tolerated by the patient) and removal from the family, necessary due to the infectious state, contributed to the worsening of the mood. Muscle strength recovery and consequent autonomy in ADLs gave the patient a positive emotional boost, strengthened by reuniting with relatives after COVID-19 restrictions imposed during hospitalization in the Rehabilitation Unit relaxed. At discharge he expressed his happiness recognizing the efficacy of drug therapies and rehabilitation treatments.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SC wrote the first draft, was responsible for data collection, performed data interpretation. LS performed the literature search and revised data interpretation. FG performed data interpretation and the literature search. AI prepared **Figure 2**, performed data analysis, and interpretation. GB revised data interpretation. DD conceived the study, prepared **Figure 1**/**Supplementary Material**, performed statistical analysis, revised data interpretation, and the final manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.602554/full#supplementary-material

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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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Continuity of Care During COVID-19 Lockdown: A Survey on Stakeholders' Experience With Telerehabilitation

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Objective: To explore professionals', adult patients', and children's caregivers' perception and satisfaction with telerehabilitation during COVID-19 lockdown.

Design: An observational transversal study on a web-based survey was conducted in order to explore participants' perception and satisfaction of telerehabilitation during COVID-19 lockdown.

Setting: The study was conducted at our Outpatient Neurorehabilitation Service.

Subjects: All rehabilitation professionals, adult patients, and children's caregivers who accepted telerehabilitation were recruited.

Interventions: Participants had to respond to the Client Satisfaction Questionnaire-8 and to a purpose-built questionnaire on their perception and satisfaction of the service provided.

Main Measures: Data were analyzed by qualitative statistics and logistic regression models.

Results: All 144 caregivers, 25 adult patients, and 50 professionals reported a medium-high level of perception and a high level of satisfaction. Results showed a correlation among caregivers of children aged 0–3 and feeling overwhelmed with remote care (OR = 3.27), a low perception of telerehabilitation for enhancing goals (OR = 6.51), and a high perception of feeling helped in organizing daily activity (OR = 2.96). For caregivers of children aged over 6 years, changes in the therapy plan were related to a low perception of feeling in line with the in-person therapy (OR = 2.61 and OR = 9.61) and a low satisfaction (OR = 5.54 and OR = 4.97). Changes in therapy were related to concern (OR = 4.20). Caregivers under 40 and professionals showed a high probability to perceive telerehabilitation as supportive (OR = 2.27 and OR = 5.68). Level of experience with remote media was shown to influence perception and satisfaction.

Interpretation: Telerehabilitation can be a useful practice both during a health emergency and in addition to in-presence therapy.

Keywords: continuity of care, COVID-19, telerehabilitation, caregivers, rehabilitation professionals, perception, satisfaction

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INTRODUCTION

During public health crises, as in the COVID-19 pandemic, telemedicine can be a viable opportunity for reducing risk of infection while offering solutions to the constant demands of care.

Evidence on the merits of this service is provided by NATO, which, during various crises, developed a multinational telemedicine system deployed with military forces (1). Another example is China, which, during the SARS pandemic, began to examine telemedicine and integrated medical systems for future use in similar circumstances (2).

International health agencies such as WHO are fundamental for large-scale deployment of telemedicine services. Embedding its practice into routine service delivery with guidelines is the most effective way to prove its important role in health care.

The primary purpose of this study was to analyze the perception of remote rehabilitation during lockdown by adult patients, children's caregivers, and rehabilitation professionals and to verify their level of satisfaction with the service provided. Possible individual factors influencing stakeholders' perception of telerehabilitation were examined by a multivariate analysis. Treatment effectiveness was not investigated in this study. As a survey study, it should be interpreted with caution and findings cannot be generalized but rather be considered as suggestions. In addition, as a monocentric study, results may be related to the service provided by our department rather than to telerehabilitation itself.

MATERIALS AND METHODS

Study Design

An observational transversal study on a web-based survey was conducted in order to explore participants' perception and satisfaction of telerehabilitation during COVID-19 lockdown.

The study was approved by the Independent Ethic Committee of the Research Institute of the Santa Lucia Foundation.

Therapists, adult patients, and children caregivers in charge were asked to complete a two-section survey on their perception and satisfaction of an in-home video telerehabilitation approach. The survey included two sections: an informant section and a section assessing the perception of remote rehabilitation. Adult patients and children's caregivers' survey included an additional section on the level of satisfaction with the service provided, the Client Satisfaction Questionnaire-8 (CSQ-8) (3–5).

An introductory explanation of the purpose of the questionnaire preceded the survey. Three questionnaires in Italian were developed, validated, and administered.

A review of the literature was performed in order to detect questionnaires that evaluate telerehabilitation. Members of the consensus panel, a psychologist, two physicians, and a physical therapist, generated and outlined the items. A draft was assessed through a validation procedure and then tested in study samples. Ten therapists, 10 caregivers, and 10 patients were recruited to assess relevance of draft questions.

The first version consisted of 62 items for all three study groups. A consensus panel rated the contents and purpose of each item and selected three 25-item closed question questionnaires. Relevance and clarity of each statement were then assessed by experts on a four-point Likert-type scale (6).

An item-level content validity index (I-CVI) was computed for relevance and simplicity. A score of 0.78 was selected as the threshold for an acceptable I-CVI (7, 8). A scale-level content validity index was calculated as the average across items' I-CVI (S-CVI/Ave) and as the proportion of items that all experts rated as relevant or simple (S-CVI/UA, scale-level content validity index universal agreement), with selected thresholds of 0.90 and 0.80 for an acceptable S-CVI/Ave and S-CVI/UA, respectively (7, 9). The items were revised, thus generating a 20-item questionnaire for therapists and 15-item ones each for caregivers and for patients.

Each question was assigned with a score (0–5 points). The sum of the scores ranges from a minimum to a maximum score equivalent to the worst and best perception of telerehabilitation during lockdown.

The CSQ-8 is a self-administered eight-item standardized questionnaire, developed by Larsen et al., aimed to assess the client/patient satisfaction with services provided (3–5). It is a four-point Likert scale that estimates several aspects of a service provision. For each item, four scored answers are possible. The sum of all items is the total score ranging from a minimum of 8 to a maximum of 32, so that the higher the score, the higher the level of satisfaction. The CSQ-8 has previously been used to measure the level of satisfaction of children's caregivers and with a remote rehabilitation service (10, 11). A written formal license agreement to use the Italian version of the scale on an electronic platform was provided by the copyright holder before starting our study.

Setting

Due to lockdown, outpatient rehabilitation services were suddenly interrupted. In response to this situation, a prompt adaptation of delivery modes in order to support ongoing services was called for. Remote delivery of care seemed to be the ideal approach for providing access to therapy sessions, although not typically used in the department. The service was proposed to both children and adults in charge. Professionals were involved in initial contacts of patients and families in order to collect information on technical, personal resources, and permission for remote treatment. Despite the initial difficulties due to unavailability of technical equipment, remote care began within a week after lockdown. Team members adapted some aspects of previous in-person therapy plans in order to remotely continue progress toward goals.

Treatment plans included physical, speech, occupational, and cognitive–behavioral therapy for the group of children, and neuropsychological therapy and psychological support to adolescents, adult patients, and families. Sessions were conducted from the workplace to the patient's home, via tablet, smartphone, or PC using video meeting systems such as Google Meet or Skype. Activity did not follow a standardized scheme but was individualized for each patient based on his/her clinical features and type of device used. Caregiver mediation depended on the patient's age, level of cognitive function, type, severity of functional impairment, and level of task difficulty. Efforts were

made to ensure treatment was provided to the patient by the same professionals before lockdown. Number of sessions, treatment type, and duration (50 min) were in line with the original Individual Rehabilitation Plan. Research participation consent forms were emailed to patients or to minors' parents or legal guardians, guaranteeing anonymity. Remote treatment began in March while the invite to complete the online survey hosted by Google Forms was sent in May, after 2 months of treatment.

Participants

All professionals, adult patients, and children's caregivers of the Outpatient Neurorehabilitation Service were recruited. At the beginning of lockdown, 362 patients, comprising 270 children (primarily with cerebral palsy, genetic disorders, neuromuscular diseases, and prematurity) and 92 adults with complex disorders (primarily stroke, acute brain injury, spinal cord injury, Parkinson disease, and multiple sclerosis), were in charge. Consent was given by 265 families of minors and by 48 adult patients. Only the professionals that worked for at least 1 month during the project were considered qualified.

Variables

Each survey included a first section for recording several variables, namely, demographic and other personal information. The assessed variables for rehabilitators were as follows: age (21–30 years, 31–40 years, 41–60 years, or >60 years), professional position (Physical, Neurodevelopmental, Speech, Occupational Therapists, and Psychologist), years of work experience (<5 years, 5–10 years, 10–20 years, or >20 years), remote media skill level (none, low, sufficient, high, or very high), and previous experience with remote care (yes or none). Patients were asked about their age (<20 years, 21–40 years, 41–60 years, or >60 years), number of therapy sessions (2, 4–6, or >6), rehabilitation plan and type of therapies, level of familiarity with remote media (none, low, sufficient, high, or very high), need for assistance to perform exercises (yes or no), and support availability (yes or none). Information regarding caregivers and their children included sex of caregiver (male or female), age of caregiver (<40 years, >40 years, or not reported), age of the child (0–3 years, 4–6 years, >6 years, or not reported), rehabilitation plan and therapies performed during remote mode (rehabilitation programs respected, modified, or information not reported), and caregiver's experience with remote media (yes or none). This information served to define the sample and to analyze possible correlations with different levels of perception and satisfaction of remote treatment.

Data Analysis and Statistics

Research data were downloaded from Google Forms platform, exported to a Microsoft Excel spreadsheet for data analysis. Both qualitative and quantitative statistical analysis were performed (12–14).

Sample characteristics were expressed in percentages (%), while data on the perception and satisfaction statements were analyzed by a descriptive qualitative method and by median and standard deviation measures.

Forward, stepwise, and Wald logistic regressions were performed in order to investigate the correlations between the examined variables and the level of perception and satisfaction expressed, thus allowing us to hypothesize how the experience of telerehabilitation during lockdown was influenced by demographic, personal factors, or therapy plan.

The logistic model was not applied due to the small sample of adult participants.

Dependent variables were as follows: level of agreement of statements expressed by participants (not at all, little, enough, highly, or strongly) and level of satisfaction (quite dissatisfied, indifferent or mildly dissatisfied, mostly satisfied, or very satisfied).

Independent variables (0 = if absent and 1 = if present) were different for the two groups. For the caregivers' group, demographic and personal information were considered. Given the number of health professionals participating in the study, a smaller number of independent variables were examined: age (<40/>40 years), professional role, type of patient treated (adults/children), years of work experience (<10 years/>10 years), skill with remote media (yes/not), and previous experience with remote care delivery (yes/not).

Data analyses were performed using the SPSS 17.0 Statistical Package for Social Sciences.

RESULTS

Participation rate for professionals was 100%. Only 2 physiotherapists and 1 speech therapist out of the 53 professionals in service during March did not meet inclusion criteria and were excluded from the study; 50 took part in the study. In the adult group of patients and in the group of children's caregivers, participation rate to the survey was, respectively, 58.06% ($n = 25$) and 67.56% ($n = 144$).

Data from an online survey on 25 adult patients, 144 children's caregivers, and 50 professionals were collected and analyzed.

Process leading to the final number of participants and selection stages are shown in **Figure 1**.

The professionals' sample included 20 physical therapists (40%), 12 speech therapists (18%), 9 neurodevelopmental therapists (24%), 4 occupational therapists (10%), and 5 psychologists (8%).

Eighteen were aged between 41 and 60 years (36%), 14 were under 30 years of age (28%), 13 were aged between 31 and 40 (26%), and 5 were over 60 years of age (10%). Thirty-four had a work experience of over 10 years (68%); 13 (26%) reported no familiarity with remote media and 18 (36%) reported previous remote treatment experiences.

The adult sample primarily consisted of patients over the age of 60 (44%); 17 of them (65.4%) underwent biweekly treatment; mainly physical therapy, both before (80%) and after (72%) lockdown; 9 (36%) declared no confidence with remote media; 10 (40%) needed assistance to perform the proposed exercises; and 2 (7.7%) reported difficulties in availability of caregiver assistance.

As for the 144 caregivers, 102 were females (70.83%) and 78 (54.16%) were above 40 years of age. The children's sample

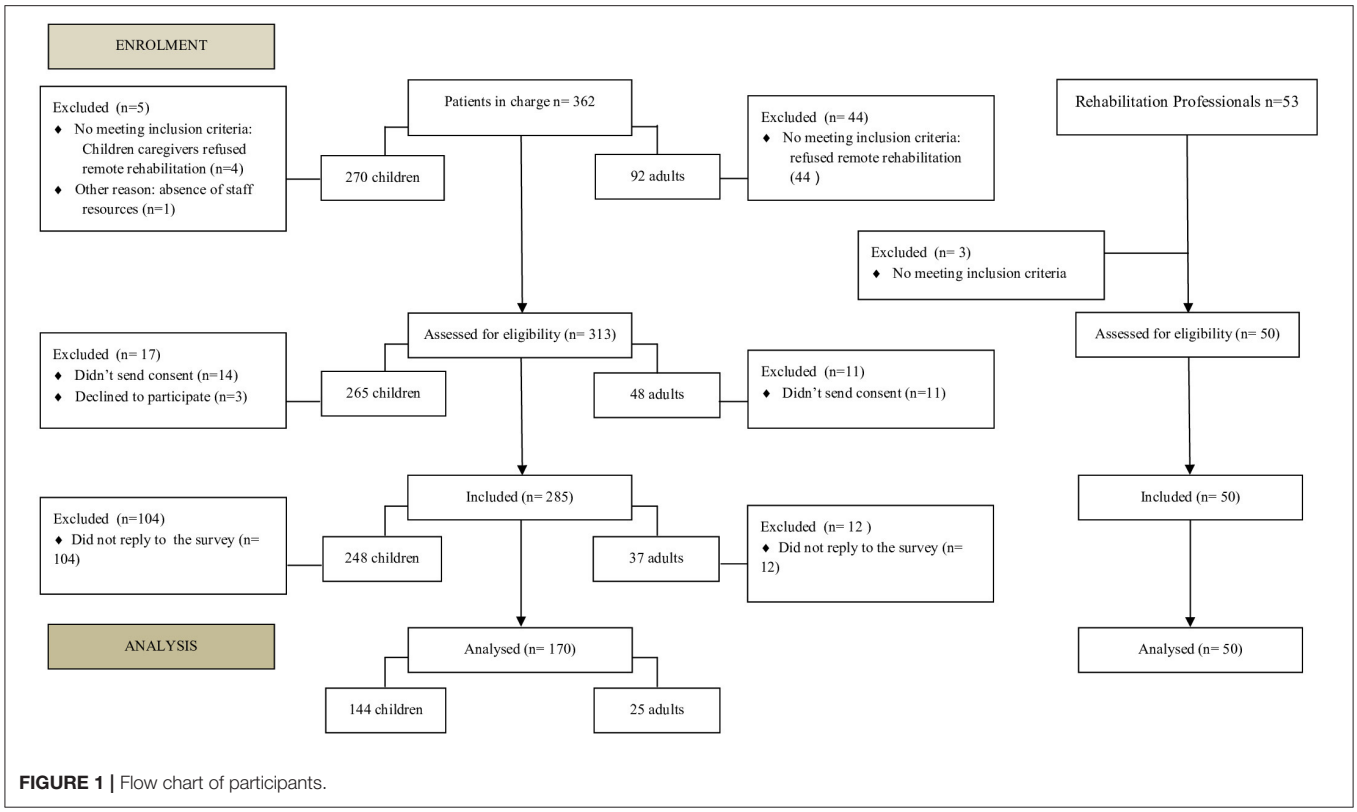


FIGURE 1 | Flow chart of participants.

consisted of 48 (33.33%) aged from 0 to 3 years, 40 (27.77%) aged from 4 to 6 years, and 50 (34.72%) above 6 years of age. Six (4.17%) caregivers did not reveal the age of their child. As for the therapy plan, 127 caregivers (88.19%) reported continuity of rehabilitation plan, while 16 caregivers (11.11%) referred changes. Eighty-five caregivers (59.03%) reported no familiarity with remote media. One caregiver did not provide personal information.

Children's caregivers sample obtained a mean score of 53.27 (SD 10.60) on the perception questionnaire. This score falls in a medium-high range considering 15 as the worst perception and 75 as the best perception.

Figure 2A shows the mean scores and the standard deviations of the 15 statement responses. These results must be interpreted taking into account that, for each statement, score 1 represents the worst perception and score 5 represents the best perception. Some were negative statements; the graph shows the perception values already converted into the five-point Likert scale.

The mean total score of the patient's perceptions questionnaire was 50.76 (SD 8.23) (**Figure 2B**).

Results of the professionals' sample (**Figure 2C**) show an average total score of 67.66 (SD 8.57) where 100 corresponds to the best and 20 corresponds to the worst perception.

The results of the CSQ-8 questionnaire showed a mean score of 26.8 (SD 4) corresponding to a medium-high level of satisfaction with the telerehabilitation service, in both adults and children's caregivers' sample (**Figure 3**).

Tables 1, **2** show results of the regression model selection and estimated changes in log odds and related standard errors. Results showed a correlation among caregivers of children aged 0–3 and feeling overwhelmed with remote care (OR = 3.27); a low perception of telerehabilitation for enhancing goals (OR = 6.51) and a high perception of feeling helped in organizing daily activity (OR = 2.96). For caregivers of children aged over 6 years, changes in the therapy plan were related to a low perception of feeling in line with the in-person therapy (OR = 2.61 and OR = 9.61) and a low satisfaction (OR = 5.54 and OR = 4.97). Changes in therapy were related to concern (OR = 4.20). Caregivers under 40 and professionals showed a high probability to perceive telerehabilitation as supportive (OR = 2.27 and OR = 5.68). Level of experience with remote media was shown to influence perception and satisfaction.

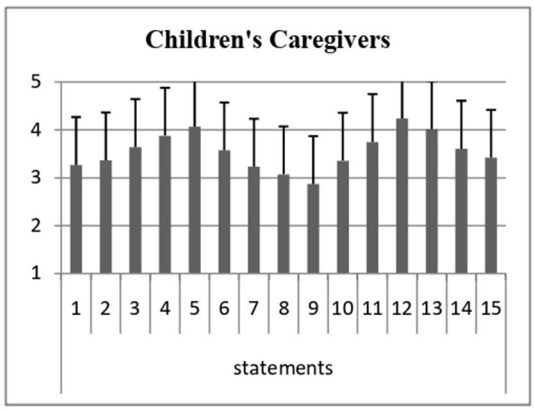
DISCUSSION

Lockdown restriction measures imposed by the COVID-19 diffusion included the interruption of nonessential services such as rehabilitation services for non-urgent cases resulting in an ethical dilemma, regarding the right of access to care and of continuity of care (15–17). As an answer to this, telerehabilitation was proposed to all patients in charge at our rehabilitation outpatient department.

Perception and Satisfaction of Telerehabilitation by Caregivers of Disabled Children

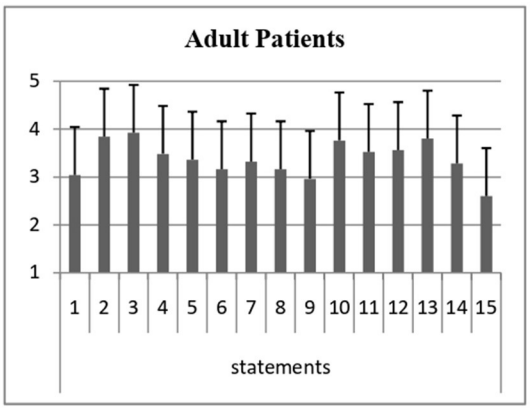
Results of the perception questionnaire revealed an overall medium-high level of positive perception of remote treatment;

A



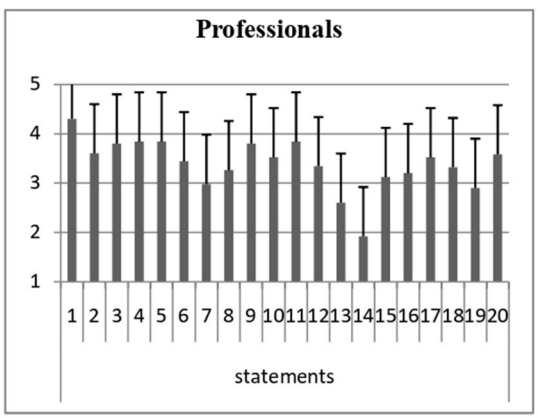
1.Telerehabilitation helps me organize my days with my child
2.Telerehabilitation makes me feel in line with the in-person therapy plan
3.Continuing the therapy plan via telerehabilitation makes me feel less concerned about my child's health
4.Continuing the treatment plan through telerehabilitation makes me feel supported in this moment of social isolation
5.The remote rehabilitation service was activated at the right time
6.Telerehabilitation allows therapists to learn about aspects of my child's everyday life
7.Telerehabilitation can be effective for maintaining my child's therapeutic goals
8.Telerehabilitation can be an effective means for enhancing my child's therapeutic goals
9.I am concerned about the possible consequences of the lack of traditional therapy
10.Telerehabilitation allowed me to better understand my child's abilities
11.I am satisfied with the amount of telerehabilitation time dedicated to my child
12.I am satisfied with the therapist's continuity
13.I had difficulties in carrying out the therapeutic programs
14.Connection problems affected the quality of the therapy session
15.Playing the role of the therapist with my child is overwhelming

B



1.Telerehabilitation helps me organize my days
2.It is important for me to continue my therapy schedule
3.Continuing the treatment plan via telerehabilitation makes me feel supported in this moment of social isolation
4.Telerehabilitation makes me feel in line with the in-person therapy plan
5.Telerehabilitation allows me greater control over my program schedule
6.Telerehabilitation allows therapists to learn about aspects of my everyday life
7.Telerehabilitation allows the therapist to get to know my skills better
8.Telerehabilitation can be effective for maintaining my therapeutic goals
9.Telerehabilitation can be an effective means for enhancing therapeutic goals
10.Telerehabilitation can help can help people with disability that are confined to their home
11.Telerehabilitation can be a useful addition to traditional therapy
12.I am satisfied with the duration of telerehabilitation
13.I am satisfied with the therapist's continuity
14.As a patient, telerehabilitation has taught me more about myself
15.Telerehabilitation cannot replace my traditional therapy

C



1.Telerehabilitation supports users and their families during this period of social isolation
2.Continuing the treatment plan via telerehabilitation makes me feel less concerned for my patient's health
3.As a health professional providing treatment via telerehabilitation during this health emergency makes me feel safe
4.I feel that my skills are useful to patients and / or to their families right now
5. Telerehabilitation can make the patient and / or family more competent
6.Telerehabilitation can be effective in maintaining the goals achieved
7.Telerehabilitation can be effective for the progress of therapeutic goals
8.Telerehabilitation can have unexpected health benefits for patients
9.Telerehabilitation can effectively replace traditional therapy during a health emergency
10.Telerehabilitation can be a useful method in addition to traditional therapy
11.I feel I can support my patients and / or their families during this health emergency
12.I feel prepared for the tasks required by telerehabilitation
13.Using remote media during the therapy session is tiring
14.Lack of physical contact is an important limitation to my work
15.Connection problems influenced the quality of the telerehabilitation sessions
16. It is difficult to develop therapy programs for telerehabilitation
17.I had difficulties making the patient and / or family comply to my programs
18.Some telerehabilitation interventions can be used to support traditional therapy
19. My telerehabilitation experience will change the way I deal with patients and families when I return to traditional therapy
20.My telerehabilitation experience will change my evaluation of critical family issues and their environmental resources when I return to traditional therapy

FIGURE 2 | (A) Results of children's caregivers' perception questionnaire. **(B)** Results of adult patients' perception questionnaire. **(C)** Results of rehabilitation professionals' perception questionnaire. Means and SD values are represented.

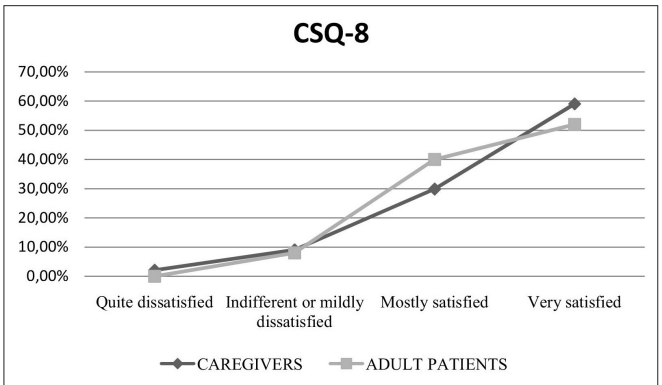


FIGURE 3 | Results of the CSQ-8 of children's caregivers' and adult patients' samples.

thus, telerehabilitation could be suggested as an alternative method during a health emergency. Caregivers expressed a good perception of the timely service activation, the specialist's constant presence and the feasibility of the required task. These results are supported by the efforts made to quickly activate the service, to ensure continuity of care by the same therapists and by guaranteeing the treatment plan (88.19%). Good perception of the feasibility of the required tasks may depend on the patient-designed treatment conducted by the same therapist who knew the child and his/her family.

Caregiver's concern about the possible consequences of interrupting the in-person therapy is probably due to parental anxieties and worries about their child's condition (18–21). Parents of children with complex needs often feel they do not have enough resources to take care of their children. In addition to this, during lockdown, parents had to play many different roles, including that of therapists, increasing their sense of inadequacy and inducing fears about the possible consequences of poor practice (22–24). Based on the logit regression, playing the role of therapists was perceived as overwhelming by parents of children aged 0–3 years. This burden could be aggravated by the attention and care required by babies and toddlers in general and by fear of COVID-19 (25, 26).

Logit regression reported a relationship between a low perception of the effectiveness of telerehabilitation in the enhancement of therapeutic goals and parents of 0- to 3-year-old children.

Parents are aware that before the age of 2, the brain is still developing and there is a critical developmental window in which an early intervention may influence brain development, and this knowledge could explain results (19, 27).

The same group of parents showed a correlation with the statement that "telerehabilitation helps them to organize the daily schedule." Mothers of disabled children seem to have a higher level of stress induced by daily routines (28). Lockdown caused changes in daily schedule, increasing parents' stress level (26, 29). Remote sessions might have allowed parents to maintain a fixed appointment within an uncertain family routine.

Logistic model also showed a higher probability of caregivers of children over 6 years of age to express a low level of agreement with the statement that "telerehabilitation makes them feel in line with the in-person therapy plan." Changes in therapeutic goals, expectations, and concerns vary with child's age and clinical condition.

Parents of children with cerebral palsy, under the age of 2 and aged between 2 and 4, are more concerned about motor skills while parents of children aged over 6 years are mainly concerned about worsening of clinical conditions (30). In-person therapy suspension may have increased parent's worries about the child's abilities worsening and could have led them to perceive telerehabilitation as an interruption of continuity of care and to express a low level of satisfaction.

The logistic regression model revealed a correlation between the group of caregivers of children whose amount and type of therapy was not guaranteed and a low level of satisfaction with the telerehabilitation service, confirming that the continuity of care and of therapists influences parents' satisfaction of therapy intervention (31). Moreover, results showed further correlations among this group of caregivers and statements regarding "not feeling in line with the in-person therapy" and being "concerned about the possible consequences of the lack of traditional therapy." These results are supported by the interruption of the treatment plan, by the increased concerns, and by the changes in the treatment plan during telerehabilitation.

Logistic regression showed a negative relation between the group of caregivers who expressed "no experience with remote media" and a very high level of satisfaction about the service provided, confirming previous research (32, 33).

Caregivers under the age of 40 showed a higher probability to express that "telerehabilitation made them feel supported during lockdown"; this could be related to the emotional impact of social isolation on this age group (34–37).

Other important personal characteristics of the caregiver group may have influenced the perception of telerehabilitation, such as the severity of the child's disability, the presence of siblings and their age, and if caregivers were working remotely or in the workplace. The analysis of these additional factors could provide more elements for the interpretation of caregivers' perception of telerehabilitation.

CSQ-8 results of caregivers' sample showed a high level of satisfaction with the telerehabilitation service provided, and this finding is in line with data reported in the literature (26, 33, 38). These data do not refer to the level of satisfaction in telerehabilitation itself (3).

Perception and Satisfaction of Telerehabilitation by Adult Patients

Compared to pediatric patients, adherence rate of adults to telerehabilitation was lower (8.14 and 52.17%, respectively). This can be due both to the greater level of skepticism and to the frequent need of a not-easy-to-find caregiver's assistance to execute the requested exercises. Skepticism about the potential efficacy of telerehabilitation in promoting improvement and goal enhancement has been reported elsewhere in the literature, and

TABLE 1 | Results of forward stepwise logistic regression relative to the children's caregivers' sample.

Independent variables	Dependent variables	*B*	SE	*p*	OR	95% CI	
Child aged 0–3 years	High level of agreement with the sentence: *"Telerehabilitation helps me organize my days with my child"*	1.08	0.41	0.008	2.96	1.32	6.64
	Very low level of agreement with the sentence: *"Telerehabilitation can be effective means for enhancing my child's therapeutic goals"*	1.87	0.75	0.013	6.51	1.47	28.75
	High level of agreement with the sentence: *"Playing the role of the therapist with my child is overwhelming"*	1.18	0.50	0.019	3.27	1.21	8.78
Rehabilitation programs modified	Very low level of agreement with the sentence: *"Telerehabilitation makes me feel in line with the in-person therapy plan"*	2.26	0.86	0.009	9.61	1.75	52.59
	Low level of agreement with the sentence: *"Continuing the treatment plan via telerehabilitation makes me feel less concerned about my child's health"*	2.76	1.04	0.008	15.83	2.03	122.9
	Very high level of agreement with the sentence: "*I am concerned about the possible consequences of the lack of traditional therapy"*	1.43	0.58	0.014	4.20	1.34	13.12
	Very low level of agreement with the sentence: *"Telerehabilitation has allowed me to better understand my child's ability"*	1.73	0.78	0.027	5.67	1.21	26.51
	Low level of satisfaction	1.59	0.80	0.048	4.97	1.01	23.80
Child aged >6 years	Low level of agreement with the sentence: *"Telerehabilitation makes me feel in line with the in-person therapy plan"*	0.96	0.45	0.036	2.61	1.06	6.43
	Low level of satisfaction	1.71	0.68	0.013	5.54	1.14	21.31
No experience with remote media	Very high level of satisfaction	−0.76	0.34	0.028	0.46	0.23	0.92
Caregiver aged <40 years	Very high level of agreement with the sentence: *"Continuing the treatment plan through telerehabilitation makes me feel supported in this moment of social isolation"*	8.24	0.37	0.028	2.27	1.09	4.75

Only significant independent variables are shown (B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval).

it could explain reluctance to consider telerehabilitation as a replacement of face-to-face therapy (39, 40). This reluctance may also be related to the lack of knowledge and experience of this practice, despite the fact that telerehabilitation has shown its efficacy on motor, speech, and cognitive outcomes of adults with neurological disabilities, according to the recent review by Maresca et al. (41–44).

These observations suggest that telerehabilitation should not be generalized. Before proposing this method, its pros and cons, its acceptance, technological resources, confidence with remote media, need and availability of a caregiver's assistance, stress level, and compliance should be considered (45).

Due to the small sample size, a multivariate analysis could not be carried out; thus, the results of this sample's perception and satisfaction with telerehabilitation should be interpreted only as hypotheses.

As for the caregivers' group, adults showed a high level of satisfaction, in line with data reported in previous studies on videoconferencing-delivered interventions (46–49).

Perception of Rehabilitation Professionals

Professionals also expressed a medium-high level of telerehabilitation perception.

Specialists' answers showed that telerehabilitation allowed them to use their professional abilities for offering support, continuity of care, and a safe environment during lockdown (39).

Alternating telerehabilitation with face-to-face therapy could guarantee both safety of all stakeholders and continuity of care during the phase following lockdown (15).

Professionals reported a high level of agreement with the statement regarding the potential effect of telerehabilitation in enhancing the sense of competence of patients and caregivers in relation to the disability. This perception, based on a screen-mediated observation during remote treatment, has been assessed in previous studies in which professionals' feedback during sessions has shown to make patients and caregivers proactive, thus empowering their ability to care for their loved ones (23, 49–59). Based on the logit regression, remote media skilled professionals and those below the age of 40 have a

TABLE 2 | Results of forward stepwise logistic regression relative to the Rehabilitation Professionals' sample.

Independent variables	Dependent variable	*B*	SE	*p*	OR	95% CI	
NDDs/PTs/OTs	High level of agreement with the sentence: "*Telerehabilitation is important to support users and their families in this time of social isolation*"	1.74	0.67	0.01	5.68	1.51	21.42
	High level of agreement with the sentence: *"Telerehabilitation can be effective in maintaining the goals achieved"*	1.66	0.79	0.036	5.28	1.14	25.09
No experience with delivering care remotely	Very high level of agreement with the sentence: *"Telerehabilitation can be a suitable model of intervention to replace traditional therapy in emergency situations"*	2.12	1.01	0.037	8.30	1.14	60.53
Previous experience with delivering care remotely	High level of agreement with the sentence: *"Telerehabilitation can be useful as a method in addition to traditional therapy"*	2.25	0.80	0.005	9.52	1.96	46.15
Confidence with remote media	High level of agreement with the sentence: *"Telerehabilitation can make the patient and/or the family more competent"*	2.00	.093	0.032	7.43	1.19	43.39
Age < 40 years		2.26	1.07	0.035	9.58	1.17	78.76

Only significant independent variables are shown (B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; NDDs, neurodevelopmental therapists; PTs, physical therapists; OTs, occupational therapists; ST, speech therapists; PSY, Psychologists).

higher probability to report that telerehabilitation could favor the patient's/family's sense of competence.

In line with the family-centered model, an integration of in-presence therapy with a self-performed or caregiver-mediated home treatment in telerehabilitation could be suggested.

Only a medium level of agreement with the potential benefit of telerehabilitation in enhancing therapeutic goals was reported by professionals. This may be related to skepticism and concern for their patients' clinical outcome. The lack of adequate training, the sudden activation of a treatment method unknown to most of them, and the effort required for adapting the treatment method may be responsible for the fatigue expressed by professionals (15).

Results show that therapists perceived the lack of physical contact as a fundamental limitation to their work as indicated in other studies (60, 61).

Logit regression analysis showed a significant association between the group of physical, occupational, and neurodevelopmental therapists and a good perception of telerehabilitation as a feasible method for maintaining therapeutic goals. Although data are based only on clinical observations made during video calls and not by formal assessment of therapeutic goals, these results are in line with previous studies (62–66). No significant correlations were observed among the level of agreement with the statements and the group of speech therapists and psychologists.

The different level of confidence with remote media and with remote delivered treatment was found to be significantly related to a different perception of telerehabilitation. Based on the logistic analysis, professionals with previous experience in remote delivered treatment have greater odds to perceive telerehabilitation as useful in addition to traditional therapy while those without experience have greater odds to perceive telerehabilitation as a replacement of traditional therapy only in emergency situations. Specific training and dedicated funds are suggested in order to make this a more feasible approach (4, 67). In line with Maresca et al., studies aimed to assess cost-effectiveness of telerehabilitation should be carried out in order to endorse this practice during and beyond periods of health crisis (41).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Independent Ethic Committee of the Research Institute of the Santa Lucia Foundation. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CAs: survey design, interpretation of data, and manuscript writing. CAn: critical writing revision. HC and TG: survey design. PG: contribution to the design. SP: statistical analysis and interpretation of data. DM: survey design, survey creation, and interpretation of data. All authors have approved the final version of the article and contributed to the study design.

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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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CASE REPORT
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Case Report: Posterior Reversible Leukoencephalopathy Syndrome (PRES) as a Biologically Predictable Neurological Association in Severe COVID-19. First Reported Case From Australia and Review of Internationally Published Cases

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Reports of different types of neurological manifestations of COVID-19 are rapidly increasing, including changes of posterior reversible leukoencephalopathy syndrome (PRES). Here we describe the first reported case of COVID-19 and PRES in Australia diagnosed on basis of MRI brain imaging and confirmed clinically by presence of confusion, delirium, headaches, also associated with hypertension and blood pressure variability and stable long-term kidney problems. He made full recovery as his blood pressure was controlled and clinical status was supported with appropriate supportive therapy. Although traditionally a rare condition, PRES is likely to be more common among patients with COVID-19 pathobiology there is Renin downregulation of ACE2 receptors, involvement of Renin-Angiotensin-Aldosterone system, endotheliitis, cytokine storm, and hyper-immune response. Thus we advocate clinical suspicion and early brain imaging with MRI brain among vulnerable patients with known co-morbidities, and diagnosed with COVID-19 given that hypertension and blood pressure variability are often exacerbated by acute SARS-CoV-2 immune reactions. Such acute hypertensive encephalopathy was able to be reversed with timely supportive therapy ensuring re-hydration and re-establishment of blood pressure control.

Keywords: posterior reversible encephalopathy syndrome (PRES), COVID-19, SARS-CoV-2, hypertension, case report

INTRODUCTION

A new β corona virus, severe acute respiratory syndrome coronavirus2 (SARS-CoV2) emerged as a novel cause of pneumonia in December 2019. Since then the SARS-CoV2 has spread to over 216 countries and is now regarded as a major world pandemic (1). As of 21st of December, the mortality rate of COVID-19 (disease caused by SARS-CoV2 infection in humans) is being

reported as 2.20% with the number of confirmed deaths as 1,699,878 and 77,184,964 recorded cases worldwide. Reports of different types of neurological manifestations of COVID-19 are rapidly increasing including a number involving COVID19 and posterior reversible leukoencephalopathy syndrome (PRES) and acute disseminated encephalomyelitis (ADEM) (2) confirmed with brain imaging). Several studies have described that Corona viruses are associated with CNS disease such as ADEM (3–5) as evidence of more long-lasting impact.

We present, to our knowledge the first reported case of posterior reversible encephalopathy syndrome (PRES) associated with severe acute respiratory syndrome coronavirus2 (SARS-CoV2) in Australia. A comprehensive literature review revealed that 18 cases since December 2019 had been documented worldwide by late August 2020 though as shown in **Table 1** it is noteworthy than only 5/14 cases occurred in COVID patients without serious history of co-morbidities.

A 55-year-old man with known hypertension compliant with medications, obesity, chronic renal impairment secondary to hypertensive nephropathy [baseline eGFR 24 (normal >60)], a 35 pack-year history of smoking, obstructive sleep apnea and hypercholesterolaemia was part of a family cluster of acute infections with SARS-CoV2 1 week prior to the admission to our hospital. The index case and the family (wife and four children) were positive for SARS-CoV2. In particular, he was experiencing headaches, fever, and dry cough for the prior 7 days. There was no report of nausea and/or vomiting during the preceding week. Prior to hospitalization, the family physician had prescribed oral dexamethasone 6 mg daily. On day seven, his daughter and wife found to him significantly lethargic, confused and disorientated and brought him to the Emergency Department (E.D) where he was admitted to hospital.

Apart from his altered mentation, he appeared normal on examination in the ED. At the time of admission, his respiratory

TABLE 1 | Studies of PRES in COVID-19.

Author	Study design	Age/Sex	Comorbidities	Laboratory features	Neuroimaging features
Coolen et al. (6)	Case series	NA	NA	NA	Superior parietal precentral and parieto-occipital cortico- subcortical swelling with marked supratentorial white matter changes
Franceschi et al. (7)	Case series	48M	Obesity	NA	Vasogenic edema posterior parieto-occipital region, extensive petechiae on SWI throughout the corpus callosum
		67F	HTN, DM, IHD, Gout	NA	Restricted diffusion with edema of the parieto-occipital lobes, right frontal, basal ganglia, and cerebellar hemispheres
Princiotta Cariddi et al. (8)	Case report	64F	HPN, AF, Dyslipidemia, OSA, hyperuricemia	High CRP Normal CSF NLR = 7	Bilateral parieto-occipital FLAIR changes with subacute hemorrhages
Parauda et al. (9)	Case series	64–74 (2M, 2F)	1) HT,DM 2) DM, Dyslipidemia	High D-dimer, ferritin, LDH, CRP	Parieto-occipital FLAIR changes, microbleeds in SWI
Doo et al. (10)	Case series	55M, 64M	1) DM 2) Ex-smoker	NA	Extensive parieto-occipital edema
Kaya et al. (11)	Case report	38M	None	High CRP and ferritin, marked lymphopenia	Extensive edema of bilateral (left occipital, frontal cortical splenium of the corpus callosum)
Gomez-Enjuto et al. (12)	Case report	74M	Multiple myeloma	NA	Bilateral parieto-occipital and frontal FLAIR changes
Conte et al. (13)	Case report	63F	None	NA	FLAIR hyperintensities in both hemispheres, evidence of SAH with effusion on left pre-central sulcus, gad-enhancement in the posterior white matter
Rogg et al. (14)	Case report	59M	None	NA	FLAIR changes in the posterior white matter
Kishfy et al. (15)	Case series	58M 67F	1) HTN, Dyslipidemia 2) HTN, Obesity	High inflammatory markers in both with nadir in recovery phase	FLAIR hyperintensities in both occipital lobes, both temporal lobes
Anand et al. (16)	Case series	61F	None	NA	Symmetric white matter T2 hypertintensities involving the parieto-occipital lobe without diffusion restriction
		62F	HIV	Crea 4.33 mg/dL CSF: high protein, high glucose with pleocytosus	Diffuse white matter T2 hypertintensities involving the parieto-occipital, frontal, and temporal loves with partial sulcal effacement

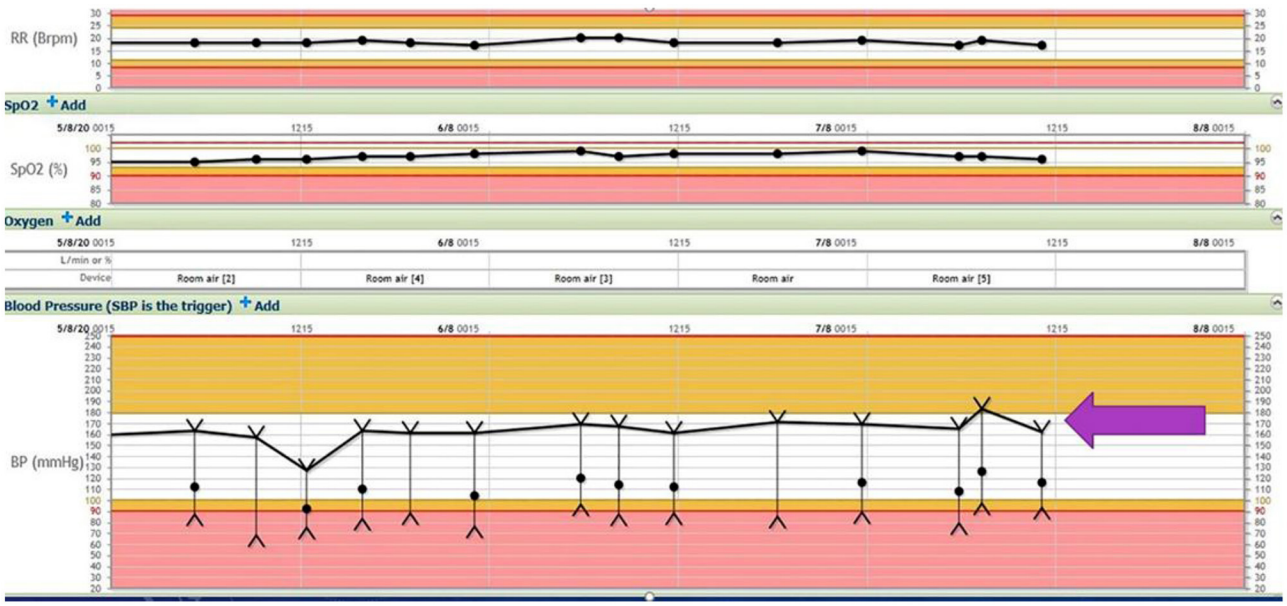


FIGURE 1 | Respiratory rate, oxygen saturation, and blood pressure variability (block arrow) throughout the hospital stay (SBP 180–140 mmHg, DBP 60–100 mmHg).

rate was 18 and his blood pressure was 171/85 mmHg, with a mean arterial pressure of 116. His blood pressure variability is shown in **Figure 1** below.

His blood examination displayed a total white cell count (WCC) of 11.5, a neutrophil count of 9.9 and a lymphocyte count of 0.6. His neutrophil-lymphocyte ratio (NLR) was 16.5 compared to expected value of <2 for his age group. C- reactive protein was also significantly elevated (132 mg/L compared to expected <5 mg/L) at admission. There was mild elevation in his creatinine levels from baseline. He was maintained on Moxonodine 200 mcg bid and his usual blood pressure medication, Prazosin 1 mg bid. He was found to be coherent on the third day after admission and was discharged home. On discharge, his total WCC had improved to 7.8, with a neutrophil count of 5.8 and lymphocyte count of 0.6. His NLR was thus 13.

A CT scan of his brain on admission showed bilateral hypointensities around his posterior parietal-occipital regions (see **Figure 2**). A subsequent cranial MRI taken on the same day revealed bilateral parieto-occipital T2 FLAIR (fluid attenuation and inversion recovery) hyperintensities compatible with PRES given the recovering symptoms compared to VANDAL with severe illness. There were diffuse petechial hemorrhages (17) shown on SWI (susceptibility-weighted images) throughout the basal ganglia and deep white matter indicative of cerebral microbleeds (**Figures 3** and **4**). Multiple small foci of increased diffusion weighted imaging (DWI) signals with corresponding low apparent diffusion coefficient (ADC) signal were also noted in the deep white matter of the bilateral centrum semi ovale and corona radiata (not shown as the changes are barely visible on the workstation console even). These could potentially be related to chronic hypertension, although possibilities involving acute COVID-19 related microangiopathy cannot be completely discounted [well-described in VANDAL (18)].

DISCUSSION

Almost 25 years have elapsed since PRES was first described (19). Interestingly, the COVID19 pandemic has also shown a marked increase in the number of PRES cases as indicated in **Table 1**. Readily available MRI brain imaging now helps clinicians diagnose these conditions (PRES as well as VANDAL) easily though imaging after COVID infection is unlikely to be definitive if prior scans are not available. Despite the poor understanding of the exact pathophysiology of PRES, several different potential pathogenic mechanisms have been suggested. These include endothelial injury related to rapid changes in blood pressure (particularly hypertension) and the effects of infections like SARS-CoV-2 and cytokines on the endothelium disrupting the blood-brain barrier and causing associated cerebral oedema and changes to the auto-regulation of intracranial pressure raising the possibility of VANDAL, in milder form.

Normal clinical presentation of PRES includes altered mentation, headaches, visual disturbances, and seizures in patients with other underlying comorbidities. Fluctuations in blood pressure are a characteristic sign of PRES both in COVID patients and in other non-COVID associated diagnosis.

A leading theory of the pathophysiology of PRES suggests that rising hypertension exceeding the upper limit of autoregulation of cerebral blood flow culminates in hyperfusion and blood-brain barrier disruption along with the extravasation of macromolecules and plasma to interstitial tissues (20, 21).

Acute hypertension has been suggested to cause endothelial dysfunction in susceptible patients as multiple mechanisms lead

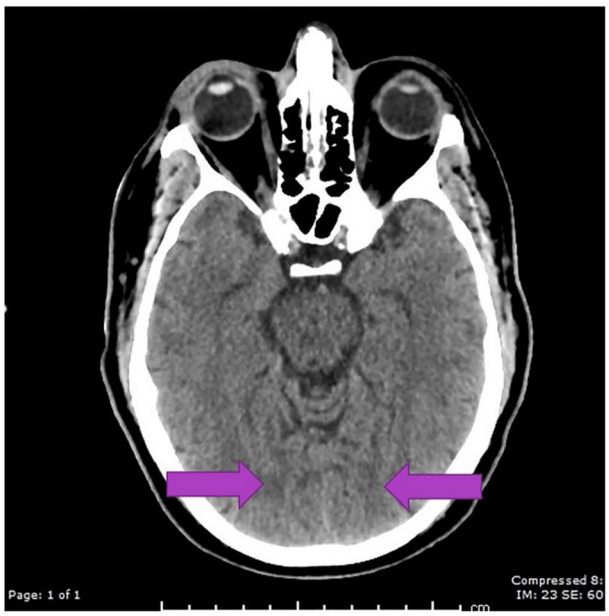


FIGURE 2 | C.T. scan with bilateral posterior parietal and occipital hypo intensities suggestive of PRES.

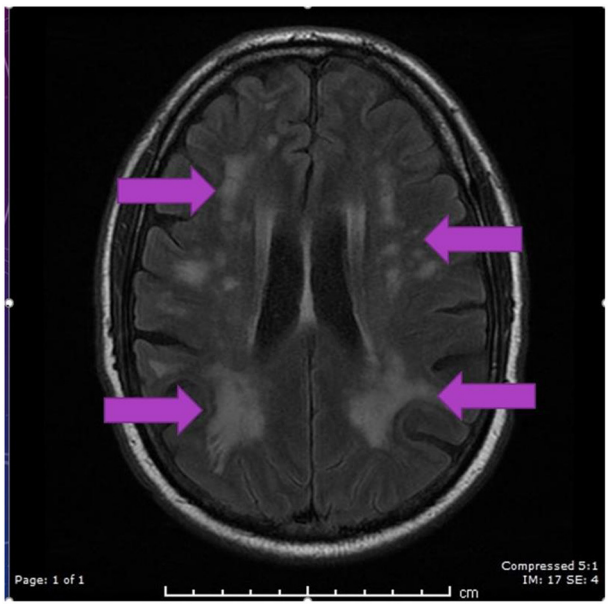


FIGURE 3 | MRI axial FLAIR image demonstrating hyperintensities in periventricular regions in both parietal, occipital and frontal regions secondary to PRES.

to an eventual breakdown of the blood-brain barrier (22). The patient's mean baseline blood pressure, blood pressure variability, proportional rise in blood pressure and rapidity of changes to blood pressure are all key factors that could potentially lead to blood-brain barrier breakdown and thus vasogenic edema (21). The direct effects of excessive circulating cytokines can cause endothelial dysfunction and PRES (23). The relationship between COVID-19 and endothelial dysfunction is notably well-recognized (24, 25).

Furthermore, it is known that COVID 19 attaches to ACE 2 receptors on endothelial cells (lung parenchyma as well as brain parenchyma) and brain microglia (26) inducing an alteration in the Renin Angiotensin Aldosterone System (RAAS) that favors the classical pathway, resulting in vasoconstriction and potential changes in blood pressure (27). This may directly or indirectly affect the cerebral vasculature, which may lead to PRES (20) or the recently described Viral Associated Necrotizing Disseminated Acute Leukocepthalopathy (18, 28).

There is no specific treatment for PRES, but symptoms are thought to be reversible once the underlying cause is removed (21). It is widely believed that appropriate treatment of hypertension, and associated inflammation is of great importance for treating PRES. A main theory of the pathophysiology of PRES suggests that rapidly rising hypertension particularly in patients with kidney problems overshoots the upper limit of autoregulation so that insufficient cerebral autoregulation leads to ongoing hyper perfusion, disruption of the blood brain barrier, endothelial dysfunction, and oedema (21). This theory is supported by a series of papers suggesting the existence of a relationship between acute hypertension and PRES relationship as well as showing that clinical and radiological improvement may be brought about by appropriate treatment of blood pressure.

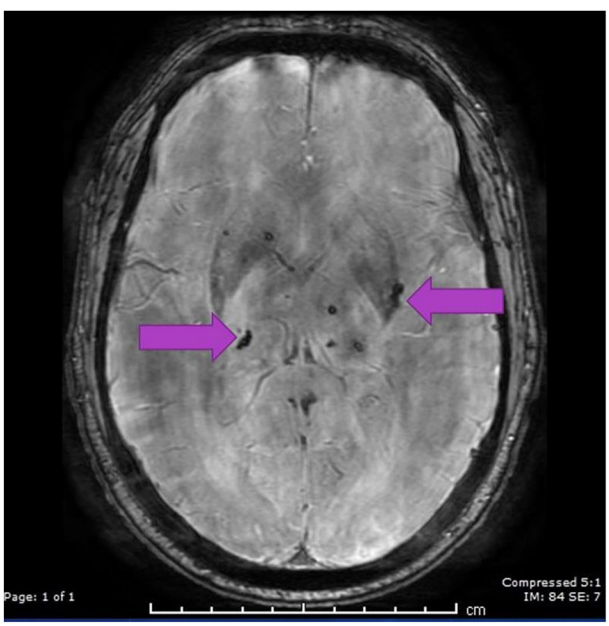


FIGURE 4 | SWI image showing cerebral microbleeds in the basal ganglia region.

While the pathophysiology of PRES or COVID induced VANDAL symptoms remains controversial, we advocate for

tight blood pressure control and MRI imaging in all COVID-19 patients who show neurological symptoms from headaches to confusion and cognitive impairment, particularly in those with hypertension, as a matter of priority both at the time of the admission as well as during recovery prior to leaving hospital. We could not perform the repeat brain imaging due to the rapid recovery of the patient and difficult access to imaging in the middle of the pandemic related logistic issues. Uncontrolled hypertension and blood pressure variability alongside viral inflammation and excessive immune responses are both potential but not unexpected risk factors for worse outcomes involving COVID-19 and its effects on vulnerable kidney patients, given its propensity to attack the RAAS system and ACE2 receptors. We hypothesize that hypertension and potentially blood pressure variability exacerbated by acute SARS-CoV-2 action on the RAAS and associated inflammation may be additional risk factors for endothelial dysfunction and hypertensive encephalopathy with modest blood pressure changes during acute infection with SARS-CoV2 (20, 21, 29–32).

While most patients will fully recover from PRES, the extent of recovery and exactly how reversible symptoms of PRES or VANDAL are, is not known, given the definitions of both disorders are of a symptom of an underlying co-morbidity and particularly now in the presence of COVID. In a postmortem brain MRI study Coolen et al. (6), described hemorrhagic and PRES related brain lesions in non-survivors of COVID-19 (3). Hemorrhagic lesions are also not uncommon among non-COVID related PRES, but with patterns such as intraparenchymal and subarachnoid hemorrhage favoring the later (24, 25). These premises also make PRES a misnomer in several ways (2). Interestingly, Agarwal et al. also described eight cases of critically ill COVID19 cases who demonstrated diffuse changes in the white matter evolving into necrotizing cystic cavitation after a few weeks, an entity which has been termed as Virus- Associated Necrotizing Disseminated Leukoencephalopathy (VANDAL) (26). In contrast to the outcomes described in this series, the index patient described had a good prognosis. Whether an overlap between COVID-related PRES and VANDAL exists need further investigation though is likely.

More research needs to be done into the specifics of both PRES and VANDAL disorders. COVID-19 is a very likely risk factor for PRES except the oedema seen is often more than that induced preferentially by the basilar artery. Thus, we argue that more vigilance is required to detect cognitive and neurological symptoms in these patients and to facilitate appropriate neuroimaging earlier enough and then again when symptoms dissipate. Surveillance neuroimaging is also necessary to determine radiologic outcomes. Tight control of blood pressure and reducing the risk of blood pressure variability and inflammation and hence potential for any further cytokine storms that are likely initiators endothelial cell damage allowing fluid leakage to the brain are likely to be helpful in this context.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written, informed consent was obtained from the participant for the publication of this case report (including all data and images).

AUTHOR CONTRIBUTIONS

TW conceived the idea and wrote the first draft of the manuscript. CW, CS, LK, and SC edited and contributed to the final manuscript. All authors approved the final manuscript.

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SYSTEMATIC REVIEW
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COVID-19 Pathophysiology Predicts That Ischemic Stroke Occurrence Is an Expectation, Not an Exception—A Systematic Review

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Clinical reports of neurological manifestations associated with severe coronavirus disease 2019 (COVID-19), such as acute ischemic stroke (AIS), encephalopathy, seizures, headaches, acute necrotizing encephalitis, cerebral microbleeds, posterior reversible leukoencephalopathy syndrome, hemophagocytic lymphohistiocytosis, peripheral neuropathy, cranial nerve palsies, transverse myelitis, and demyelinating disorders, are increasing rapidly. However, there are comparatively few studies investigating the potential impact of immunological responses secondary to hypoxia, oxidative stress, and excessive platelet-induced aggregation on the brain. This scoping review has focused on the pathophysiological mechanisms associated with peripheral and consequential neural (central) inflammation leading to COVID-19-related ischemic strokes. It also highlights the common biological processes shared between AIS and COVID-19 infection and the importance of the recognition that severe respiratory dysfunction and neurological impairments associated with COVID and chronic inflammation [post-COVID-19 neurological syndrome (PCNS)] may significantly impact recovery and ability to benefit from neurorehabilitation. This study provides a comprehensive review of the pathobiology of COVID-19 and ischemic stroke. It also affirms that the immunological contribution to the pathophysiology of COVID-19 is predictive of the neurological sequelae particularly ischemic stroke, which makes it the expectation rather than the exception. This work is of fundamental significance to the neurorehabilitation community given the increasing number of COVID-related ischemic strokes, the current limited knowledge regarding the risk of reinfection, and recent reports of a PCNS. It further highlights the need for global collaboration and research into new pathobiology-based neurorehabilitation treatment strategies and more integrated evidence-based care.

Keywords: COVID-19, stroke, ACE2, cytokines, pathogen associated molecular pattern, post Covid19 neurology syndrome, PCNS

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INTRODUCTION

Since the first case of coronavirus disease 2019 (COVID-19) infection was reported in Wuhan, China in December 2019, a significant number of thrombotic complications affecting the venous and arterial systems have been published in the literature (1–3), with the World Stroke Organization now recognizing that acute ischemic stroke (AIS) increases the severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) viral infection by 2.5-fold (4, 5). Similar associations between systemic infections, inflammation, and AIS are longstanding (6). However, to date, few reports are reviewing the molecular bases of the peripheral and central mechanisms induced by SARS-CoV2 infection and potential neurological manifestations with focused attention on AIS.

Neurological manifestations of COVID-19 infection were first described by Mao et al. who observed six cases of acute cerebrovascular disease (2). Subsequently, 19 cases of COVID-19-related strokes particularly affecting the young and involving medium to large arteries were reported from a tertiary center in New York (3), highlighting the need for better understanding of the potential mechanisms linking COVID-19 and AIS.

Stroke has been associated with other earlier coronavirus infections. In 2002, AIS was first detailed by Umapathi et al., in 4 of 206 patients who presented with large vessel occlusion associated with SARS-CoV infection in Singapore in 2002 (7). Two other patients with AIS were also described in Middle East respiratory syndrome corona virus (MERS-CoV)-infected patients in Saudi Arabia during the 2015 epidemic (8).

SARS-CoV2 is known to initially bind to the angiotensin-converting enzyme 2 (ACE2) receptors of epithelial and endothelial cells where an immediate immunological activation occurs that can, in severe cases, eventually lead to hypercoagulability or thrombophilia and increased tendency of clots forming in the blood and potentially AIS (9). However, there is limited information on the physiological abnormalities and mechanisms linking COVID-19 and AIS, although a number of mechanisms have been proposed. The major mechanisms that have been proposed to date include systemic innate immunity-mediated hyperinflammation, neurovascular endothelial dysfunction, endotheliitis, central nervous system renin–angiotensin–aldosterone system (RAAS) dysregulation, oxidative stress, and excessive platelet aggregation (10–12). Thus, this scoping review aimed to elucidate potential pathophysiological mechanisms predisposing patients with COVID-19 to a higher risk for neurovascular events.

METHODOLOGY

The authors of this scoping review used the Arksey and O'Malley methodology to identify and extract useful literature (13). The steps undertaken include (1) research questions identification; (2) relevant literature identification; (3) screening and selection of relevant literature; (4) data charting; and (5) analyzing, summarizing, and reporting the results.

Identification and Development of the Research Question

This focused on the general research question: "Are there mechanisms associated with COVID-19 infection that are likely to predispose patients to ischemic stroke?"

The following are the specific areas of interest:

a. Can current understanding of the immunological mechanisms associated with the inflammatory responses to severe COVID-19 potentially predispose a patient to AIS?

b. Are there other potential pathophysiological mechanisms predisposing COVID-19 patients to upregulate procoagulable mechanisms leading to thrombi formation and potentially AIS?

Relevant Literature Identification

A literature review of articles regarding cases and mechanisms underlying the co-occurrence of COVID-19-and AIS, published in English between January 2000 and August 12th, was carried out up to August 15th, 2020. Only studies (qualitative and quantitative studies, systematic reviews, metanalysis, case reports, and case series) that directly or indirectly link pathophysiological mechanisms to ischemic stroke and COVID-19 infection have been included in the final review (see **Table 1** detailing the studies).

Screening and Selection of Relevant Literature

In the first step, MEDLINE, Cochrane, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched to identify useful keywords. Subsequently, the identified keywords were used to search the same databases for relevant studies. The literature was first screened at the title and the abstract level; then, full-text articles were assessed for eligibility. The manual bibliographic search of identified studies was also done in the last step of the literature search. The following keywords were used: COVID-19, coronavirus, mechanism, inflammation, thrombosis, embolism, endotheliitis, arteritis, neuroinflammation, and ACE2 receptors. Two researchers (CS and TW) reviewed relevant articles independently. Any disagreement for inclusion was resolved by a third author (LK).

Data Charting and Analysis

The included studies were charted, and the following parameters were taken into account: publication year, type of study, aims and objectives of the study, and study findings and conclusion. Included studies were analyzed extensively and are listed in **Table 1**.

RESULTS AND ANALYSIS

A total of 1,539 studies were identified in the electronic search. After removal of duplicates and screening at the title level, 230 articles were further reviewed at the abstract level, yielding 88 articles requiring assessment. Fifty-eight further articles were excluded, as these papers were not addressing the predefined research questions. A thorough review by two authors (CS and TW) deemed these papers to contain secondary information with repetition rather than an original contribution to the research

TABLE 1 | Summary of the main studies on the mechanisms of COVID-19-related strokes.

Publication date	Author	Type of study	Objectives	Conclusion
July 18, 2020	Kempuraj et al. (14)	Review article	To understand the relationship between COVID-19 infection and the neuroinflammatory responses in the brain, especially concerning psychological stress, mast cell activation, and cytokine storm–associated responses.	COVID-19 19 can worsen neuroinflammation thru activation of mast cells, neurons, astrocytes, microglia, endothelial cells, and increase inflammatory cytokine and chemokine levels in the CNS
June 26, 2020	van den Berg et al. (15)	Review article	To review the role of NLRP3 inflammasome dysregulation in the severe COVID-1919 infection.	NLRP3 inflammasome and its associated pathways plays an important role in severe COVID-19 19 infection especially in patients with impaired immune function and predisposes patients with pre-existing suboptimal immune responses to poor outcomes.
June 19, 2020	Rodrigues-Diez et al. (16)	Review article	To discuss the potential benefits of statins in COVID-1919 infection.	Statins could reduce viral replication by autophagy activation and exert anti-inflammatory properties particularly on NF-κB and NLRP3 inflammasomes. It can also modulate coagulation responses.
April 14, 2020	Zuo et al. (17)	Prospective Cohort study	To assess the role of neutrophil extracellular traps (NETs) in COVID-19 19 infection and identify the relationship to severity of illness.	High levels of NETS in patients with COVID-19 19 may contribute to cytokine release and respiratory failure.
June 2, 2020	Tomar et al. (17)	Review article	To identify the role of enhanced neutrophil infiltration and the release of NETs, complement activation and vascular thrombosis during necroinflammation in COVID-19	NET formation induces production of proinflammatory cytokines leading to tissue inflammation responsible for cytokine storm and sepsis.
June 29, 2020	Middleton et al. (18)	Prospective Cohort study	To assess the role of neutrophil extracellular traps (NETs) in COVID-19 19 infection and identify the relationship to severity and progression of illness.	Neutrophils of COVID-19 19 patients displayed excessive NET at baseline and was blocked by neonatal NET-Inhibitory factor. Levels also correlate with intubation and death.
May 2010	Hermus et al. (19)	Review article	To identify the biomarkers associated with carotid plaque formation	Various biomarkers linked to inflammation, lipid accumulation, thrombosis and angiogenesis have been related to plaque formation and vulnerability.
July 2020	Mohamud et al. (20)	Case series	To describe six cases of COVID-19 positive patients with associated intraluminal carotid artery thrombus.	Inflammation related to COVID-19 19 may lead to plaque rupture of previously known vulnerable atheroma leading to thrombosis an ischemic stroke.
June 27, 2020	Ueland et al. (21)	Letter to the editor/prospective Cohort study	To identify relationship of plasma markers reflecting inflammation and fibrosis and respiratory failure in hospitalized COVID-19 patients.	Methyl-metalloproteinases (MMP) may be an early indicator of respiratory failure in COVID-19 patients and underscore the role ECM remodeling and fibrosis in this disorder.
June 5, 2020	Solun et al. (22)	Review article	To review the role of matrix MMP and the kinin-kallikrein system (KKS) in the pathomechanism associated with COVID-19 19 related acute lung injury.	Overexpression of MMP results in acute lung injury and remodeling among COVID-19 19 patients and the use of its inhibitor may be a potential therapeutic strategy.
June 29, 2020	Schönrich et al. (23)	Review article	To review the role of overproduction of reactive oxygen species (ROS) in local and systemic tissue damage associated with COVID-19 19 infection.	ROS increases the formation of NETs and suppresses the adaptive immune system.
May 15, 2020	Wright et al. (24)	Prospective Cohort	To determine the correlation between thromboelastography measurements of coagulation and thromboembolic events in COVID-19 19 patients.	Failure of clot lysis at 30 min on thromboelastography is predictive of thromboembolic events in critically ill COVID-19 19 patients.
July 17, 2020	Kunutsor et al. (25)	Meta-analysis	To identify the association of CRP and VTE risk.	Elevated CRP is associated with greater VTE risk, consistent with a linear dose–response relationship.

(Continued)

TABLE 1 | Continued

Publication date	Author	Type of study	Objectives	Conclusion
July 9, 2020	Zhang et al. (26)	Cross-sectional study	To determine the coagulation profiles of routine hemostasis tests, natural anticoagulants, coagulant factors and antiphospholipid antibodies in critically ill COVID-19 patients.	The low activities of natural anticoagulants, elevated factor VIII level and the presence of antiphospholipid antibodies, together, may contribute to the etiopathology of coagulopathy in COVID-19 patients.
June 11, 2020	DiNicolantonio et al. (27)	Review article	To identify the role of endothelial tissue expression of tissue factor in COVID-19 infection	SARS-CoV-2 infection of endothelial cells evokes the expression of TF which is contingent on endosomal NADPH oxidase activation.
June 9, 2002	Bautista-Vargas et al. (28)	Review article	To identify the role of tissue factor (TF) in the hypercoagulability associated with COVID-19 19 infection.	TF may be a critical mediator associated with the development of thrombotic phenomena in COVID-19.
September 2015	Saha et al. (29)	Review article	To identify the mechanisms associated with tissue factor production and atherothrombosis.	TF is essential in the initiation of the extrinsic pathway of the coagulation cascade and appears to be a critical determinant of atherosclerotic plaque thrombogenicity.
December 5, 2002	Akerström et al. (30)	Experimental study	To identify the role of nitric oxide in SARS-CoV infection.	SARS-CoV infection inhibits viral replication by affecting RNA replication and reduction in expressed spiked protein production.
July 2020	Cheng et al (31)	Review article	To identify the correlation between angiotensin-converting enzyme 2 (ACE2) and severe risk factors for coronavirus disease 2019	ACE2 is an essential part of the RAS, and it has extensive vascular and organ protection functions in hypertension, diabetes, cardiovascular disease, and ARDS
May 7, 2020	Hess et al. (32)	Review article	To identify the role of ACE in COVID-19 related strokes.	Binding to and depletion of ACE2 may tip the RAS balance in favor of the ACE-1-angiotensin II-AT1 axis and contribute to endothelial dysfunction, organ damage, and stroke.
August 22, 2008	McColl et al. (6)	Review article	To explore the impact of systemic infections and inflammation on stroke susceptibility	The role of systemic infections and inflammation in stroke (onset of the stroke as well as post stroke outcome)
July 2, 2020	Ellul et al. (33)	Review article	To identify the clinical manifestation of neurological disorders caused by COVID-19	The wide assortment of neurological disorders affecting 901 patients by May 2020 (at the time of the review)
August 7, 2019	Albensi B. C. (34)	Review article	To explore the importance and science around NF-?B activity with a view to correlate this with COVID-19 and immune involvement	NF-?B is an important transcription factor with critical roles in mitochondrial function, apoptosis, mechanisms of disease in COVID-19 and brain involvement as well
September 3, 2020	Wijeratne et al. (35)	Review article	To identify the role of inflammation affecting vascular systems as well as the importance of NLR as a potential biomarker in this context	NLR is a useful and easily available biomarker in atheromatous vascular disease supporting the same role in COVID-19 and large vessel disease
June 2020	Boldrini et al. (36)	Special article	To identify the impact of COVId-19 outbreak on rehabilitation services in Italy	Increasing pressure from the acute services to transfer the patients to rehabilitation services while the challenges to provide rehabilitation services in the outpatient as well as home settings due the restrictions
June 25, 2020	Varatharaj et al. (37)	Research paper (nationwide, cross speciality surveillance study)	To identify the epidemiology of acute neurological and psychiatric complications of COVID-19 as reported by the national registry in UK.	One hundred and Twenty five patients with complete data set noted 57 had an ischemic stroke (74%), nine had intracerebral hemorrhage (12%) and one with (1%) CNS vasculitis. Thirty nine patients (31%) had altered mental status while 69% had a neuropsychiatric syndrome.
July 20, 2020	Spence et al. (11)	Review	To identify the mechanisms of stroke in COVID-19	Vasculitis, hypercoagulability, endothelialinjury, microvascular thrombosis, cytokine storm, systemic hypoxia, fresh DVT, cardiac alterations

(Continued)

TABLE 1 | Continued

Publication date	Author	Type of study	Objectives	Conclusion
September 10, 2020	Wijeratne et al. (38)	Case Report and review	1.To correlate the CRP, D-dimer levels, NLR ratio changes with variety of clinical events at the intensive care unit and neurorehabilitation ward. 2. To explore the utility of bedside tablet use such as MRF visual fields and Lee-Rayan eye-hand coordination test during neurorehabilitation	The in-depth case study illustrates the significant of close monitoring of simple blood tests such as CRP, NLR with predicable ability of clinical worsening through fast recognition of pattern changes.
June 26, 2020	South et al. (39)	Review	To identify the risk of stroke in the context of preceding infection, including COVID-19	SARS-CoV-2 global pandemic is not the first viral infection to be linked with stroke. The current pandemic is an ideal opportunity to acquire valuable insight toward the relationship between stroke and infections
September 2020	Sivan et al. (40)	Short communication (research paper)	To explore the authors, work on development of an integrated rehabilitation pathway with systematic, efficient tele-rehabilitation model	COVID-19 Yorkshire Rehabilitation Screen(C19-YRS) (previously developed telephone screening tool) can be incorporated toward an efficient, systematic, telerehabilitation pathway

questions. A total of 30 articles were included in the study. The details of the said studies are outlined in **Table 1**. The search process is summarized in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) in **Figure 1**.

At the time of this submission (as of September 5th, 2020, WHO situation report), the global number of confirmed SARS-CoV2 cases were 26,171,112 with 865,154 confirmed deaths with a mortality rate of ∼3.3%. It is also important to note that only a small proportion of COVID-19-infected individuals progress to severe disease, and of these, a smaller number experience stroke and/or death. The most likely predisposing factors to serious COVID-19 disease states are age, sex, and immune system inability to deal with environmental infection together with genetic factors, and associated cardiovascular risk comorbidities such as hypertension, diabetes, obesity, neurological disorders, and medication interactions. Indeed, it appears that exaggerated immune responses to infection and chronic inflammation may be the key factor in the pathogenesis of severe COVID-19 and associated cerebrovascular complications.

Inflammatory Mechanisms of COVID-19

Initial Inflammatory Responses (Key References Are in Table 1; at the End of the Paper)

It is currently accepted that the SARS-CoV2 virus, like other coronaviruses, attacks host cells by binding to ACE2 (12, 41–43). Initial virus recognition occurs via the epithelial cells of the olfactory and respiratory tract of the infected person (39, 43) and would be expected to immediately activate the innate immune system of individual cells and the associated vascular supply (44). The cells within the respiratory epithelia are assumed to release the first set of cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) (45) that then activate further proinflammatory macrophages and monocytes to accumulate in the alveoli.

The recruited monocytes and macrophages are a further rich source of cytokines and monocyte chemoattractant protein-1 with an additional army of immune-related cells coming to play a major component (45), as described in **Tables 2**, **3**. At this stage, the majority of individuals will be asymptomatic, while some may experience flu-like symptoms, sore throat, myalgia, diarrhea, fever and headache, etc.

The intrinsic pathogenicity of severe coronavirus infection in vulnerable people ensures that the acute severe inflammatory response to the COVID-induced respiratory distress results in decreased levels of circulating lymphocytes, secondary hemophagocytic lymphohistiocytosis (HLH) (46–50) shifts immune defenses toward natural killer (NK) and circulating macrophages (macrophage activation syndrome), and increased neutrophils. An early and important mediator to this phenomenon is the significant elevation of proinflammatory cytokines that fuel various processes in cerebrovascular ischemia (**Tables 2**, **3**). Indeed, sepsis-induced stimulation of the immune system leads to a clonal expansion of antigen-specific T lymphocytes, which result in the further release of proinflammatory cytokines and activation of cells such as macrophages and cytotoxic T lymphocytes, which are otherwise known as the HLH (51, 52), and are thought to be caused by

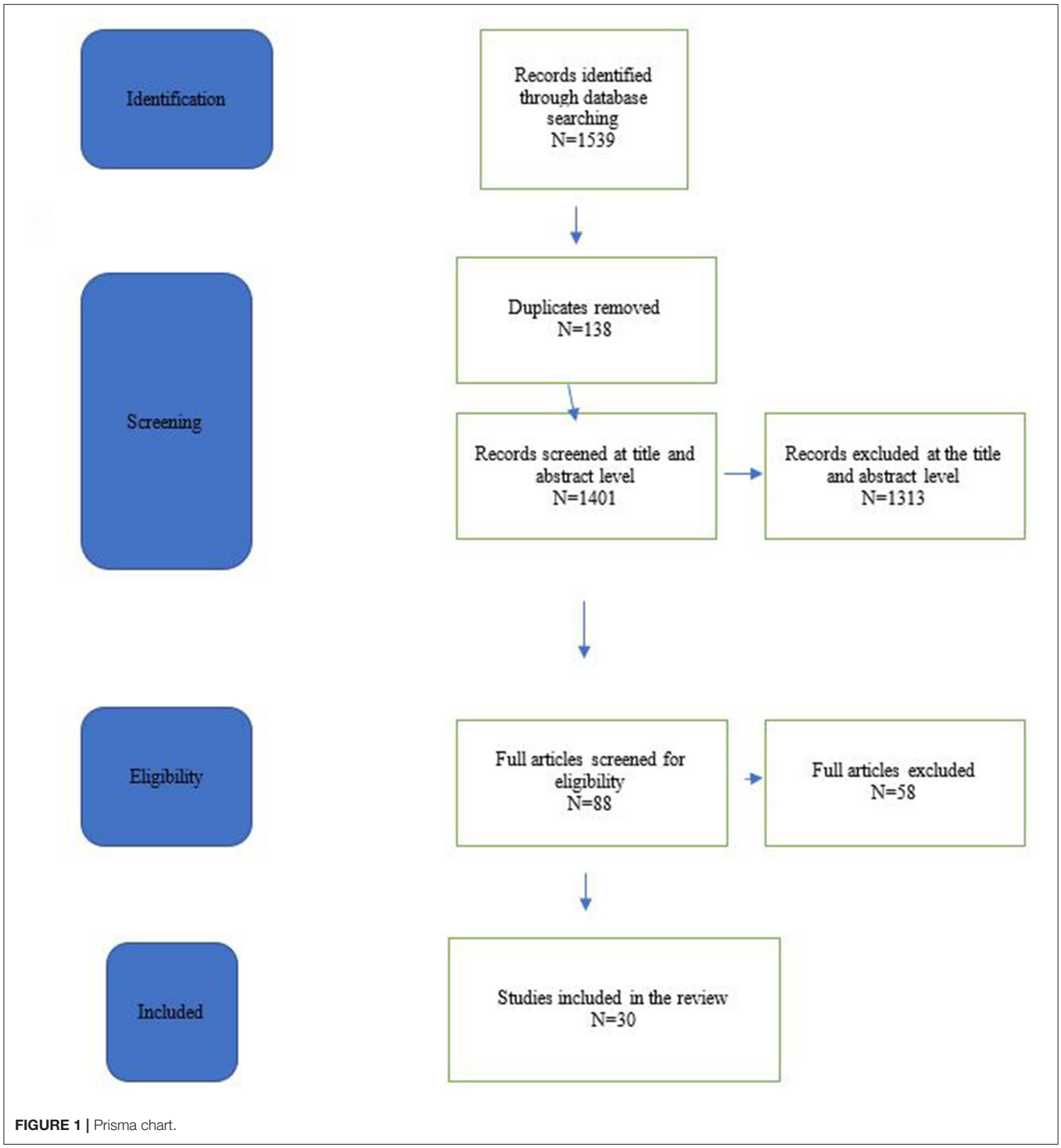


FIGURE 1 | Prisma chart.

a dysfunction of the normal regulatory mechanisms (52). As a result of the build-up of proinflammatory immune responses, an imbalance favoring the mass increase in neutrophil to leukocyte ratio, and inflammatory cytokines such as TNF, interferon-γ, IL-1, IL-6, IL-18, and IL-33 propels global inflammatory activity (52–55), which is known to lead to multiorgan dysfunction among critically ill patients (45).

Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasomes play an important role in innate immunity and are directly activated by the virus itself via the small viral protein, viroporin protein 3a, that is known to modify cellular membranes and facilitate virus release from host-infected cells (56–58). This multiprotein complex in the cytosol drives a cascade of reactions resulting in the formation

TABLE 2 | Pathophysiology of COVID-19 and acute ischemic stroke.

Pathophysiology of COVID-19 and Acute Ischemic Stroke—Chronological Order
1. Binding of SARS-CoV-2 to ACE-2 on the surface of alveolar pneumocytes (ACE2 is the receptor for host cell entry of SARS-CoV-2. ACE-2 is widely expressed on the alveolar epithelial cells, endothelial cells, enterocytes of the small intestine and arterial smooth muscle cells) (46)
2. Viral infection activates intracellular pattern recognition receptors (PRRs) in the host. PRRs sense pathogen associated molecular patterns (PAMPs) [not this is very similar to pathophysiology of AIS where acute ischemia induced damage associated molecular patterns (DAMPs) perform exactly the same task] (10, 47–49)
3. PAMPs sets off cytolytic immune responses with type one interferon and natural killer cells (NK) with aim of removing the pathogens (50)
4. Endothelial activation secondary to direct viral activation
5. Innate immune response with the recruitment of macrophages, neutrophils, and monocytes to the alveoli.
6. Further innate immune reaction with T helper cells 1&17 T cells and ongoing recruitment of monocytes, macrophages and neutrophils (51)
7. Endothelial activation secondary to direct viral action
8. Endothelial activation secondary to persistent inflammation
9. Activation of cell adhesion molecules and further recruitment of T cells, monocytes and macrophages
10. Release of tissues factors from the activated endothelium
11. Recruitment of intravascular neutrophils
12. Release of neutrophil extracellular traps (NET) from the activated endothelium
13. Release of von Willebrand factor (vWF) and micro thrombosis (52)
14. Maladapted innate immune response and procoagulant activity lead to systemic cytokine rise
15. Increased platelet aggregation and thrombo-embolism
16. Activation of cell adhesion molecules and ongoing recruitment of monocytes, macrophages and neutrophils within the cerebral blood vessels
17. Endothelial activation in cerebral blood vessels
18. Endothelial dysfunction in the brain
19. Local immune and inflammatory activity in the brain
20. Disruption of the blood-brain barrier
21. Activation of microglia in the brain
22. Further recruitment of resident immune cells in the brain
23. Increased inflammatory activity in the brain
24. Micro-thrombosis, thrombo-embolism in the brain
25. Hypoperfusion of cerebral tissues
26. Acute Ischemic stroke

**Attempts have been made to assimilate all available current evidence to formulate this table. However, we are aware the pandemic is still evolving, and additional molecular mechanisms and pathways are likely to be discovered as time goes by.*

of proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-18 (IL-18), pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), which are usually tightly regulated in patients with normal immune systems (56). Animal studies related to SARS-CoV infection have demonstrated that the overactivation of the NLRP3 inflammasome contributes to the significantly increased virulence and the high incidence of acute lung injury (59, 60). This is also one of the rationales behind the Greek Study in the Effects of Colchicine in COVID-19 Complications Prevention (GRECCO) trial, which is investigating the utility of colchicine, as a non-specific inhibitor of the NLRP3 inflammasome, in the treatment of COVID-19 infection (61, 62). By inhibiting this pathway along with nuclear factor kappa B (NF-KB) inhibition of the innate immune response (63), statins have also been shown to be potentially beneficial for patients with COVID19 infection via intervention through this pathway (64).

In patients with stroke, it has been shown that the NLRP3 inflammasome plays a significant role in cerebral atherogenesis by similar activation of the immune system and increase in macrophages, neutrophils, lymphocytes, and vascular smooth muscle cell, which also play an important role in plaque instability (65–67). The neuronal cell death, which can be attributed to the NLRP3 inflammasome activation, has also been shown to be reversible with immunoglobulin in 3-month-old mice stroke models (65). However, in patients with impaired immune responses, such as the elderly, there is an unprecedented activation of the NLRP3 inflammasome coupled with mitochondrial dysfunction and increased proportions of the mitochondrial reactive oxygen species, which further worsen tissue damage and initiate cell death (66). In patients with obesity and diabetes in which NLRP3 inflammasomes are already basally activated, and the immune responses are suboptimal, viral-induced activation of the former may worsen a preexisting chronic inflammatory state (67). Hence, this factor may be related to the poor outcomes of elderly patients with COVID-19 and stroke and with traditional cardiovascular risk factors such as obesity and diabetes (10).

Inflammation-Induced Plaque Progression and Vulnerability

COVID-19 inflammation induces a prothrombotic milieu among patients who are at risk of vascular events and those with the pre-existing atheromatous disease. Among patients with coronary disease, evidence suggests that virally induced inflammatory infiltrates such as T cells, macrophages, and neutrophils populate the atheromatous plaque leading to a cascade of events including vascular permeability, endothelial disruption, and exposure of prothrombotic elements such as collagen, tissue factor, and platelet adhesion molecules, which

TABLE 3 | Summary of Pathophysiological mechanisms of COVDI-19 related Acute Ischemic Strokes.

Inflammatory mediators of ischemic stroke	The role of cytokines	• First released by the respiratory epithelium (45) • Further released by T lymphocytes activates other cellular mediators mediating secondary hemophagocytic lymphohistiocytosis (58, 59)
	NLRP3 inflammasomes	• Activated by viroporin protein 3a (63–65) • Drives production of inflammatory cytokines, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (63) • May induce plaque instability by overdriving response of cellular mediators such as macrophages, neutrophils, lymphocytes and vascular smooth muscle cell (70–72)
	Inflammation-induced plaque vulnerability	• Predominance of T cells, macrophages and neutrophils populating an atheromatous plaque leading to plaque rupture (73) • Characterized by elevation of proteolyic biomarkers such as metalloproteinases (MMPs) and cathepsin cysteine proteases (CCP's) (19, 21, 22, 75)
	Oxidized Low-Density Lipoproteins (oxLDL)	• A marker of increased oxidative stress (23) • COVID-19-related disruption of the receptor-mediated uptake of oxLDL (78)
	Neutrophil extracellular traps (NETs)	• Networks of chromatin, proteins and oxidant enzymes that protrude from membranes of activated neutrophil and mediate infection containment (17) • Also a marker of inflammation-related thrombosis (17, 25, 35, 101–106)
Coagulatory disfunction	D-dimer	• Mediates immunologic defense systems resulting in thrombi formation (107) • Increased level is a biomarker of fibrinolytic shutdown leading to massive fibrin formation resulting in thrombosis (108).
	Natural anticoagulants and antiphospholipid antibodies	• COVID-19 induced decrease in the amounts of physiological anticoagulants and increased levels of coagulant factors and antiphospholipid antibodies (26, 109, 110)
Endotheliopathy	Endothelium-driven activation of the extrinsic coagulation system	• Imbalance in the ACE2 and angiotension II (AT-II) receptors leads to the upregulation of tissue factor (27, 28) • Tissue factor interacts with Factor VII to activate the extrinsic coagulation system (27, 28)
	Endothelium-driven nitrous oxide deficiency	• COVI-19 related endotheliopathy results in the suppression of nitric oxide synthase (NOS), resulting in nitric oxide deficiency (30) • Results in loss of vasodilatory effect and promotes adhesion of platelets and leukocytes to the vessel wall (111)
Renin Angiotensin Aldosterone System (RAAS) and ACE-2 deficiency	Alterations in the balance between the classical RAAS and the ACE2 pathways	• Promotes organ damaging effects of the classical RAAS pathway (112) • Promotes overactivity of the sympathetic nervous system resulting in the exacerbation of traditional stroke risk factors (113)

all play a role in thrombogenesis (68). Furthermore, it is known that carotid artery plaques with features of a thin fibrous cap, large core lipid, intraplaque bleeding, and the abundance of monocyte-derived macrophages and activated smooth muscle cells cause instability and vulnerability to plaque rupture (69). The presence of proteolytic enzymes such as metalloproteinases (MMPs) and cathepsin cysteine proteases (CCPs), which are secreted by activated macrophages, promote degradation of the extracellular matrix and plaque fragility and potentially result in thromboembolism (16, 34) while making acute ischemic stroke a likely event in the potential trajectories of patients with systemic COVID-19 infection.

Indeed Mohamud et al. have described five cases of acute ischemic stroke associated with an intraluminal carotid artery thrombus with concomitant COVID-19 symptoms 0–14 days before the onset of stroke (70). A proposed mechanism of this co-occurrence is inflammation-related plaque rupture as manifested by the elevated levels of inflammatory biomarkers such as lactate dehydrogenase, C-reactive protein, ferritin, D-dimer, and interleukin (70). Another study reported a case of symptomatic intracranial stenosis in a confirmed COVID-19 patient in a hyperinflammatory state, as evidenced by elevated acute inflammatory biomarkers (71). A similar hyperimmune trend was described in another patient with symptomatic posterior circulation stenosis and concomitant stroke (72). While these biomarkers are not specific for plaque rupture, there is evidence to suggest tha tplaque-rupture-specific MMPs implicate temporal association with the onset of acute respiratory failure among COVID-19 patients (73). Moreover, it has been proposed that aprotinin, a protease inhibitor that inhibits MMPs, may provide benefit for patients with COVID-19-related acute respiratory distress syndrome in experimental studies (74). However, at least in severe cases, the use of aprotinin to inhibit clot breakdown may need to be cautioned if the likelihood of COVID-19 inducing a proinflammatory hypercoagulation response to the SARS-CoV2 virus is considered.

Another putative mechanism that can lead to plaque progression in patients with COVID-19 infection is the disruption of the receptor-mediated uptake of oxidized low-density lipoproteins (oxLDL) by the monocyte-derived

macrophages with exposure to proinflammatory stimuli (19). Indeed, animal and human studies indicate that increased expression of lectin-like oxidized lipoprotein 1 receptor (LOX-1) is a risk factor for stroke and promotes restenosis among patients with preexisting cardiovascular disease (75). It is also evident that COVID-19 infection results in a disproportionate increase in reactive oxygen species, which translate to lipid oxidation and increased oxLDL levels (20). Thus, this is presumably another one of the reasons why elderly patients with preexisting cardiovascular risk have a higher propensity of developing severe COVID-19 illness (76) and AIS.

The Role of Peripheral Biomarkers to COVID-19 That Are Also Characteristic of Ischemic Stroke

The pathognomonic features of sepsis-induced inflammation among patients with coronavirus infection is manifested peripherally as neutrophilia in combination with marked lymphopenia (77). This is characterized by the marked increase in various inflammatory biomarkers such as the neutrophil to lymphocyte ratio (NLR), C-reactive protein, and serum ferritin (21–23, 78–84). In a prospective cohort study involving patients with concomitant COVID-19 and ischemic stroke, 9 of the 10 patients have elevated NLR (85). Similarly, the majority of AIS patients presented recently (86, 87) and in various COVID-19 and AIS case series has reported increased NLR values (72, 88–91). A significant degree of lymphopenia coupled with viral-induced neutrophilia and the migration of the neutrophils to the ischemic core may explain the elevated NLR among patients with ischemic stroke (92).

CRP is another inflammatory biomarker that is disproportionately increased among patients with coronavirus infection and AIS. The largest cohort study involving 32 ischemic stroke patients with concomitant COVID-19 infection reported that elevated CRP occurred in more than 90% of the patients (93, 94). All of the six ischemic stroke patients reported by Beyroutti et al. and three of the four patients observed by Tunc et al. showed elevated CRP levels (72, 89). AIS patients described in various case reports and case series with COVID-19 infection have also been reported to have raised CRP levels (16, 38, 91, 95–98) While CRP is a marker of inflammation, a meta-analysis likewise confirms its role in thromboembolic events (98). On the other hand, serum ferritin, an acute phase reactant and an inflammatory biomarker has also been reported to be elevated among patients with COVID-19 and AIS (85, 88, 89, 99, 100). Apart from its role in systemic inflammation, serum ferritin likewise predicts the degree of neural damage among patients with AIS as characterized by its correlation with markers of blood–brain barrier damage such as glutamate, interleukin-6, matrix metalloproteinase-9, and cellular fibronectin (35, 82).

Neutrophil Increase, Lymphocyte Decrease, and Neutrophil Extracellular Traps in Thrombin in General and Previously Associated With Acute Ischemic Stroke

As alluded to above, COVID-19 infection is associated with reduced leukocyte number and increased neutrophil to leukocyte ratio and so makes the recent evidence of dysregulated neutrophil extracellular traps (NETs) predictable (101–103). NETs are neutrophil-produced extracellular networks of chromatin, proteins, and oxidant enzymes that protrude from membranes of activated neutrophil and mediate infection containment (101). NETs also play a role in thrombus formation. Evidence indicates that, in patients with COVID-19 infection, there is an upsurge of NET production that further propagates inflammation and thrombosis (101–103). The NET formation is characterized by elevated levels of cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3) (25, 101). A study of normal subjects compared with patients with COVID-19 infection has shown that the latter have higher levels of cell-free DNA, MPO-DNA, and Cit-H3 with both MPO-DNA and Cit-H3 being significantly elevated in mechanically ventilated patients (101). Pulmonary autopsies of patients with confirmed COVID-19 patients also confirm the presence of NET-containing microthrombi with neutrophil–platelet infiltration (103, 104).

The evidence of the role of NETs in AIS is well-described (17, 18, 105, 106, 114). Laridan et al. examined specimens of thrombi of patients undergoing endovascular thrombectomy and found that Cit-H3, the hallmark for NETs, was observed in the majority of the samples (17). Interestingly, patients with cardioembolic etiology have been shown to have a higher burden of NETs (102). Another study revealed that the presence of NETs may convey reperfusion resistance to mechanical and systemic revascularization procedures (17). Whether the role of neutrophils and NET in coronavirus-related stroke is secondary to micro- or macrothrombosis needs further elucidation.

Viral-Induced Coagulation Dysfunction

Another important mechanism resulting in life-threatening systemic thromboembolic events among patients with coronavirus infection is the disruption of the coagulation pathways. Pro- and hypercoagulation affecting macro- and microvascular systems have also been implicated in various vascular events such as ischemic strokes. The International Society of Thrombosis and Hemostasis (ISTH) recognizes this unique phenomenon of sepsis-induced coagulopathy and proposed monitoring of platelet, D-dimer, PT, and fibrinogen among COVID-19 patients needing admission (115).

Fibrinolytic Shutdown

The imbalance between coagulation and fibrinolysis favoring the former manifests hematologically as an increase in D-dimer levels (115, 116). This is an immunological defense for the body to contain the viral infection, which results in thrombi formation (116). Furthermore, this implies a shutdown in the fibrinolytic system to clear the necrotic debris leading to massive fibrin formation, which also orchestrates coagulopathy (117). This shutdown has been further analyzed among critically ill COVID-19 patients where it has been demonstrated that, apart from the elevation D-dimer levels, more than 50% of the patients failed to lyse clots on thromboelastography (118–120) and hence increasing the likelihood of AIS as a further manifestation of COVID-19.

The tendency for 5% (this is still a gross underestimation, as we may never know the exact number strokes among deaths and even the mild strokes that might not present to the hospitals, as almost 40% of the stroke patients are not attending the hospitals during the pandemic time) of patients with COVID-19-related strokes to show spectacularly elevated D-dimer levels has been reported in several studies (91, 121, 122). Among the 32 cases reported by Yaghi et al., almost 50% showed D-dimer levels elevated to more than five times the normal range (94). Five of the six cases described by Beyrouti et al. also demonstrated D-dimer levels elevated more than 5–150 times above the normal limit (72). Avula et al., Lodigiani et al., Oxley et al., Berekashvili et al., and Wijeratne et al. also observed similar trends in the patients they described (3, 85, 88, 91, 123).

Venous thrombosis has also been described in a number of cases of COVID-19 infection resulting in fatal outcomes (107). Unsurprisingly, D-dimer levels were disproportionately elevated among patients with cerebral venous thrombosis (107, 108, 124). Another biomarker of fibrinolytic shutdown is the accumulation of fibrinogen and fibrin degradation products (119), and again, such retrospective analysis comparing COVID-19 and non-COVID-19 patients revealed higher fibrinogen levels in the former (123). Similarly, patients described in the literature with stroke and active COVID-19 infection have elevated serum fibrinogen levels (3, 72, 85).

The abnormalities of the coagulation biomarkers associated with COVID infection have been used to justify the use of systemic anticoagulation even in the acute stroke period. However, the outcomes for COVID patients are inconsistent (89, 123). Two of the five patients described by Lodigiani et al. who received Nadroparin died, and two of the four patients in Tunc's case series remain bedridden despite heparinization at the time of the publication (89, 123). Among the 32 COVID-19-related AIS described by Yaghi et al., 25 of whom received anticoagulation, more than 80% died or remained critically ill at the time of the publication (94). While the reason for poor neurological outcomes among these patients is multifactorial, a potential contributor is heparin resistance, especially among critically ill COVID-19 patients (24, 125).

For the small number of cases of COVID-19 patients who have also suffered AIS and received reperfusion therapy, consisting of intravenous thrombolysis or endovascular thrombectomy or a combination of both, the outcomes have not been particularly positive. In a case series regarding four patients with COVID-19-related AIS who also received systemic thrombolysis, all died (126). Similarly, in COVID-19-infected stroke patients reported in a healthcare system in New York who received alteplase and mechanical thrombectomy, the neurological outcomes were also poor (94). Currently, there is inadequate data to determine whether patients with COVID-19-related strokes may have resistance to tPA; however, it is known that the activation of the renin–angiotensin–aldosterone system results in the formation of plasminogen activator inhibitor (PAI-1), an inhibitor of tPA (127). Thus, it remains to be investigated whether these poor outcomes are related to counteractive mechanisms of PAI-I, increased thrombus burden, or resistance to tPA (128).

The Role of Natural Anticoagulants and Antiphospholipid Antibodies

Hypercoagulability is another sequela of COVID-19, especially in critically ill patients. One of the putative mechanisms, to which this is attributed, is the depletion of physiological anticoagulants and increased levels of coagulant factors and antiphospholipid antibodies (129–131). In a cross-sectional study of COVID-19-positive critically ill patients in China, it has been shown that the plasma levels of natural anticoagulants such as protein C, protein S, and antithrombin were below physiologically normal levels (127). The same study revealed that more than 50% of the patients developed antiphospholipid antibodies (127) that have been suggested to play a role in the pathogenesis of COVID-19-related strokes. Zhang et al. described three patients with multiple cerebral infarctions who tested positive for anticardiolipin immunoglobulin A (IgA) antibodies as well as anti-β_2-glycoprotein I IgA and IgG antibodies (130). On the other hand, five of the six COVID-19-associated stroke patients described by Beyroutti et al. did not show antiphospholipid antibodies, but all of them were positive for lupus anticoagulant (LA) (72). Two other severe stroke patients with poor neurological outcome and concomitant COVID-19 infection have also been reported as testing negative for both antiphospholipid antibodies and LA (99, 100). Thus, while there is inconsistency in the trend of these procoagulant factors in ischemic stroke patients, Zhang has proposed a possible secondary antiphospholipid antibody syndrome especially in patients who have thrombotic manifestations and positive serum antibodies (130). If this was the case, then the initiation of therapeutic anticoagulation would be required for these patients (130). However, it has not translated to screening of all COVID-19 patients, as a transient increase in these parameters is expected in viral infections (129).

The Role of the Endothelium

A component of Virchow's triad, endothelial dysfunction is another major contributor to SARS-CoV-associated thrombosis. The virus has been shown to demonstrate a predilection to invade vascular endothelial cells by attaching to the ACE2 protein, which facilitates subsequent invasion (9, 132, 133).

Endothelium-Driven Activation of the Extrinsic Coagulation System

COVID-19 promotes an imbalance between ACE2 and angiotensin II (AT-II) receptors leading to the upregulation of the latter, which is responsible for the tonic production of platelet tissue factor (TF or factor111) in platelets and macrophages, and further interaction with factor VII to activate the extrinsic coagulation system (134, 135). TF is essential for fibrin formation at the site of vascular injury and may also be an important factor contributing to thrombogenesis, especially with the induction of inflammatory cells originating from the subendothelium (26).

Increased expression of TF has previously also been shown to be associated with thrombus formation in patients with ischemic stroke (109, 110). The EPICOR study in 2015 revealed that patients with elevated TF doubled the risk of stroke (109). Experimental studies also demonstrated that the inhibition of

TNF-α-induced TF significantly reduces atheromatous plaque formation (30). Whether inflammation-induced tissue factor formation has a role in intracranial thrombosis in COVID patients particularly remains speculative.

Endothelium-Driven Nitrous Oxide Deficiency

Healthy endothelium is necessary to produce nitric oxide (NO), which is known as a vasodilator and plays a role in preventing thrombosis (27). SARS-CoV2-related endotheliopathy results in the suppression of nitric oxide synthase (NOS), resulting in nitric oxide deficiency (133). *In vitro* studies performed in 2009 on SARS-CoV also revealed that nitrous oxide inhibited viral entry replication by decreasing spike (S) protein expression and via its effects on the cysteine proteases encoded in the SARS-CoV (133).

Endothelium-derived nitrous oxide affects the cerebral circulation by its tonic vasodilatory effect and the prevention of adhesion of platelets and leukocytes to the vessel wall, both of which have an obligatory role in stroke pathogenesis (28). A study comparing stroke patients and healthy controls revealed that the levels of asymmetrical dimethylarginine (ADMA), a NOS inhibitor, is increased in the former, making it a risk factor for stroke (29). To date, few studies, if any, are looking into the potential role of NO in the treatment and prevention of COVID-19-related strokes; however, there is evidence to suggest that NO may also have a potential benefit for pulmonary-related COVID-19 complications (136).

THE ROLE OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM AND ACE2 DEFICIENCY

A unique characteristic of the SARS-CoV2 infection is its avid interaction with the ACE2 receptors, which affect the RAAS to a significant degree (137). It is known that viral-induced ACE2 deficiency results in significant alterations in the balance between the classical RAAS and the counterregulatory ACE2, which is essential for maintaining homeostatic mechanisms in the body (137). In particular, ACE2, which is ubiquitous in the brain, heart, and the vascular systems protects patients from the organ-damaging effects of the classical RAAS (138). This COVID-19-related disruption of the RAAS axes is likely to contribute to stroke pathogenesis, as it promotes inflammation, vasoconstriction, and end-organ damage (139, 140).

Various COVID-19 registries have shown that there is an increased fatality rate among patients with preexisting cardiovascular diseases such as hypertension and diabetes (140). Similarly, a majority of patients with AIS and COVID-19 report hypertension as a classical risk factor (111). The contribution of hypertension in the outcomes of patients with COVID-19 infection is likely explained in various mechanisms. Still, overactivity of the classical RAAS along with viral-induced endothelial vasoconstriction may be factors adding to the neurological exacerbation of COVID infection (140). Worse neurological outcomes among patients with COVID and ischemic strokes may be attributable to the unimpeded activity of the classical RAAS pathway in the brain, which has also been implicated in higher brain functions such as memory and cognition (141). Furthermore, upregulation of the classical RAAS pathway is likely to result in the overactivity of the sympathetic nervous system, which may exacerbate preexisting traditional risk factors for stroke such as hypertension, diabetes, and cardiac dysrhythmias (142).

COVID, NEUROLOGICAL MANIFESTATIONS AND IMPLICATIONS FOR NEUROREHABILITATION

Neurorehabilitation for patients recovering from severe COVID and AIS is set to be extra challenging in times of pandemic with its requirements for social distancing and, in many cases, need for online delivery in the immediate post-COVID stages. Currently, there are little reliable data about how well individuals with severe respiratory system and lung damage will recover or whether scarring will make such patients vulnerable to other viral infections (31). Furthermore, questions remain regarding whether the hypoxia engendered during the acute hospitalization phase will have lasting effects on the brain and nerve tissue especially on high metabolic demand areas including the sympathetic system and the fast visual attention and eye movements pathways (112) and long motor pathways.

Helms et al. first described the occurrence of dysexecutive syndrome in 36% of patients of critically ill COVID survivors in a French cohort characterized by lack of attention and disorganized movement with commands (143). Various case reports likewise described cases of patients who had severe impairments in executive function in the postacute stage who had significant recovery after aggressive neurorehabilitation (37, 144). In the same manner, varying degrees of depression and anxiety have also been identified after the acute stage of infection among COVID survivors (36, 145, 146). Interestingly, a meta-analysis of observational studies also notes that, among patients with previous SARS and MERS-CoV infection, neuropsychiatric manifestations such as depression, anxiety, irritability, memory impairment, sleep deprivation, and posttraumatic disorder were strikingly prevalent (147). One would also expect that psychological anxiety and the physiologically high immune responses (psychoneuroimmunological outcomes) would also lead to various psychiatric sequelae that have adverse effects on mental health of patients (32, 148). The neurological sequelae of SARS-CoV2 infection have gained recent publicity in social and print media (Facebook "Long haul COVID support groups"). Symptoms include persistent "brain fog," fatigue, breathlessness, anxiety, depressive mood, and motor weakness, affecting subsets of young, middle aged, and older patients including a significant proportion who showed only mild symptoms, during the infected stage (40, 149). We have suggested that these symptoms comprise aspects of *PCNS* and hypothesized that such a syndrome is due to persistent inflammation following COVID-19 infection (113, 150). These complications are undeniably posing significant challenges ahead for the neurorehabilitation fraternity.

Mathew et al. identified a subgroup of patients with T-cell activation characteristic of acute viral response plasmablast responses reaching over 30% of the circulating cells with three

different immunotypes associated with poor clinical trajectories supporting the current understanding of the pathobiology (151).

Fridman et al. found the frequency of stroke to be high among patients with severe COVID-19 with a very high inpatient mortality across all age groups demonstrating further evidence to the shared pathobiology as one go through the cluster analysis of this paper (143).

Overall, our review of the pathobiological basis of COVID-19 demonstrates that it is a multisystem illness with high likelihood of long-term physical, cognitive, psychological, and social sequalae in those who survive the illness. The scale of the burden of the disease and impact is enormous globally.

Furthermore, there is also no doubt that the current pandemic is overwhelming the neurorehabilitation sector globally. While it is too early to comment about the potential pandemic of long-term neurological issues for the millions of infected patients worldwide, the current review predicts the high likelihood of this possibility. Similarly, Boldrini et al. has noted that the two main factors already impacting the neurorehabilitation sector during the first phase of the pandemic (144) are the following:

(i) increased pressure from the acute care services to transfer the patients to rehabilitation medicine services;
(ii) increased difficulties without patient rehabilitation activities and home-based rehabilitation due to the restrictions enforced by the local and national authorities (144).

Indeed, the challenges described by Boldrini et al. above make the situation even more complex. It is critical to create an efficient healthcare delivery system tailored to each individual, each community, and each country. It is equally important to understand the biological underpinning behind the illness and post-COVID-19 complications. Tailor-made, individualized, targeted neurorehabilitation program should be developed with the available resources (e.g., telemedicine can be tested with easily available smart phone-based deliverables such as WhatsApp, Viber, Facetime, and Google Talk where professional personnel are not always available and sophisticated technology are not around). Family members can be a really useful resource in these challenging circumstances (36, 37, 145, 146).

To this end, we recommend considerations of Mantovani et al. (152) who recently collected and reviewed relevant evidence-based recommendations on the efficacy of cognitive rehabilitation, based on a comprehensive evaluation of 491 papers presenting the latest evidence-based practice for neurorehabiliation of traumatic brain injury (TBI) patients whose pathobiology bears many similarities to that presented in this review in the context of COVID-19 and systemic involvement (147, 152, 153).

Mantovani et al. as well offer a road map and a comprehensive perspective on the role of tele-neurorehabilitation and virtual rehabilitation to gain adequate cognitive stimulation in the era of physical distancing and lockdowns related to COVID-19 pandemic, reminding us of the potential opportunities globally (152). For further details, see Mantovani et al. and the 29 recommendations on evidence-based cognitive rehabilitation in the context of stroke and TBI nominated by the Cognitive Rehabilitation Task Force (CRTF), which suggests that a more comprehensive biological understanding of the various systems affected by TBI should lead to more collaborative translational research utilizing artificial intelligence and novel technology to find better individually designed precision solutions (e.g., video-consults, tablet-based measurements, and use of wearable devices). Lastly, the integration of services, including private and public partnerships such as university–public hospital partnerships and partnerships with community organizations and volunteers, are likely to create excellent opportunities for the future (112, 154, 155) and better evidence-based neurorehabilitation pathways.

In support of this more generalized theoretical approach, our group has demonstrated here the expected neurological impact of shared pathobiology between AIS and COVID-19 here, and the debilitating condition that characterizes PCNS (150) manifests as chronic fatigue, impaired thinking, depression, anxiety, breathing difficulties, and muscle weakness (40, 40, 149, 150). Thus, we suggest that treatment with known Food and Drug Administration (FDA)-approved immunomodulatory hormones such as melatonin (14, 15, 33, 156–162) and nutraceuticals such as curcumin (163) might be expected to enhance the likelihood of PCNS patients benefitting from any neurorehabilitation interventions as a matter of priority.

CONCLUSION

Our review has shown here that severe COVID-19 infection has the potential to lead to the disruption of most physiological systems and results in various multisystemic thrombotic phenomena including acute ischemic stroke. While inflammation orchestrates its pathogenesis, the further perturbation of the coagulation system resulting in fibrinolytic shutdown likewise contributes to neurological manifestation. Furthermore, the predilection of the virus to attach to ACE2 receptors in various cells, including the vascular endothelial system, may also disrupt the renin–angiotensin system, which further contributes to stroke pathogenesis. Clearly, there is a gap in the understanding of this phenomenon, and large-scale human and animal studies are necessary, as this co-occurrence results in deleterious outcomes.

The impact of COVID-19 in the human brain is as such that millions of patients are likely to experience problems with normal functioning requiring far more psychoneuroimmunological evidence-based understanding of neurorehabilitation services that are able to overcome incipient recovery problems.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

TW conceived the idea. TW and CS performed the literature search independently. TW, CS, SC, and LK contributed to the manuscript writing with critical revisions. All authors read the final manuscript and agreed.

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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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Education, Training, and Practices of Neurorehabilitation in India During the COVID-19 Pandemic

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Background: Corona virus disease (COVID-19) was declared a pandemic by the World Health Organization in March 2020. This has affected service delivery among all medical disciplines in India including neurorehabilitation services.

Aims and Objectives: The aims and objectives of the study were to assess the effect of COVID-19 pandemic on neurorehabilitation services across India.

Methodology: A prospective nationwide survey study was undertaken by the Indian Federation of Neurorehabilitation during the pandemic. A questionnaire was prepared using Google forms software consisting of four sections: demography, neurorehabilitation practice before COVID-19 pandemic, neurorehabilitation practice during COVID-19 pandemic, and continuing medical education during COVID-19 pandemic.

Results: Responses (872) were received from neurorehabilitation professionals across the country out of which 2.2% professionals did not give consent for participating in the survey. Participants (36.6%) were practicing traditional or independent referral basis rehabilitation, while 63.4% participants were practicing multidisciplinary rehabilitation. On an average, respective units were conducting 500–750 therapy sessions per month. Majority of the rehabilitation units in India lacked a physiatrist, rehabilitation nurse, music therapist, cognitive therapist, and urologist. Approximately 80% of the rehabilitation units have the basic rehabilitation modalities and advance technology was present in only 20% of the rehabilitation units. During COVID-19 pandemic, 19.5% centers were providing elective services, 50.3% emergency services, 15.6% new outpatient services, and 22.7% were providing follow-up outpatient services. Centers (51.5%) were providing telerehabilitation services for neurological conditions during the times of COVID-19 pandemic. Professionals (61.1%) providing telerehabilitation were working from home. Among the patients who needed neurorehabilitation, 28% were doing their exercises independently, 31% were supervised by caregivers, 17% were supervised by therapists, and 24% were not receiving any therapy. Participants (95.5%) wanted to receive more training in the field of neurorehabilitation. The participants utilized webinars (71%), online courses (22%), case discussion forums (19%), panel discussions (13%), and literature search (8%) during COVID-19 pandemic to continue education.

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Conclusion: The study reflects the situation of neurorehabilitation service delivery in India during the pandemic as the respondents were from all parts of the country and included most components of the neurorehabilitation team. Neurorehabilitation services were severely affected across India during the COVID-19 pandemic. Tele-neurorehabilitation has emerged as a new service delivery model during the pandemic. Online means of education has emerged as the primary source of continuing medical education during the pandemic.

Keywords: neurorehabiliation, COVID-19, India, pandemic, education

INTRODUCTION

A new type of respiratory disorder was reported in Wuhan, China, which was identified as a novel virus on December 31, 2019. The World Health Organization called it the novel COVID-19 virus on February 11, 2020. Coronavirus also known as COVID-19 belongs to a group of pathogens that target the pulmonary system in humans. They are primarily non-segmented positive sense RNA viruses (1). The World Health Organization declared it as a pandemic on March 11, 2020. India received its first case of the COVID-19 pandemic on January 30 in the state of Kerala; the patient had a positive history of travel to Wuhan, China. As of August 22, 2020, 23,121,145 people in 213 countries and two international conveyances have been infected by the COVID-19 virus. In India, the situation is unpleasant, with an estimated population of 1.3 billion, the total number of COVID-19 positive cases are 2,975,000 which is the 3rd highest number of cases trailing behind Brazil and the United States (2).

During the early stage of the spread of the virus in India, there was not much burden on the chronic health care settings and outpatients departments, but as the situation escalated, a nationwide lockdown was enforced, and the movement of the common people was reduced to only for essentials. Many sectors in India have been affected due to the COVID-19 pandemic. The primary and acute services and gradually health care sector were over burdened with exponential increase in the number of cases. The neurorehabilitation sector was also affected due to these changing trends. Critical patients with neurological complications were shifted from intensive care units to inpatient wards as more and more beds were needed in the critical care units. Many outpatient departments stopped functioning or those which functioned were working at 25% capacity due to the restrictions imposed by the local governing bodies. This had a significant impact on the patients undergoing neurorehabilitation as their functional recovery was hampered due to the non-availability of rehabilitation services.

Since there was no data available on practice of neurorehabilitation services, neurorehabilitation training and education in India and developing countries during the COVID-19 pandemic, the Indian Federation of Neurorehabilitation conducted this study to determine the effects of COVID-19 pandemic on neurorehabilitation services across India, to determine the measures taken by the rehabilitation professionals and institutes providing neurorehabilitation during the pandemic, and also, to assess the effect of pandemic on education and training, and the role of e-learning.

METHODOLOGY

We conducted a descriptive, cross sectional nationwide survey among neurorehabilitation professionals in India during the period of corona virus (COVID-19) outbreak from April–May 2020. The structure, need and the purpose of the study were explained to the participants, and the point that participation is voluntary was explained before taking the consent. All participants were included in the study only after they provided their written informed consent. The responses of the participants were kept anonymous.

An electronic questionnaire for the survey was developed by a group of experts consisting of neurologist, rehabilitation physician, pediatric, orthopedic surgeons, neurosurgeon, and physiotherapist (**Supplementary Material**). The electronic version of the questionnaire consisted of four sections:

1. Demographics
2. Neurorehabilitation practice before COVID-19 pandemic
3. Neurorehabilitation practice during COVID-19 pandemic
4. Continuing medical education during COVID-19 pandemic

The questionnaire consisted of 35 questions which included both open ended and close ended questions.

The questionnaire was scrutinized by two independent experts in the field of neurorehabilitation and research. The pilot study was conducted on 30 participants. Following the pilot study format of 12 questions was modified and two questions were clubbed. The changed questionnaire after the pilot was again face validated. The questionnaire was circulated to 3,368 neurorehabilitation professionals across the country via electronic mail. Only one response was accepted from each professional, and they were not allowed to change their answers once the response was submitted. The data was analyzed using descriptive statistics which included mean, standard deviation, frequency distribution, and percentages.

RESULTS

A total of 872 responses from neurorehabilitation professionals across the country were received. Professionals (853, 97.82%) gave electronic informed consent for participating in this survey.

Demographics

There were representations from all the states and union territories of India (**Figure 1**).

Table 1 shows the demographics of the study population in terms of area of practice, qualifications, experience in the field of neurorehabilitation, type of rehabilitation services offered, and the type of institute affiliation. Majority of the participants (727, 85.22%) were young rehabilitation professionals, practicing in urban setup (76.8%), and 658 (77.13%) participants were females and 195 (22.86%) participants were males. The participants were representative of all the professionals in a multidisciplinary team: physical therapy, 534 (62.6%), speech therapy, 112 (13.1%), occupational therapy, 101 (11.8%), physical medicine and rehabilitation, 45 (5.3%), neurology, 22 (2.6%), psychology, 8 (1%), orthopedics, 6 (0.7%), pediatrics, 3 (0.4%), and others, 22 (2.5%).

Neurorehabilitation Practices Before the COVID−19 Pandemic

The most common diseases treated were: cerebral palsy (87.5%), Parkinson's disease (85.3%), traumatic brain injury (76.9%), migraine (32%), psychiatric disorders (30.2%), and chronic fatigue syndrome (20.2%). **Figure 2** shows how the participants of the study rate their rehabilitation units on a scale of 1–5, with 1 being average and 5 being advanced. Majority of them rate their rehabilitation units 4 (40.8%) and 3 (32.9%) on a scale of 1–5.

The participants reported that on an average, their respective rehabilitation units were conducting ∼500–750 therapy sessions per month. When asked regarding the composition of their respective multidisciplinary rehabilitation teams, majority of the neurorehabilitation teams in India did not have a physiatrist, rehabilitation nurse, music therapist, cognitive therapist, and urologist. Participants (706, 80.96%) reported that their neurorehabilitation units had basic rehabilitation modalities such as tilt board, parallel bars, mirror therapy, etc. Only 20% of the participants worked in neurorehabilitation units which had advanced rehabilitation modalities such as rehabilitation robotics, virtual reality training, and functional electrical stimulation, etc.

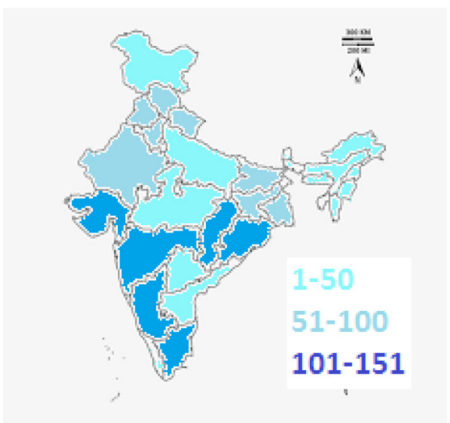


FIGURE 1 | Map of India showing the number of responses from different states.

Neurorehabilitation Practices During the COVID-19 Pandemic

As reported by the participants practicing in the urban set up, 680 (77.98%) participants were providing only emergency services, 732 (83.94%) were providing neurorehabilitation using teleconsultation and telerehabilitation; 170 (19.49%) were

TABLE 1 | Demographics of the study population.

Age group	Number of participants	Percentage
20–29 years	491	57.56%
30–39 years	236	27.66%
40–49 years	85	9.96%
50–59 years	24	2.81%
60 years and above	17	2.01%
Total	853	100%
Qualifications	**Number**	**Percentage**
Physiotherapist	534	62.6%
Speech and Language Pathologist	112	13.1%
Occupational Therapist	101	11.8%
Rehab Physician	45	5.3%
Neurologist	22	2.5%
Others	22	2.5%
Psychologist	8	1%
Orthopedic surgeon	6	0.7%
Pediatrician	3	0.4%
Experience in the field of neurorehabilitation	**Number**	**Frequency**
Undergraduate student	114	13.4%
Post Graduate student	155	18.2%
PhD student	13	1.6%
Fresher	71	8.1%
1–5 years	204	24%
6–10 years	127	14.9%
11–15 years	88	10.4%
>15 years	81	9.4%
Type of rehabilitation services provided		
Traditional	312	36.6%
Multidisciplinary	541	63.4%
Type of institute affiliated		
Teaching institute	357	41.9%
Private Hospital	156	18.3%
Government Hospital	68	7.9%
Specialized Rehabilitation Center	47	5.5%
Private Outpatient Clinic	181	21.2%
Others	44	5.2%

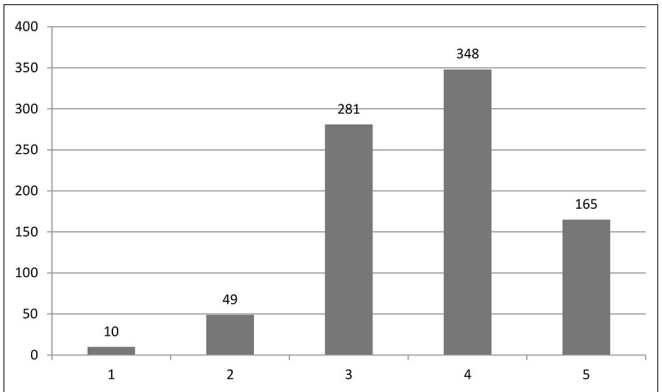


FIGURE 2 | Self-rating of their respective rehabilitation units by the participants.

TABLE 2 | Duty schedule for rehabilitation professionals during the pandemic times.

	Number	Frequency
Daily	187	21.9%
Three times a week	66	7.7%
Two times a week	42	4.9%
Once a week	37	4.3%
Work from Home	521	61.1%

providing elective services, and only 70 (8%) were able to provide outpatient rehabilitation services. Majority of the rural set ups, 438 (50.3%) were providing outpatient services for new patients, and 532 (61.1%) were providing follow up services during the pandemic. **Table 2** shows how often the neurorehabilitation professionals were called for duty during the pandemic times.

Effect of COVID-19 Pandemic for People With Disabilities

Out of the total patients requiring rehabilitation services during the pandemic at the units where the participants practice, 34% of their patients were receiving rehabilitation using telemedicine, 8% of their patients were admitted in the inpatient rehabilitation units, 32% of their patients were receiving rehabilitation by a trained family member or a caregiver for mobility, self-care, and communications needs, 17% of their patients were receiving home based or community based rehabilitation by a trained rehabilitation professional, and 9% of their patients were not receiving any form of neurorehabilitation care.

When we asked the participants "What are the three worst effects of COVID-19 pandemic for people with disabilities?" Participants (505, 57.91%) responded to the question. The responses are tabulated in **Table 3**.

Those professionals providing neurorehabilitation services by coming in direct contact with patients wore masks, gloves, personal protective equipment, and followed disinfection regimen as advised by the World Health Organization (3) and Ministry of Health and Family Welfare, Government of India (4). The participants also reported that proper development of telerehabilitation protocols, proper training in telerehabilitation, and incorporation of family in the rehabilitation process can play a major role in adapting to the situation, and also providing diligent neurorehabilitation services. Majority of the participants answered that assessment, participation restriction, nonavailability of medications, poor follow up, difficulty using telerehabilitation for old age patients, fear of COVID infection especially in patients with Parkinson's disease, and multiple sclerosis, were the worst effects of COVID 19 pandemic on patients with neurological disabilities.

Continuing Medical Education During and After COVID 19 Pandemic

Participants (320, 36.8%) felt that the curriculum was not adequate in undergraduates and post graduate courses; 832 (95.5%) participants wanted to receive more training in the field of neurorehabilitation during the pandemic. The time available during pandemic was utilized to continue education by participating in webinars (71%), online courses (22%), case discussion forums (19%), panel discussions (13%), and literature search (8%). During COVID-19 pandemic, 40% of the participants attended <5 webinars, 46.5% attended 5–10 webinars, and 13.5% attended more than 10 webinars per week. Sixty-three percentage participants felt that there will be a shift toward online courses, and 41% felt that things will be the same as it was before the pandemic.

When we asked the participants "How will education change in the future after COVID-19?," the total 56% number of responders answered the question. The responses were categorized as predictive, positive, and negative, and after combining repetitive responses together, are listed in **Table 4**.

When we asked the participants "What will happen to neurorehabilitation post 2020?" Sixty percent of the participants responded to this question. A summary of responses is listed in **Table 5**.

DISCUSSION

Neurological disorders remain a public health issue in India and the other developing countries. Neurorehabilitation is the main stay treatment to aid recovery and to minimize the morbidity in functional activities as a consequence of the disorder. There are various differences that exist in terms of neurorehabilitation service delivery in various parts of the country. Our study provides an overview of the influence of COVID-19 pandemic on the neurorehabilitation services and education in India.

Due to the surge in cases, the government and private institutes were converted to dedicated COVID care units, therefore inpatient neurorehabilitation admissions were reduced, emergency services were not available at certain centers for neurological diseases, and elective surgeries were canceled (5–8). However, certain centers were still taking care of emergency services as, early and prompt neurological interventions were needed to reduce the extent of injury and reduce the morbidity and mortality.

TABLE 3 | The effects of COVID 19 pandemic on people with disabilities.

Psychological effects	Physical effects	Social effects	Effects on rehabilitation
• Feeling of loneliness, helpless and anxious • Depression • Dependence • Morbidity mortality • Loss of confidence • Anxiety • Fear of death • Regression in condition • Mental breakdown • No motivation to do the exercises • Frustration • Susceptible to abuse • Behavioral issues	• Respiratory parameters • Musculoskeletal insufficiency • Irregular rehab session • Stiffness • Contractures • Loss of the achieved mobility • Loss of functional gains during recovery and lack of comprehensive rehab services • Atrophy • Pressure sores	• Altered routine • Lack of peer contact, friends and family contact • Reduced mobility due to being home bound • Participation restrictions • Transportation and daily needs • Earning loss, unable to get required rehab and reaching out to society	• Not able to come to hospitals • Lack of therapy/rehab • Lack of medical personnel • Danger of relapse of conditions due to nonavailability of medical care • Inability to consult a doctor when a genuine need is there • Fatigue

TABLE 4 | How will education change in the future after COVID-19?

Predictions	Positive effects	Negative effects
• The online training will be an integrated part of education • Totally changed Online • Will be more virtual and lots of discussions • Pattern of assessment of examination may also change • More online education • Will overcome the traditional method of learning • Everything will change not education • More usage of technology and less dependent on writing work • Technology will continue to play a key role in educating future generations • Education around the globe should become education about the globe. • Education will become more virtual and technology dependent. Interaction may be compromised up to some extent. • Preparedness for unforeseen circumstances and alternative ways to cope for lack of resources in times of health crises will be a part of the education system. • People since now learnt the proper educational use of online classes it might be an evolution in education system. • It will be more of web and VR based. Physical meetings will be less frequent	• With social awareness more accessibility through online mode. • Will improve access to international standards • Enough time to learn new things, and relearn the subjects • More holistic approach. • It would be better as it is getting global • Many researchers would be enlightened with new ideas, and that can bring huge change after lockdown! • Education to go more in depth • Connecting more fellows, students, and researchers virtually and involving them in E learning, e rehab • Use of technology and more visual aids will facilitate better understanding • Reaching out to rural areas will now gain widespread acceptance. • Education always brings change in your way of thinking provided one uses education more effectively and for the benefit of the world. • Use of technology and more visual aids will facilitate better understanding. • Reaching out to rural areas will now gain widespread acceptance. • Now we can attend lectures by sitting in any part of the world and upgrade our knowledge. • More will be ready for online courses and study for which people were not ready earlier specially in India • Now people are free to read with no chaos of environment, no pollution, no exam or assignment. just read and find out your weakness, your backlogs, try to cover it more • The scope of learning will increase	• It will be tough • Less practical experience • Less hands-on experience • Personal contact will disappear • Less social interaction with others • The education system may not change but to complete the academic year they may rush with left over syllabus and lectures and may affect the performance of the students and might not be at that satisfactory level

Post stroke rehabilitation is likely to be suboptimum during the pandemic and should focus on the most immediate needs of the patients. Telerehabilitation resources if available may be utilized (5). The pandemic made stroke care even more challenging. There is a need for public health systems in both developed and developing countries to improve awareness, implement proper strategies of triage, acute treatment, well-defined rehabilitation plans, telemedicine services, and virtual

TABLE 5 | Views on neurorehabilitation post 2020.

What will change?	Positive aspects	Suggestions
• It will be different and we shall adapt • The only thing that I can think of is telerehabilitation • Done with great precautions to avoid any infection. Include more of home- based programs, easily carried out by relatives and actively by patient if possible, goal oriented programs. • Lot of work will have to be done due to increased cases of stroke post COVID-19 • Likely to incorporate more technology features • No difference post 2020 • The whole world is changing, and it is difficult to predict even for a day ahead. Hence, difficult to answer. • We may see a huge surge of post COVID-19 patients with neurologic sequelae. Our work may increase manifold. We need to be prepared. The frontline warriors today are fighting with the actual disease. • As recent research suggest probability of increase in cases of extra pyramidal involvement, this may be a challenge in neurorehabilitation	• Should become more advanced with patients becoming more aware • Good and advanced equipment should come into use for assistive technology • Good and explorative • With advanced knowledge many patients should be able to receive adequate treatment in holistic manner • More awareness • Neurorehabilitation will reach another destination holding the hands of telerehabilitation • Better understanding • More surge of disability expected as many will get delayed care at this juncture. So neurorehabilitation will need to gear up for that • Effective • Team approach would increase **Negative aspects** • Anxious about the changing techniques and quality reductions in improvements of neuro cases	• Standardization of scales • Qualified,accessible, affordable, and use of technology is the need of the hour in all forms of rehab • A lot of areas to be researched. • It is a field with a huge scope for growth. • It is also underrepresented. There is need for a unified national rehab council in India. • Need a lot of awareness and facilities at grassroots level • India should develop multidisciplinary rehabilitation unitsat each district in every corner of the country, uniformity of the services to all. • Dedicated Neuro-rehab Hospitals minimum 500 beds required to be made at the earliest. This is the need of the time. • De recognition of sub-standard colleges. • Multidisciplinary approach should be available for all the citizens of India at its best inclusive of rural, semi urban, and urban. • Policy makers and general public would become more aware toward especially needy persons

check-ins (6). Persons with Parkinson disease infected with COVID-19 are likely to have a motor and non-motor deterioration. As a result of social distancing, immobilization, and lockdowns necessitated by COVID-19, exercise, as well as physiotherapy or other rehabilitative services, maybe interrupted for PD patients. This lack of physical activity may lead to a worsening in the motor as well as non-motor symptoms (7). The longer the duration of ICU stay, the higher is the risk for long-term physical, cognitive, and emotional impairments needing comprehensive and early rehabilitation. We have to practically expand rehabilitation services in a resource-limited country, such as India, This would help to deal with the rapid increase in demand of post acute care facilities, be it in hospital services, in the form of inpatient or outpatient rehabilitation or home care facilities, including telemedicine (8).

Our research showed that majority of the rehabilitation units does not have a rehabilitation physician or a neurologist in the multidisciplinary team. One of the reasons for this can be discrepancy in the supply and demand of neurology services in our country as reported in the study by Khadilkar et al. (9) who found that among 1,800 neurologists in the country majority work in the metropolitan cities, thus, there is a scarcity of trained neurologists in rehabilitation services. Similarly, in a SWOT analysis, Shrivastava et al. reported that the lack of physiatrist in India due to education policies, as only a few medical colleges are providing post graduate training in physical medicine and rehabilitation, and lack of awareness of this new medical specialty among the medical fraternity, and the masses (10). Majority of the rehabilitation physicians are working in the metropolitan regions, leading to lack of adequate trained manpower in rural areas. Similarly, most of the members of the neurorehabilitation team including psychologist, speech and language pathologist, occupational therapist, and physical therapist also work in the urban areas. There is a substantial lack in the number of health care professionals for rehabilitation in low and middle income countries and frequently, the types of health care professionals needed for rehabilitation teams are not at all available. A few examples: high-income countries have, on average, more than 900 physiotherapists per million inhabitants; the corresponding number is <10 physiotherapists in many countries in Sub- Saharan Africa and the South-East Asia Region. Further, high income countries have more than 300 speech and language therapists per 1 million inhabitants, while some low-income countries in the African region have no speech and language therapists for the entire population. With this, there is thus a huge demand for education in neurorehabilitation. The need includes (a) the establishment of qualifying program for various disciplines in many countries, (b) specialized training in neurorehabilitation for health care professionals holding their basic professional qualification (physicians and allied health professionals), (c) continued medical education for those who have received specialized training, and (d) fast knowledge distribution in new challenging situations or "game-changing" opportunities for clinical practice (11). We suggest that proper training and appointments of neurorehabilitation professionals, and formation of specialized neurorehabilitation units especially in rural areas should be done to bridge this gap.

Countries across the globe have reported disruption of neurorehabilitation services during pandemic due to reduction in the number of beds for non-COVID patients and shifting of healthcare workers to COVID emergency duties (12–16).

There were different types of challenges in running neurorehabilitation services including clinical service challenge, health challenges for staff, clinical practice challenge, and capacity challenge. A sudden surge in admission of patients

with a COVID-19 positive diagnosis has challenged all services, and has an impact on rehabilitation caseload management. Initially, the demand on the service increased mainly due to staff shortage, related to staff that had become infected with the virus, following government health instructions to self-isolate and stay at home until they were better (12). COVID-19 pandemic is strongly impacting all domains of our healthcare systems, including neurorehabilitation. In Italy, the first European country to be affected, medical activities were postponed to allow shifting of staff and facilities to intensive care, with neurorehabilitation limited to time-dependent diseases, including COVID-19 complications. Hospital access to people with chronic neurodegenerative conditions such as multiple sclerosis, movement disorders or dementia, more at risk of serious consequences from the infection, has been postponed (13).

COVID-19 has rapidly become a pandemic emergency, distressing health systems in each affected country. COVID-19 determines the need for healthcare in a large number of people in an extremely short time and, like a tsunami wave choking healthcare services. Rehabilitation services are also affected by this epidemic which forces radical changes both in the organization and in the operating methods (14). Unexpected rapid changes and reorganization of medical services that occurred during the pandemic lead to an impact in the practice of neurorehabilitation. The idiosyncrasies typical of neurorehabilitation management, especially in acute facilities that makes it susceptible as a vector of dissemination of COVID but also because of the need of finding new wards and intensive care units for COVID patients, the interventions in neurorehabilitation has suffered enormous changes (15). Our department is generally populated with a mixed age group of patients with numerous multiple comorbidities, which places them in a very risky situation. Immediate departmental recommendations have been put in place to safeguard these patients, including limitation of the number of visitors, higher thresholds for home visits and ward leave, limitations on social dining, and therapy sessions limited to the immediate bed space until newly admitted patients experience sufficient isolation (16).

A significant finding from our study has been how rural centers responded differently to pandemic than urban centers. Whereas, urban centers relied on telerehabilitation, rural centers were able to provide the outpatient services and follow up in more than 50% of respondents.

Due to the pandemic there has been an increase in the use of teleconsultation and telerehabilitation, which is feasible, easy, and cost effective to provide quality neurorehabilitation services (17). It is difficult to provide rehabilitation services to large numbers in public hospitals in the era of social distancing. Therefore, there is a need to change to newer and alternate mode of delivering the neurorehabilitation services like teleneurorehabilitation. The "new normal" has necessitated that practitioners and therapists quickly adapt to the changing needs of delivering rehabilitation care to patients. Findings from our study indicate that there has been uniform enthusiasm among rehabilitation professionals for use of telerehabilitation who have adapted to the technology well (18). This can be used in future to fill in the large gap between demand and supply on quality neurorehabilitation services in India (5–8). Telerehabilitation can be used for assessment, treatment, and follow up services, and even for educating the patients with neurological conditions. Telerehabilitation is beneficial for the patient psychologically as well, since the patient is rehabilitated in his home environment (19).

Remote communication technologies are increasingly regarded as potential effective options to support health care interventions, including neurorehabilitation and cognitive rehabilitation. Among them, telemedicine, virtual reality, augmented reality, and serious games could be in the forefront of these efforts (20). Growing evidence supports active video games and low-cost virtual reality as viable therapeutic interventions for children with physical disabilities. These technologies are especially well-accepted by pediatric populations for the ludic and motivating features that lend themselves to nearly seamless incorporation into telerehabilitation (21). Mobile Based Rehabilitation (MBR) offers many advantages: social distancing can be maintained by the indirect interaction/digital interaction of patient and therapist, easy and cost-effective method, reduces the travel costs and time consumption, convenient to access at any time, and entertaining method of rehabilitation, using games and virtual environments improves participation. Disadvantages of MBR includes difficult application for patients who have learning disabilities, cognitive impairment or psychological problems, access to the rural population due to poor resources, problems with network connectivity, and no manual contact with the therapists (22).

Our research has highlighted the effects of pandemic for the people with disabilities not only include physical effects such as increase in contractures and effect on therapy and treatment but also social effects like not being able to meet peers, family and friends, and participation restrictions, and psychological effects like frustration and depression. A list of these effects from open ended question will help the neurorehabilitation experts to plan comprehensive services for disasters and pandemics for the future. About 36% of the participants reported moderate to severe psychological impact, 25% showed mild to severe levels of anxiety, 41% reported depressive symptoms, and 41% felt stressed. Women, young, and those who lost their job during the health crisis showed the strongest negative psychological symptoms. We found factors associated with better mental health, such as being satisfied with the information received about the health crisis, conducting leisure activities, and the perception of being in good health (23). Early identification of distress and timely psychological interventions can, not only prevent crisis at times of pandemics but also help in containing its extent. The specific response to the mental distress of children who are quarantined should also be considered when designing psychological intervention strategies in response to COVID-19. Vigilance about the health of the elderly in long-term care is essential not only for their health but also to protect the health care system from being overwhelmed by severe COVID-19 cases (24).

There was an increase in participation for e-learning through webinars during the pandemic among the neurorehabilitation professionals. Carrying on this culture in the future to digitalize medical education, will be beneficial to the students and the staff as well, and it has been well accepted at present due to the current scenario (25). As reported in a few studies, e-learning has its own merits and demerits, it can be concluded that although traditional learning cannot be replaced by e-learning but adjusting and accepting the new normal is the way forward (26). Our research shows that education will change in the future and suggests that most accept a deviation to online teaching through web and VRbased systems. One of the findings from our study has been that responders have also looked at positive aspects of the change like Global access, Accessibility of education without barriers of geography and freedom to choose the subjects. Also responders feel that the change will stimulate new ideas and research. The concerns include adaptability, practical training, and distancing with less social interaction which is important part of education. The education policy makers will need to look at these aspects to minimize the effects. The boost which telerehabilitation has received due to the pandemic will go a long way in reducing the costs, treatment gap, and morbidities associated with neurological conditions

About the future of neurorehabilitation after 2020, our study indicated that it will be different and we will need to adapt. There will be surge in cases due to neurological consequences due to COVID-19 as well as sequel and complications due to lack of optimal care and therapy during pandemic. The suggestions for the future include that the neurorehabilitation should be accessible, affordable, and reachable to community and there is huge scope for improvements.

The results of our survey have lessons for the neurorehabilitation organizations, institutions, and professionals across the globe particularly developing countries. The study highlights the limitations in the reach of the neurorehabilitation services and effect of disasters such as COVID-19 pandemic on the delivery of neurorehabilitation services. It also highlights the potential use of technology in rehabilitation and education.

The limitations of the study include that it may represent views of 872 among 3,368 professionals contacted and may not present the true proportion of professionals in neurorehabilitation services. The questionnaire with multiple choice answers can influence the response process and have limitations of truthfulness and response bias. A questionnaire based survey also has limitations of over simplification of a complex reality and difficulty in determining the validity of data.

One of the unique features of our survey was inclusion of open ended questions. The answers to closed questions are influenced by the values chosen by investigators for each response category offered and that respondents may avoid extreme categories (27). Open ended questions allow unrestricted inquiry and lateral thinking, and should be included in a survey based research.

The survey has revealed positive aspects of the effect of COVID-19 pandemic in a developing country, and findings of the survey will be very useful for providing directions for future development of neurorehabilitation services, training, and education for all countries across the Globe.

CONCLUSION

This study shows that there is paucity and imbalance of neurorehabilitation care in our country. There were social and psychological effects in addition to adverse physical effects to people needing neurorehabilitation during the pandemic. There was a difference in response of urban and rural centers to the pandemic where most of urban centers preferred telemedicine and stopped outpatient services, whereas more than 50% of rural centers continued outpatient services with precautions. Many professionals utilized the pandemic period to enhance their knowledge and skills through on line education such as webinars. The future of the neurorehabilitation is for a change if we utilize the learning from the pandemic period to make it accessible, affordable, and available. This study will guide health and education policy makers to design guidelines for neurorehabilitation training, continued education, and service delivery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS developed the idea and guided the survey process. AS did the analysis and the write up process of the article. TN constructed the survey and analysis of the survey. DP helped in the process of development and conducting the survey. HS did the analysis of the survey and write up of the survey. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.626399/full#supplementary-material

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Impact of COVID-19 on the Speech and Language Therapy Profession and Their Patients

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Introduction: The UK's response to the COVID-19 pandemic presented multiple challenges to healthcare services including the suspension of non-urgent care. The impact on neurorehabilitation professions, including speech and language therapy (SLT), has been substantial.

Objectives: To review the changes to SLT services triggered by the COVID-19 pandemic with respect to referral rates, service delivery and outcomes, as well as examining the contribution of SLTs to the neurorehabilitation of COVID-19 patients.

Methods: Two surveys were distributed to Royal College of Speech and Language Therapists (RCSLT) members exploring experiences of service provision at 6 weeks and 22 weeks after the pandemic was declared in the UK. Responses to closed-ended questions, including questions regarding referral numbers were analyzed descriptively and compared at the two time-points. A database comprising routine clinical data from SLT services across the UK was used to compare information on patients receiving services prior to and during the pandemic. Data on COVID-19 patients was extracted, and findings are provided descriptively.

Results: Referrals to SLT services during the acute COVID-19 period in the UK were substantially less than in the same period in 2019. A number of service changes were common including adopting more flexible approaches to provision (such as tele-therapy) and being unable to provide services to some patients. Database analysis suggests fewer patients have accessed SLT since the pandemic began, including a reduction in neurorehabilitation patients. For those who received SLT, the outcomes did not change. SLTs supported a range of needs of COVID-19 patients. Treatment outcomes for COVID-19 patients with dysphagia were positive.

Discussion: The pandemic has affected neurorehabilitation and SLT services broadly: referral patterns are different, usual care has been disrupted and interventions have been modified affecting the impact on patient outcomes both positively and negatively. Some patients with COVID-19 require and benefit from SLT intervention.

Keywords: speech and language therapy, COVID-19, outcome measurement, service provision, disruption theory

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INTRODUCTION

Rehabilitation and enablement services have been modified significantly over the last decade in response to changes in demography and increasing care in the community, leading to demand outstripping capacity progressively over many years. People are living longer with complex health needs and there is increased evidence of the impact of rehabilitation services on improving independence and well-being leading to greater expectations and demand (1). Following the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) and the subsequent global health emergency (2), neurorehabilitation services entered the response when the requirement was already outstripping supply. An important element of the multi-disciplinary approach to neurorehabilitation is speech and language therapy (SLT), which attends to the assessment and management of those with speech, language, communication and swallowing disorders. As such, this profession was similarly affected by the demand and supply contention.

The evidence indicates a large and important role of neurorehabilitation services in the response to COVID-19. It is well-documented that the virus commonly affects the functioning of the nervous system and patients sustain a degree of ill-health for several weeks post-infection (3). Common symptoms observed in post-acute COVID-19 patients include dyspnea (or shortness of breath) and muscle weakness causing mobility difficulties (4). Moreover, COVID-19 patients can experience fatigue, neuropsychological and cognitive problems, dysphagia (swallowing difficulties), and general impairments in their activities of daily living (5). Rehabilitation services, thus, are warranted and indeed critical for treating COVID-19 patients. Consequently, strains are put on non-COVID-19 related rehabilitation services, especially those occupying hospital bed spaces, as the need for re-organization arises following the increase in patient admittance (6).

By the end of February 2020, the first case of within-country transmission of COVID-19 in the UK was recorded and on March 18, 2020, UK National Health Service (NHS) providers were given the directive to postpone all non-urgent and elective activity. By March 19, 2020 many community health services were stopped. A UK-wide lockdown shortly followed on March 23, 2020, and by March 25, 2020, all NHS hospital visits were suspended, and services were told to plan for the redeployment of clinical staff, including speech and language therapists (SLTs), to attend to critical COVID-19 related services (7, 8). Individuals who were identified as being "extremely vulnerable" to catching the virus and experiencing severely ill health or death, received a governmental directive to "shield" and completely self-isolate for the lockdown period (9).

As the spread of the virus accelerated and hospitalizations surged, thus did the demand for SLTs to be part of the team managing critically ill COVID-19 patients. Dysphagia (an impairment in swallowing function) emerged as a frequent complication in such patients with estimates of around 30% of those admitted to hospital with COVID-19 needing a swallow assessment (10), and many who were intubated requiring swallow rehabilitation (11). Not only does an impairment in swallow function result in difficulties with oral feeding, but it is also a risk factor for developing aspiration pneumonia, which has also been documented in COVID-19 patients (12). However, early evidence does indicate that dysphagic COVID-19 patients can make a recovery following swallow rehabilitation (13) which in the UK is carried out by SLTs. Some questions remain as to the extent of late swallowing complications, potentially arising from virus-induced bulbar nerve damage (14) which may highlight the need for ongoing intervention. Thus, SLTs are an integral part of the intensive care unit team (15) and the longer-term rehabilitation team. Moreover, SLTs have a role in the management of dysphonia, another frequently reported symptom of the virus, reported in patients with mild to moderate COVID-19 (16). Furthermore, high rates of difficulties with vocal function following intubation has been reported (17). Thus, the pandemic has had a wide-ranging impact on SLT services arising from the suspension of many therapy services, the redeployment of clinicians, and the demand for specialists within critical, acute and rehabilitation services. Consequently, disruption to SLT services has been noted.

The theory of disruption (18) suggests that a sudden break or interruption of usual practice and break with established routines and models may lead to innovation as well as unintended consequences, both positive and negative. The Royal College of Speech and Language Therapists (RCSLT), the professional body for SLTs in the UK, was aware at an early stage that the pandemic would lead to breaks with established models of service provision. This offered the opportunity to examine the impact on service provision and patient outcomes.

There are two key ways of learning from major disruption. Firstly, being able to compare data, such as referral rates, patient characteristics, care pathways and outcomes, during a period of disruption with that recorded beforehand, is likely to give useful insight into intended and unintended consequences. The second source of information is the reactive experience of practitioners. This paper aims to utilize both methods to explore the changes to SLT practice and service delivery arising from the pandemic, specifically by asking the following two research questions:

1. How has COVID-19 impacted on SLT both generally, and in neurorehabilitation, in terms of (a) referral rates, (b) service provision and (c) therapy outcomes?
2. What is the contribution of SLT in COVID-19 management?

METHODS

A mixed methods approach was taken, including the distribution of two surveys to SLTs in the UK exploring their experiences following the outbreak of the pandemic at two different time points, and interrogation of a UK database (*The RCSLT Online Outcome Tool)*. Neither contribution to the database nor participation in the survey was mandated and were not specific to SLTs working in neurorehabilitation alone.

Surveys

Two surveys were developed using Survey Monkey (19) and distributed to ∼17,000 RCSLT members through different communication channels including newsletters and social media.

The first survey was open between 23 April and 29 April 2020, inclusive, and the second ran between 12 August and 7 September 2020, inclusive. The questions for both surveys were developed iteratively by a working group consisting of SLTs and piloted by SLTs not involved in the development. They comprised open- and closed-ended questions. The analysis of and findings from the latter are reported here.

The surveys aimed to explore the experiences of UK-based SLTs by asking a series of closed-ended questions. The first survey included 15 questions, including 13 multiple choice questions, referring to the nature of changes in roles, responsibilities and duties, the extent to which intervention was being provided to individuals requiring speech and language therapy, any changes that were of benefit to clinical practice, service delivery and/or patients. The second survey included 3 questions contained in the first survey, and 46 additional questions about referral data and those developed from the often-reported experiences from the first survey, including teletherapy, workforce capacity and the barriers service users faced when accessing services. For each multiple-choice question in both surveys, participants were asked to select all statements which reflected their experience, which is analyzed descriptively regarding how often statements were selected. The full versions of both surveys can be found in the **Supplementary Material**.

To explore the impact of COVID-19 on SLT *referral rates* across speech and language therapy services, the responses to the questions on the second survey of "how many referrals did your service receive for speech, language and communication needs in the following periods" and "how many referrals did your service receive for dysphagia in the following periods" (periods specified as: 1 April−31 May and 1 June−31 July in 2019 and 2020) were combined, and a percentage change across the 2 years calculated. Data specifically for referrals from neurorehabilitation services was not collected.

To examine the impact on *service provision* we present findings from the surveys regarding reported experiences around changes in the roles, responsibilities and duties of SLTs, the provision of intervention and the barriers to accessing services, alongside an analysis of changes observed in the ROOT data for treatment episodes ending between 1 March 2019 and 31 August 2019 and 1 March 2020 and 31 August 2020, i.e. prior to and during the pandemic.

The RCSLT Online Outcome Tool

The RCSLT had been supporting SLT services with routinely collecting data prior to the pandemic. The national database, the "ROOT" (20), supports SLTs from across the UK with collecting and collating data on referrals, case mix, presentation and outcomes of individuals of all ages receiving SLT. It generates reports which contributes to quality assurance and benchmarking (21). The data collected includes de-personalized patient information, including: gender, age, medical diagnosis, and descriptors on the swallowing or communication condition [using codes given in the International Statistical Classification of Diseases and Related Health Problems-10th Revision (22) herein, "ICD10 codes"], as well as information from the Therapy Outcome Measure (TOM) (23–26).

The TOM is designed to be a simple, reliable, cross-disciplinary, and cross-client group method of gathering information on the impact of enablement and rehabilitation. It has been rigorously tested for reliability and clinical validity (23–26) and comprises four domains, the first three of which are based on the WHO's International Classification of Functioning (ICF) definitions of Impairment, Activity and Participation (27). The fourth domain of well-being, of both the individual and the carer, was added to the TOM due to the finding that having an impact on well-being is an objective of most neurorehabilitation services and thus needs to be separately identified in the outcome measure. The TOM has an 11-point ordinal scale. A rating from 0 to 5 is made on each domain, where a score of 0 is profound, 3 is moderate and 5 is considered normal for the age, sex, and culture of the individual (25). A score of 0.5 or ½ a point may be used to indicate if the person is slightly better or worse than the descriptor (23–26).

The ROOT is opt-in (i.e., it is not mandatory for all SLT services to contribute to) and currently comprises data from a range of service types including NHS, independent and third-sector funded services. Timing of data entry is not regulated and is dependent on the SLTs or support staff to input information either "live" or periodically.

To examine the impact on *service provision*, the number and proportion of episodes of care from every area of SLT, and those of the 5 most frequently recorded neurological disorders (in the 2019 period) were extracted from the ROOT data and are compared with 2020 data descriptively.

To evaluate the impact of COVID-19 on *therapy outcomes*, initial and final TOM ratings were extracted for episodes of care from every area of SLT, and those of the most frequently recorded neurological disorder for the same 2019 and 2020 period as detailed earlier. Average changes in the TOM were calculated and are presented descriptively.

Finally, to inform on the *contribution of SLT in COVID-19 management,* data from the ROOT on patients who were recorded as positive for COVID-19 was extracted. This was interrogated to explore the overall numbers of patients presenting to SLT services (within the services that were contributing data), with a diagnosis of COVID-19 (by age and gender) and the focus of SLT intervention for these patients. The SLT role in neurorehabilitation of COVID-19 patients was specifically examined by analyzing the change in the 'impairment' TOM before and after an episode of care of patients with a SLT diagnosis of dysphagia secondary to COVID-19. These are reported in categories which reflect the goal of intervention of these patients (i.e., whether the impairment is expected to improve, maintain at the same level, or if intervention is part of a managed decline). The average change in the TOM ratings was calculated and are presented descriptively.

Ethical Considerations

This project involved use of anonymised audit data to evaluate current services as part of a service evaluation. SLTs provided minimal de-personalized data on all referred patients e.g., age, gender, diagnoses, and TOM ratings at the beginning and end of an episode of care to the ROOT database, and

thorough information governance procedures were adhered to. Participants in the survey were anonymous and there were no inducements to take part.

RESULTS

Surveys of RCSLT members conducted in April 2020 and August-September 2020 received 544 and 413 responses, respectively. At the time of reporting, the ROOT contains data on 45,174 episodes of care from 39,534 patients, which are from 34 SLT services across the UK. Here, both sources of data are combined to answer the specific research questions.

The Impact of COVID-19 on SLT Referral Rates

Table 1 shows the number of referrals received for speech, language and communication needs (SLCN) (from 68 SLT services) and dysphagia (from 52 SLT services) and the change in referral rate between the two time periods prior to and during the pandemic, as reported by participants of survey 2. It indicates a substantial reduction in referrals for SLCN (−31.10% change) although a relatively stable rate of dysphagia referrals (−1.29% change).

The Impact of COVID-19 on SLT Service Provision

95.6% of respondents (520/544) to the first survey said that the pandemic was having an impact on their professional roles, responsibilities and duties. They reported changes including use of different methods of service delivery, and a reduction in clinical caseload (referrals and serviced current caseload) being most commonly cited.

Table 2 shows several common changes to service delivery experienced by SLTs during the acute COVID-19 period (April 2020), with nearly two-thirds of respondents identifying that an *altered method of service delivery* occurred in this period (63.1%), and almost half reporting that they were no longer seeing patients directly (face-to-face) (48.9%).

Table 3 explores the service provision changes in more detail but focuses on the provision for patients who *were* continuing to receive intervention in April 2020. The most commonly reported change to provision was more therapy being delivered remotely via telephone consultations (60.7%), with a high volume of respondents also citing the following changes: patients seen less frequently (44.5%), more video consultations (43.6%), more advice given to others (41.2%), alternative delivery of care due to PPE considerations (38.2%) and providing information via leaflets (28.3%).

Respondents reported that a significant proportion of patients were not receiving intervention, when in normal circumstances they would, for the both the acute COVID-19 period (April 2020) and later in August-September (2020). This demonstrates a negative shift over time, in that 74.6% responded that they did have patients who should be receiving intervention but who were not in April, which increased to 83.5% in the second survey in August-September. See **Table 4.**

The barriers to providing these patients with services are given in more detail (**Table 5**), across the two time points. The most frequently cited barrier in April was that services could

TABLE 2 | Frequently reported changes experienced by SLTs in April 2020, and number and percentage of respondents identifying these.

Changes reported	*n*	Percentage of all respondents (%)
Altered method of service delivery (e.g., remote delivery)	343	63.1
Reduction in routine clinical caseload	340	62.5
Reduction in referrals for patient/client groups on routine clinical caseload	278	51.1
No longer seeing patients directly	266	48.9
Restriction to the location of service delivery caused by closure of usual place of work (e.g., school, clinic)	240	44.1
Increased non-clinical tasks and/or projects	228	41.9

TABLE 3 | Six commonly reported changes in service provision for patients on routine caseloads who were continuing to receive intervention in April 2020, and number and percentage of respondents identifying these.

Change in provision	*n*	Percentage of all respondents (%)
More remote provision of therapy—via telephone consultations	330	60.7
Patients seen less frequently	242	44.5
More remote provision of therapy—via video consultations	237	43.6
More advice provided to others	224	41.2
Care being delivered in a different way due to considerations about PPE	208	38.2
Providing information *via* leaflets	154	28.3

TABLE 1 | Number of referrals received for speech, language and communication needs (SLCN) (from 68 SLT services) and dysphagia (from 52 SLT services).

		Total number of referrals 1 April−31 July 2019	Total number of referrals 1 April−31 July 2020	2020 referrals expressed as a percentage of 2019 referrals (%)	Percentage change (%)
SLT need	SLCN	10,081	6,946	68.9	−31.1
	Dysphagia	5,020	4,955	98.7	−1.3

TABLE 4 | Number of respondents reporting whether they had patients on their caseload who were not receiving intervention but would usually do so.

Response	April 2020		August-September 2020	
	n	Percentage of respondents (%)	*n*	Percentage of respondents (%)
Yes	406	74.6	313	83.5
No	97	17.8	53	14.1
Not applicable/no response	41	7.5	9	2.4

TABLE 5 | Number of respondents reporting common barriers to accessing services for patients on their caseload who were not receiving intervention.

Barrier	April 2020		August-September 2020		% change
	n	Percentage of respondents (%)	*n*	Percentage of respondents (%)	
Staff availability	51	9.4	69	18.4	+9%
No suitable venue/closure of usual place of work (e.g., school, clinic) or service	181	33.3	126	33.6	+0.3%
Closure of caseloads	84	15.4	*	*	
As a result of changes to service delivery based on national guidance or local policy (of the SLT service or another setting/service)	203	37.3	160	42.7	+5.4%
Limited access to correct type of PPE	30	5.5	14	3.7	−1.8%
Risks associated with aerosol generating procedures (AGP)	87	16.0	*	*	
SLT not able to provide teletherapy/service does not have access to teletherapy	42	7.7	43	11.5	+3.8%
Patients do not have access to teletherapy	115	21.1	196	52.3	+31.2
Teletherapy was not appropriate	*	*	200	53.3	
Patients not wishing to continue with intervention at the current time	160	29.4	160	42.7	+13.3%
Patients on my caseload have been discharged with advice to re-refer if required	64	11.8	*	*	
Individual/household was shielding	*	*	91	24.3	
Families' health and well-being needs	*	*	50	13.3	
Lack of access to interpreters/bilingual co-workers	*	*	32	8.5	
Other	79	14.5	58	15.5	+1%
No response	144	26.5	65	17.3	−9.3%

*N.b respondents could select more than one option, therefore, the percentages do not total 100. *Question not included on survey.*

not be provided due to *national guidance or local policy* (37.3%). This was still a common issue in August-September (42.7%) but moreover, there was an additional issue that *teletherapy was not appropriate* for some of these patients in the August-September survey (53.3%).

The second survey sought to explore these changes in service provision in more detail, such as the use of remote consultations by the profession. Respondents estimated that, on average, 46.2% of individuals on SLT caseloads were receiving services virtually (e.g., *via* teletherapy) which had been unusual before and at an earlier stage in the pandemic.

Data from the ROOT on completed episodes of care is presented in **Table 6** detailing episodes recorded for patients with any of the 5 most common neurological disorders referred for SLT in the 2019 and 2020 periods. The number of episodes is also expressed as a percentage change across the 2 years. This illustrates a distinct reduction (of 1,523) in episodes of care either recorded or entered into the ROOT in the 2020 period compared with the 2019 period.

The Impact of COVID-19 on SLT Outcomes

Table 7 shows the mean and median change in the TOM for all the ROOT data for both time periods in 2019 and 2020, as well specifically for stroke patients. The tables indicate that outcomes were largely positive and consistent in both cohorts. Interestingly, the data suggests that stroke patients made greater progress in their therapy in 2020 than in 2019.

TABLE 6 | Completed episodes of care recorded in ROOT, for whole database and broken down for the 5 most common neurological disorders, in the 2019 and 2020 periods, and expressed as a percentage change across the 2 years.

	Number of completed episodes of care	1 March–31 August 2019	1 March–31 August 2020	% change
All SLT patients	All	3663	2140	-
Neurological medical condition	Stroke*	619	147	-
	%	16.9%	6.9%	−10.0
	Dementia*	255	42	-
	%	7.0%	2.0%	−5
	Motor neuron disease	104	60	-
	%	2.8%	2.8%	0.0
	Parkinson's disease	55	27	-
	%	1.5%	1.3%	−0.2
	Brain tumor*	23	1	-
	%	0.6%	0.0%	−0.6

**Indicates where a group of ICD10 codes have been counted together, which refer to a general condition, for example "Stroke" includes episodes recorded as relating to: Stroke, not specified as hemorrhage or infarction, and Cerebral Infarction.*

The Contribution of SLT in COVID-19 Management

The data on 163 individuals with a confirmed COVID-19 diagnosis (**Figure 1**) indicates that more males than females were referred, and a greater proportion of people from the older age group required SLT services, which is in line with the reported gender and severity differences related to COVID-19 requiring hospitalization (28).

The data in **Table 8** describes the SLT management required for the patients referred with a positive diagnosis of COVID-19, and the average change in the TOM. These individuals were treated for dysphonia, dysphagia, dysarthria and cognitive communication disorder. Some patients were orally intubated and/or had a tracheostomy as part of their management requiring assistance with oral hygiene. This shows some variability in the degree of change for different conditions, however clinically significant changes were reported for most.

Where possible, COVID-19 patients were coded for the objective of their SLT intervention: whether their impairment was anticipated to "improve," "sustain," or where they may have a "managed decline," depending on the underlying medical condition causing the speech, language, communication or swallowing disorder. **Table 9** provides data on the respective average outcomes of COVID-19 patients with dysphagia, within each intervention objective. The highly significant positive change in impairment rating of those

TABLE 7 | The average change in TOM scores for all ROOT data and specifically stroke data for both time periods in 2019 and 2020.

Time period	*n*		TOM domain				
			Impairment	Activity	Participation	Well-being	Carer well-being
All ROOT data 2019	3,663	Average (mean) change	0.62*	0.79*	0.52*	0.56*	0.56*
		Average (median) change	0.00	0.50*	0.00	0.00	0.00
All ROOT data 2020	2,140	Average (mean) change	0.54*	0.66*	0.58*	0.51*	0.69*
		Average (median) change	0.00	0.50*	0.50*	0.00	0.50*
Stroke data 2019	619	Average (mean) change	0.54*	0.64*	0.49	0.49	0.71*
		Average (median) change	0.00	0.00	0.00	0.00	0.50*
Stroke data 2020	147	Average (mean) change	1.07*	1.20*	1.19*	0.71*	0.54*
		Average (median) change	1.00*	1.00*	1.00*	0.50*	0.50*

**An increase of 0.5 or more on the TOM is a clinically significant change (21) and is marked with an asterisk.*

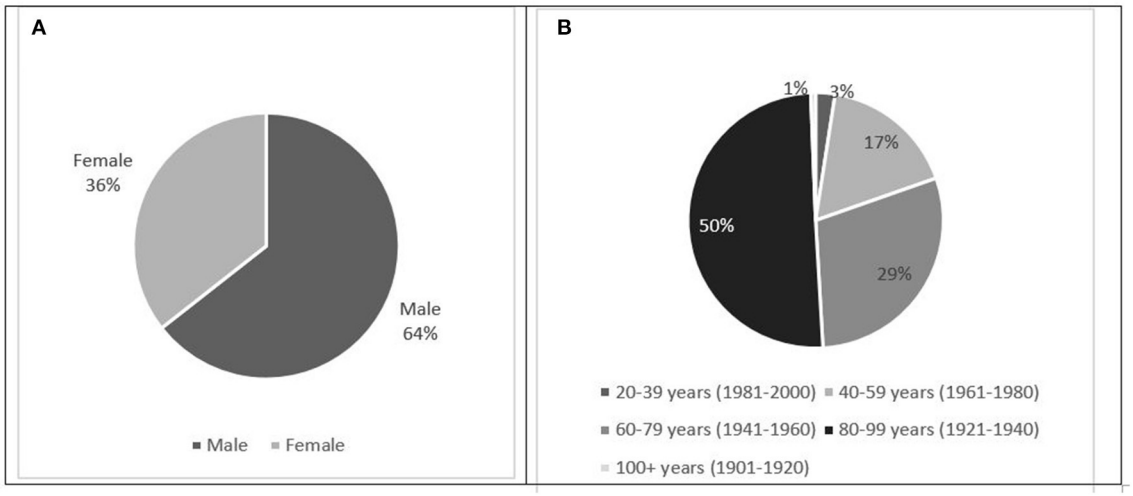


FIGURE 1 | Proportion of 163 patients with confirmed COVID-19 diagnosis at the point of referral to speech and language therapy, by gender **(A)** and age group **(B)**.

TABLE 8 | The number and average change in TOM "impairment" ratings from multiple TOM scales for COVID-19 positive patients being treated by SLT services.

	TOM scale				
	Dysphonia	**Dysphagia**	**Cognitive communication disorder**	**Tracheostomy**	**Oral hygiene**
n	69	174	83	30	82
Average (mean) change	1.02*	0.83*	0.85*	3.83*	0.19
Average (median) change	0.00	0.25	0.00	4.00*	0.00

*NB. Individuals may have more than one SLT requirement. *An increase of 0.5 or more on the TOM is a clinically significant change (24) and is marked with an asterisk.*

TABLE 9 | The number of patients with dysphagia and COVID-19, with identified specific intervention objectives (improvement, sustain, manage decline), with the corresponding median impairment scores at the start and end of treatment, and median change over time.

Intervention objective	**Number of patients (*n* = 81)**	**Median impairment score (start of treatment)**	**Median impairment score (end of treatment)**	**Median change in impairment**
Improve	26	3.00	4.50	1.50*
Sustain	16	3.00	3.00	0.00
Managed decline	14	2.00	1.00	0.00
Not specified	25	3.50	4.00	0.00

**An increase of 0.5 or more on the TOM is a clinically significant change (24).*

on the "improve" track may be associated with the role that SLTs have in dysphagia management of COVID-19 patients, forming a crucial part of the multi-disciplinary team (MDT) (29).

DISCUSSION

Despite the challenges posed on the UK healthcare system resulting from the COVID-19 pandemic, speech and language therapists have been able to adapt their ways of working, develop specialist skills and innovate strategies to manage the consequences of a new disease. On the other hand, speech and language therapy services in the UK have, for several reasons, reduced over the acute-stage of the pandemic, and it is probable that a large proportion of patients have not received the provision they would have normally been offered. The findings we present here provide a broad insight into the ways in which this has occurred from a national perspective, which appear very much in line with reports from other UK-based allied health professions (30).

Investigating such changes, and thus assessing the impact of the pandemic, is challenging. One of the advantages of a dedicated and flexible national database, such as the ROOT, is that it provides information which can be interrogated when there is a major unanticipated disruption, such as a pandemic. This allows for analysis of the impact on services and patients exposing negative and positive effects. By comparing information gathered during the first wave of the COVID-19 crisis in the UK, with that from an identical time-period in 2019, we have been able to illustrate some of the impacts of the outbreak on usual care. The survey of professionals provides further information explaining and complementing that gathered on the database and assisting with its interpretation. Whilst we acknowledge that we cannot generalize the findings from our investigations too widely due to the opt-in and non-stratified methodologies used, it can nonetheless offer a unique perspective on UK SLT provision both before and after the onset of the COVID-19 pandemic. In so doing, we have been able to investigate specific questions posed, regarding its impact.

Changes to Referrals to and Service Delivery of Speech and Language Therapy

Overall, the data presented here suggests that SLTs have observed substantial changes to the number of referrals to SLT, and the amount and process of therapy that they have delivered, following the UK's COVID-19 response. This is perhaps not surprising given the national restrictions and is in line with reports on the general landscape of non-COVID-19 NHS care during the pandemic (31). Indeed, it is clear from both datasets that, similar to other services (30), there has been a reduction in routine SLT caseloads. This may in part be caused by fewer new referrals for the assessment and treatment of speech, language and communication disorders. Additionally, it is likely to be an effect of SLTs being unable to provide intervention to individuals on existing caseloads following the closure of settings during lockdown, and patients opting not to access services at this time. The findings from the survey provide insight into these changes, specifically the 2019/20 year-on-year referrals, but also the finding relating to the high proportion of services which had to adopt different methods of service delivery. There has been an increase in the provision of services in different settings delivering therapy remotely using a variety of technologies, which is likely to have disadvantaged those from socially deprived areas (32) or the very elderly (33). The "switchover" to telehealth has been one of the widest reported changes to healthcare in this period (34, 35), despite its subsequent problematizing with regard to how this approach may exclude many patients without access to technology (36). These issues are likely to underpin the reduction in treatment episodes recorded on the ROOT for the pandemic.

Impact on Neurorehabilitation Speech and Language Therapy Services

It is possible that some neurorehabilitation patient groups have been more severely affected by the pandemic, in terms of receiving therapy. We found that not only had the number of episodes of care for stroke patients reduced substantially between the 2019 and 2020 periods (619–147), the proportion of episodes of care for stroke in the 2020 period was 10% less than the year before. Whilst it is possible that over time, as more data is imported into ROOT, this pattern adjusts, it is plausible that given the COVID-19 healthcare response, these patients are simply not being referred to SLT. Early assessment and management of stroke-related dysphagia and language difficulties by SLTs reduces pneumonia and mortality (37) and there is evidence that persistent aphasia has a more favorable outcome if provided with SLTs at an early stage (38). Therefore, this finding of reduction in referrals is of concern. One explanation could be that it is simply not safe for SLTs to deliver care to these groups in the COVID-19 context (39), or these patient groups may be less able to rapidly adapt or adhere to tele-therapy (40), leading to less engagement in this period. However, the reduction observed in stroke cases from SLTs is in line with other reports showing a concerning reduction in stroke admissions across the UK throughout the lockdown period (41). Similarly, the data shows a reduction in episodes of care for dementia patients, but relatively consistent representation of patients with Motor Neuron Disease (Amyotrophic Lateral Sclerosis), Parkinson's disease and those with brain tumors. This could potentially indicate where SLT services were particularly affected, for example, with limited access to care homes to see patients with dementia, or reduced capacity in acute hospital care for those with strokes, in comparison to the likely domiciliary care for other neurorehabilitation patients with chronic or progressive diseases.

Impact of the Pandemic on Routine Therapy Outcomes

The findings also show, interestingly and perhaps surprisingly, that the average improvement on the TOM from 2019 is indeed maintained, and in some cases, bettered, in 2020. It is clear that SLTs continue to make an impact for patients, regardless of the challenging circumstances. For the stroke patients recorded in the ROOT, the comparative average change in outcomes between 2019 and 2020 is notable; the median change in 2019 for impairment, activity and participation was 0.0, which increased to 1.0 in 2020, reflecting a positive gain of 2 half-points which is clinically significant. This is of particular interest and requires further investigation to ascertain the reasons. Yet, it is important to note that those receiving SLT in 2020 during the pandemic may be a subset of those who would do so in usual times. One consideration is that those who received intervention may have been a "less impaired" subset. It is plausible, for example, that patients with more complex needs, co-morbidities and/or those who were subject to the "shielding" regulations may have been less able to engage with services during the immediate period after the UK lockdown. Thus, this may reflect the therapy outcomes from those who were less at risk of the virus in terms of health, i.e., fewer co-morbidities and who may potentially make greater gains anyway, or those who had greater support around them from relatives/carers working at home. Another consideration may be that those from less socially deprived

areas were able to access therapy more readily than those in less-affluent areas, using virtual means (32). Furthermore, some individuals may also have experienced improved access with the extension of remote delivery of services, such as those who would ordinarily find it challenging to attend appointments, due to caring responsibilities, or travel restrictions. Another explanation could be that for those engaging in teletherapy, skills acquired through intervention whilst in the home were more easily practiced and embedded than when therapy is confined to a clinic.

Contribution of Speech and Language Therapists in Managing COVID-19

Our findings illustrate that SLT plays an important and positive role in the treatment and rehabilitation of patients with COVID-19 especially for those presenting with dysphagia, whose impairment can improve—and potentially resolve, for a subset of patients. The survey, similar to other reports (42), indicates that SLTs have adopted new roles associated with treating particular symptoms of COVID-19, such as communication with tracheostomy, and different expressions of dysphagia. The SLT profession has a growing body of data about the presentation (**Table 8**) and outcomes (**Table 9**) of individuals with COVID-19 receiving SLT intervention for the consequences of this new disease, which is further supported in the literature (12–14, 43, 44).

Going forward, it would be valuable to be able to gather information on the new ways of working from the perspective of those both receiving and in need of the service. A limitation of the study presented in this paper is the omission of information from those receiving services during this period. The RCSLT are, at the time of writing, conducting a survey to gather the experiences of individuals with speech, language, communication and swallowing needs, and their families, but the findings are not presented in this paper. Nonetheless, charities and patient associations have been collecting information on the impact of COVID-19 on their members. The impact on services was detailed in surveys conducted by the Patients' Association and the Stroke Association. The latter survey (45) received a response from 1,500 stroke survivors and carers in England, 60% of whom felt that they received less support from health and care services than was usual. Sixty-eight percent of respondents reported that they felt more anxious and depressed and more than three quarters of carers said they were providing more care and support during the pandemic than prior to it. Nine hundred and fifty-three patients responded to the survey conducted by the Patients' Association (46) which found that 67% of respondents reported that they were not seeking medical advice or intervention either because primary care services were more difficult to access or because they were avoiding contact with healthcare professionals due to anxiety related to the pandemic. These findings were not surprising given what the survey reported in this paper along with what the ROOT data indicates.

There are additional limitations to our study that should be considered when interpreting the results presented in this paper. As with all surveys, we must be cautious in our assumption that these respondents are representative of the experiences of the SLT profession within the UK. Furthermore, even though the ROOT is intended to be used by SLTs for routine data collection, it is likely that the disruption experienced by services has impacted on the ability to record outcomes data for all individuals receiving SLT compared with usual times, which may be affecting the completeness of the data in the national database. It will be important to repeat this analysis in future to explore any changes to the retrospective data. The nature of the data in the ROOT also may impede its generalizability, not least with respect to the specific UK context, but also across services within the UK, since it captures a subset of speech and language therapy services.

Despite this, we have presented an overview of the impact of COVID-19 on the role and clinical practice of SLTs in the UK, providing evidence of consequences of the pandemic, both positive and negative. The outcomes of SLT patients both prior to and during the pandemic present some interesting issues and areas for further exploration, in addition to highlighting the contribution of SLTs in COVID-19 rehabilitation. The recovery of the provision of health services once the pandemic wains will need to consider how to support those who did not receive SLT support for their speech, language, communication and swallowing needs or for their rehabilitation in a timely manner along with incorporating the new ways of working into care pathways.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this is anonymised routine patient data. Requests to access the datasets should be directed to root@rcslt.org.

AUTHOR CONTRIBUTIONS

KM and KC: data collection and analysis. PE, KM, and KC: preparation of manuscript. All authors: contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.629190/full#supplementary-material

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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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Rehabilitation of Neuromuscular Diseases During COVID-19: Pitfalls and Opportunities

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The outbreak of COVID-19 caused by SARS-CoV-2 has spread worldwide with a huge impact on the healthcare system. Compared to the previous coronaviruses-related pandemics, COVID-19 is more transmissible with potential systemic involvement and peculiar neurological manifestations, such as Guillan-Barrè syndrome up to critical illness myopathy, occurring in the intensive care setting. In this clinical scenario, people living with a neuromuscular disease (NMD) represent a vulnerable category with a high risk of a severe course of COVID-19. Moreover, in the NMD population, the management of respiratory and muscular impairments after SARS-CoV-2 infection might be troubling in terms of both pharmacological and rehabilitative approaches. To date, rehabilitation is still an unmet need in this population with several implications on NMD progression with and without SARS-CoV-2 infection. In particular, rehabilitation intervention for patients with NMD after COVID-19 are lacking. Therefore, in the current paper, we analyze the critical issues of COVID-19 on NMDs patients and propose a home-based rehabilitation program targeted for this population after mild to moderate SARS-CoV-2 infection.

Keywords: COVID-19, neuromuscular diseases, respiration disorders, muscle wasting, rehabilitation, home-based program

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INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 continues to act as a great burden for social and healthcare systems in the modern era due to unexpected contagiousness and severity of the clinical condition (1–3). Similar to other CoVs (SARS-CoV and Middle East respiratory syndrome coronavirus, MERS-CoV), SARS-CoV-2 appears to be neurotropic since peculiar manifestations (dysgeusia, anosmia, seizures, and even encephalitis) might occur in patients affected by COVID-19 (4–6).

Neurological involvement can be equally due to post-infectious immune-mediated mechanisms as in Guillan-Barrè syndrome (GBS) (7, 8) or myositis (9). Moreover, neuromuscular complications of COVID-19 such as critical illness myopathy (CIM), polyneuropathy (CIP), and polyneuromyopathy (CIPNM) might occur during intensive care stay (10).

Patients affected by neuromuscular diseases (NMDs) can experience more frequent and severe COVID-19-related complications compared to the general population (11, 12).

NMDs are rare conditions (prevalence $< 1/2{,}000$) involving anterior horn cells, peripheral nerves, neuromuscular junctions, or skeletal muscles that result in poor motor performance (13). Management of NMD patients affected by COVID-19 is challenging and requires specific

pharmacological and rehabilitation strategies even after the resolution of respiratory infection. The aim of this paper is to analyze the critical issues of COVID-19 on NMDs patients and to propose a home-based rehabilitation program for this population after SARS-CoV-2 infection.

COVID-19-RELATED RESPIRATORY AND MUSCLE IMPAIRMENTS IN NMDs

COVID-19 and Respiratory Involvement in NMDs

In patients affected by NMDs, respiratory impairment is common and includes inspiratory and expiratory muscle weakness, ineffective cough, alteration of blood gases, nocturnal sleep disorder, reduction of vital capacity, and dyspnea during activities of daily living (ADLs), strongly contributing to progressive disability (14, 15). Therefore, this population is at higher risk of recurrent lower respiratory tract infections and acute respiratory failure that increase hospitalization and mortality rates (16).

To better define the impact of COVID-19 on NMDs patients with respiratory involvement, several issues should be examined. Some pre-existing impairments might contribute to the occurrence of COVID-19 complications in NMDs, such as a force vital capacity (FVC) of <60%, use of ventilation, or swallowing dysfunctions (**Table 1**) (12). Moreover, spine deformities, such as kyphoscoliosis, commonly observed in these patients, might further worsen respiratory function by reducing chest expansion, thus contributing to an increased risk of developing respiratory distress during COVID-19 (17, 18). On the other hand, the mildest forms of NMD with stabilized cardiopulmonary function without other comorbidities seem to be associated with lower rates of COVID-19 complications and better respiratory outcomes, even after hospitalization in intensive care (18).

However, the coexistence of NMDs and COVID-19 is a dangerous duet to be managed, particularly from a rehabilitative perspective. For example, in case of interstitial pneumonia due to SARS-CoV-2 infection, supplemental oxygen therapy should be provided to avoid hypoxemia, but if this intervention is not combined with adequate ventilatory support, worsening of underlying chronic hypercapnia in NMDs patients might occur because of rapid onset of respiratory muscles exhaustion (19, 20). Otherwise, for some NMDs characterized by severe bulbar involvement, the use of ventilation devices might be poorly tolerated (21). In the case of acute respiratory distress syndrome (ARDS), endotracheal intubation is required and prone positioning is often preferred (22), but NMDs patients might be affected by limited neck mobility and/or oropharyngeal muscle atrophy so that these procedures might cause severe discomfort (23, 24).

For post-acute COVID-19 patients affected by NMDs, it is necessary to identify the signs of residual pulmonary damage, such as ground-glass opacities, consolidation, pleural effusion, and irregular solid nodules, and their implications on functioning to design a patient-tailored rehabilitation approach (25).

TABLE 1 | Risk factors of severe COVID-19 course in NMDs patients according to the World Muscle Society (WMS) (11).

Muscular weakness of the chest or diaphragm, resulting in respiratory volumes <60% predicted (FVC < 60%), especially in patients with kyphoscoliosis
Use of ventilation via mask or tracheotomy
Weak cough and weak airway clearance due to oropharyngeal weakness
Presence of tracheostoma
Cardiac involvement (and/or on medication for heart involvement)
Conditions at risk of deterioration with fever, fasting, or infection (e.g., neuromuscular junction or metabolic disorders)
Conditions at risk of rhabdomyolysis with fever, fasting, or infection
Comorbidity (e.g., diabetes and obesity)
Patients receiving steroids and immunosuppressant treatment

COVID-19 and Muscular Involvement in NMDs

At the tissue level, patients with NMDs have skeletal muscles, motor nerves, or neuromuscular junctions' damages with progressive loss of functional ability and poor perceived quality of life (13). For this population, COVID-19 represents a precipitating factor of muscle wasting, also through the deconditioning due to inactivity and the high risk of long-term bedridden.

Several factors might contribute to poor functional recovery in NMD patients affected by COVID-19 (9). During SARS-CoV-2 infection, myalgia is a frequent complaint with a prevalence ranging from 21.9 to 35.8% of COVID-19 patients (26). Pitscheider et al. have observed that muscle damage seems to occur in a similar frequency in COVID-19 and influenza infection but with higher severity in influenza, as suggested by significantly higher serum creatine kinase (CK) levels compared to COVID-19. Authors claimed that it is difficult to determine whether this finding is due to a virus-triggered inflammatory response or to direct muscle toxicity (27). It should be underlined that have been described episodes of rhabdomyolysis associated with autoimmune COVID-19-related myositis, up to the CIM (28, 29). Furthermore, as a consequence of the chronic inflammatory process, people affected by COVID-19 often develop muscle wasting with a poor physical performance that leads to mobility limitation contributing to a loss of independence and increased hospitalization and healthcare cost (30).

This infection might exacerbate the clinical and functional complaints of NMD patients. For example, Anand et al. described five cases of COVID-19-related worsening of myasthenia gravis successfully treated with intravenous immunoglobulins and steroid administration (31).

On the contrary, the pattern and severity of muscle involvement in NMD (e.g., reversible, slow, and rapidly progressing NMDs) should be carefully considered as potential prognostic factors for COVID-19 in terms of rehabilitation outcomes since progressive muscle wasting, joint contractures, and fatigue characterize NMD patients (32).

PRACTICAL CONSIDERATIONS FOR NMD PATIENTS DURING COVID-19

Management of Pharmacological Therapy

During the COVID-19 era, for people with NMDs is not recommended to discontinue ongoing treatments; for example, in those affected by Duchenne or Becker Muscular Dystrophy (DBMD), steroid cessation is not advised and eventually adjusted in case of COVID-19 to avoid adrenal insufficiency (19). Moreover, in a recent study about drugs identified as "protective" against this infectious disease, it has been demonstrated that the administration of ubiquinone, a supplement commonly used in DBMD patients, might reduce the risk of COVID-19-related hospitalization (33).

Similarly, in the inflammatory myopathies, myasthenia gravis, and peripheral nerve disease, previous administration of immunosuppressive drugs, like azathioprine or methotrexate, should not be discontinued, except in selected cases, under the supervision of neuromuscular specialists (34). Nevertheless, some pharmacological treatments that need hospitalization, such as eteplirsen and other exon skipping for DBMD and enzyme replacement therapies (ERT) like recombinant human GAA (rhGAA) in Pompe Disease (PD), have stopped during a pandemic due to the risk for these patients to contract an infection while in hospital (19). For the PD population, there are some data reporting no change in the disease course after ERT discontinuation for <3 months, while a severe deterioration of muscular and respiratory functions might occur if ERT is discontinued for over 9 months (35). An alternative option is a home infusion to minimize the exposure to COVID-19 (19). On the other hand, for spinal muscular atrophy (SMA), the administration of intrathecal nusinersen is mandatory, despite the COVID-19 pandemic, due to the proven worsening of clinical and functional condition with delayed treatment in particular for SMA 1 and young children with SMA 2, while for the adolescent or adults, injections could be delayed for a maximum of 4 months from the last administration (36, 37).

For what concern drugs commonly used to treat COVID-19 patients, a lack of reliable evidence persists (38).

In **Table 2** are reported antiviral and immunomodulatory drugs currently under evaluation according to the COVID-19 Treatment Guidelines Panel (38), their mechanism of actions, route of administration, and safety issues in NMDs patients (39, 40).

Among the adjunctive therapies, a potential role in the treatment of COVID-19 has been proposed for two vitamins: vitamin C as an antioxidant and free radical scavenger and vitamin D as a modulator of innate and adaptive immune responses (41, 42). However, the lack of compelling data requires further study to make reliable recommendations on the use of these vitamins during COVID-19 (38).

Management of Rehabilitation Needs

Rehabilitation is an unmet need in the COVID-19 era, particularly for NMDs patients. During the COVID-19 pandemic, these patients experienced serious difficulties to receive usual rehabilitation care with potential implications on disease progression as well as functional worsening and psychological distress (32); moreover, considering several respiratory and musculoskeletal sequelae, including mild cases in home-isolation, COVID-19 might significantly worsen functional outcomes achieved through rehabilitative approach in these patients (32).

According to a recent expert consensus on rehabilitation protocol for COVID-19 patients, it was proposed a comprehensive evaluation and rehabilitation intervention based on the International Classification of Functioning, Disability and Health (ICF), using ICF core set for chronic obstructive pulmonary disease (COPD) (43). Nevertheless, no systematic identification of impairment and disability according to the ICF was made for NMD patients after COVID-19. In this context, only care guidance and one expert opinion address the specific needs in this population, such as pharmacological management, the role of telemedicine, and emergency procedures, to adopt (19, 32). Regarding rehabilitative approaches to NMDs patients after COVID-19, the main issues are the lack of dedicated protocols, including measurement tools and functional outcomes to achieve, and insufficient data about the safety of rehabilitation procedures. Although telemedicine or home-based rehabilitation are potential resources to provide care for these patients, evidence supporting their use is scant (17).

In the current paper, we propose a home-based rehabilitation program for the management of respiratory and muscle impairment in NMD patients after COVID-19.

A PROPOSAL FOR HOME-BASED REHABILITATION FOR NMDs PATIENTS AFTER SARS-COV-2 INFECTION

According to the available recommendations on physiotherapy for NMDs and the respiratory and muscle impairment after COVID-19 (44–49), we designed a home-based rehabilitation program, intended for ambulatory patients affected by genetically confirmed NMDs after asymptomatic, mild, or moderate COVID-19 (i.e., at discharge from hospital or testing negative for the virus, excluding those requiring non-invasive ventilation or tracheostomy).

Our proposed approach aims to preserve and/or progressively increase respiratory muscle strength, optimize endurance and exercise tolerance, reducing fatigue in this population. Our protocol include a preliminary evaluation, useful to suggest the most appropriate rehabilitation program, consisting of the following assessments: collection of demographic and anthropometric data; vital signs measurement (body temperature, respiratory and heart rate, blood pressure, blood oxygen saturation); spirometry to measure the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), which are useful to assess the strength of respiratory muscles; evaluation of all three dimensions of motor performance (standing and transfer, axial and proximal motor function, and distal motor function) through the Motor Function Measure-32 (MFM-32) (50); timed test as the Six-Minute Walk Test (6 MWT) or Two-Minute Walk Test (2 MWT) to investigate

TABLE 2 | Mechanism of action, route of administration, and safety of drugs used in clinical practice for COVID-19 therapy.

Drugs	Route of administration	Mechanism of action	Safety issues in NMD patients
Chloroquine phosphate Hydroxychloroquine	Oral	Interfere with entry of the virus into human cells and inhibition of virus replication Increase the PH of endosomes and lysosomes, inactivating of t-cells and other cytokines Interfere with antigen presentation, decreasing the antigen–major histocompatibility complex (MHC)	Prolonged QT interval, Torsades de Pointes, Atrioventricular block, ventricular arrhythmia; neuromyopathy and myopathy
Lopinavir/Ritonavir	Oral	Inhibit the action of the enzyme 3-chymotrypsin-like protease (3-clpro) disrupting the process of viral replication and release from host cells	PR or QT prolongation
Remdesivir	Intravenous	Inhibit the viral RNA synthesis binding the viral RNA-dependent RNA polymerase (RDRP) complexes	Mild, reversible PT prolongation
Tocilizumab	Intravenous	Inhibit IL-6 receptor, blocks cytokine storm	Risk of serious opportunistic infections
Dexamethasone	Oral or Intravenous	Modulate inflammation-mediated lung injury	Risk of serious opportunistic infections
Azithromycin	Oral	Decrease the virus entry into cells Up-regulate genes involved in the innate response	QT prolongation

TABLE 3 | Our proposed evaluation protocol for people affected by NMDs post COVID-19.

Demographic and anthropometric data
Vital signs
Spirometry
ICF GENERIC-30 SET
Motor Function Measure-32 (MFM-32)
Six-Minute Walk Test (6 MWT) or Two-Minute Walk Test (2 MWT)
Fatigue Severity Scale (FSS)
EuroQoL five-dimensions (EQ-5D)
Barthel Index Dyspnea
Borg Category-Ratio Scale

aerobic capacity and endurance (51, 52); evaluation of fatigue by Fatigue Severity Scale (FSS) (53); assessment of perceived Quality of Life (QoL) through the EuroQoL five-dimensions (EQ-5D) (54); characterization of functioning and disability using ICF GENERIC-30 SET; and functional limitation due to respiratory and motor impairment through the Barthel Index Dyspnea (55) (**Table 3**). During the evaluation step, the examiner will administer the Borg Category-Ratio (CR-10) Scale pre- and post 6 MWT, together with monitoring of vital signs, to measure physical activity intensity. Moreover, Borg CR-10 will be explained to the patient for self-administration during home training, aimed to guide the exercise intensity. After these preliminary assessments, it will provide an exercise educational program describing the tailored home-based rehabilitation, according to patients' functioning and motivation, and defining appropriate exercise parameters, using the FITT principle (i.e., frequency, intensity, time, and type). Our proposed intervention is principally focused on Respiratory Muscle Training (RMT), Aerobic Reconditioning, Resistance Training, and daily sessions of Lung Recruitment Techniques.

A physiotherapist will provide theoretical instructions for each exercise together with video demonstrations available online on specific web-based platforms.

In detail, the RMT program consists of respiratory muscle strengthening using a pressure threshold loading, to increase both MIP and endurance of inspiratory muscles, with a suggested frequency of at least 3 × 30 min/week and an intensity of 30–70% MIP/MEP. Aerobic Reconditioning initially provides march on spot and step-ups and progressively introduces free walking to then move on cycling; also in this case the frequency suggested is 3 × 30 min/week, with an intensity below anaerobic threshold, established by the onset of dyspnea/fatigue symptoms or a Borg CR-10 score below 3. Resistance Training includes both open-kinetic-chain and closed-kinetic-chain exercises for upper and lower limbs for 20 min 2–3 times/week and low-intensity effort (60% of effort of one repetition maximum, 1 RM), where the one repetition maximum indicates the maximum weight that a person can lift in a single repetition. Lung Recruitment Techniques include controlled breathing (deep-slow breathing using diaphragm to improve ventilation/perfusion value), paced breathing (with respect to the effort), chest expansion breathing combined with shoulders retraction to increase respiratory compliance, active cycle of breathing techniques, and a Positive Expiratory Pressure (PEP) trainer to facilitate airway clearance and improve lung function.

Moreover, patients may register their daily number of steps through a common smartphone pedometer application to monitor their walking performance. It would be appropriate for the patient to be closely monitored (at least every month from the beginning of the training). The home-based rehabilitation program proposed being reported in **Table 4**.

CONCLUSION

During the COVID-19 era, several critical issues in the NMD population have been reported. These patients experience

TABLE 4 | Proposal of home-based rehabilitation program for NMDs patients after COVID-19.

Prescription	Frequency	Intensity	Time	Type
RMT strength	3 sessions × 30 min a week	30–70% MIP/MEP	At least 8–10 weeks	Pressure threshold loading
Aerobic reconditioning	3 sessions × 30 min a week	Below anaerobic threshold*	At least 8–10 weeks	March on spot, step-ups, free walking, cycling
Resistance training	2–3 sessions × 20 min a week	60% of 1RM	At least 8–10 weeks	OKC and CKC exercises for upper and lower limb
Lung recruitment tecniques	5–10 min × max. 3 times a day	At vital capacity level or at 3 of Borg CR-10 scale	At least 8–10 weeks	Controlled breathing; paced breathing; Chest expansion breathing; Active cycle of breathing techniques; PEP trainer

**Established by onset of dyspnea/fatigue symptoms or a score below 3 of Borg CR-10 scale.*
RMT, Respiratory Muscle Training; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; RM, repetition maximum; OKC, open-kinetic-chain; CKC, closed-kinetic-chain; Borg CR-10, Borg Category-Ratio Scale; PEP, Positive Expiratory Pressure.

changes in the management of ongoing drug treatment or may discontinue rehabilitative care. Moreover, in NMD patients, a severe course of COVID-19 might occur, with uncertain prognosis and complications often requiring intensive care stay. On the other hand, some NMD patients appear in a mild to moderate clinical course of COVID-19, with a better perspective of both respiratory and muscle recovery. In this clinical scenario, rehabilitation is still an unmet need, with a lack of operational protocol that is specific for this population. Our home-based rehabilitation program proposal is intended to preserve and/or improve respiratory muscle strength, endurance and exercise tolerance, counteracting fatigue in NMD patients after COVID-19.

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

GI and SL contributed to the conception and design of the paper. SL and AM wrote the first draft of the manuscript. All authors contributed to manuscript revision and 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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Clinical and Electrophysiological Outcome Measures of Patients With Post-Infectious Neurological Syndromes Related to COVID-19 Treated With Intensive Neurorehabilitation

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Background: The clinical spectrum of coronavirus disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, may be quite wide, including neurological symptoms. Among them, para-infectious or post-infectious neurological syndromes (PINS), caused by an inflammatory response against the central and/or peripheral nervous system, have been reported. The aim of this paper is to illustrate the functional and neurophysiological recovery in a series of subjects with COVID-19-related PINS who underwent intensive neurorehabilitation.

Materials and Methods: Five patients with PINS associated with COVID-19 were evaluated at baseline and followed up for 6 months. Three of them had polyradiculoneuropathy and two patients had myelitis. The onset of the neurological syndromes was temporally associated with the SARS-CoV-2 infection. After completing the acute neurological treatments in the intensive care unit, patients underwent a personalized multidisciplinary rehabilitation program. An in-depth clinical, functional, and electrophysiological assessment was carried out at baseline and at 3- and 6-month follow-ups.

Results: Among patients with polyradiculoneuropathy, the electrophysiological evaluation at baseline disclosed an acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in two patients and an acute motor and sensory axonal neuropathy (AMSAN) in the third patient. At follow-up, the electrophysiological features improved in one subject with AIDP and were stable in the remaining two cases. The functional assessment after neurorehabilitation showed global recovery and full independence in walking and in activities of daily life in one patient and mild improvement in the other two cases. Of the two subjects with myelitis, the baseline electrophysiological examination showed a prolonged central motor conduction time,

which returned to normal in one patient, whereas it improved but remained pathological in the other patient at follow-up. The neurorehabilitation led to a substantial functional improvement in both subjects.

Discussion and Conclusions: This is the first study to describe clinical and electrophysiological aspects along with medium-term outcome in patients with COVID-19-related neurological manifestations who underwent an intensive rehabilitation program. The functional outcome following neurorehabilitation in patients with PINS related to SARS-CoV-2 infection is variable. In our small case series, subjects with polyradiculoneuropathy had a poorer recovery compared to patients with myelitis. The clinical course largely paralleled the follow-up electrophysiological findings.

Keywords: Guillain-Barrè syndrome, acute inflammatory demyelinating polyradiculoneuropathy, acute motor sensory axonal neuropathy, myelitis, neurological rehabilitation, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is rapidly and dramatically spreading worldwide causing increasing numbers of hospitalization, intensive care admissions, and deaths (1, 2). Since the WHO declaration of pandemic on March 11, 2020, the situation is rapidly evolving, and to date, more than 6 million cases of COVID-19 have been registered globally, with severe consequences in terms of risk healthcare and collapse of economic systems (3).

Though respiratory distress and cardiovascular symptoms are the main players of the clinical picture of COVID-19, several symptoms of both central and peripheral nervous system (CNS and PNS) involvement have been related to SARS-CoV-2 infection so far (4–8).

Although a direct neurotropism and the ability of the virus to trigger an autoimmune response have been suggested (9), to date, the exact mechanisms by which SARS-CoV-2 may affect CNS and PNS still remain unclear.

The most common neurological symptoms reported in association with SARS-CoV-2 infection are dizziness, headache, ageusia, and loss of smell, while major neurological syndromes include acute cerebrovascular disease, polyradiculoneuritis [e.g., Guillain–Barré syndrome (GBS)], myelitis, acute encephalitis, meningoencephalitis, and encephalomyelitis (10–15).

Para-infectious or post-infectious neurological syndromes (PINS) associated with COVID-19 occurring shortly after the onset of respiratory symptoms are also emerging in the literature. GBS is an acute form of inflammatory polyradiculoneuropathy that often occurs after an infection or vaccination as a result of an autoimmune response triggering. GBS commonly manifests as acute ascending muscle weakness associated with sensory loss and absent or reduced deep tendon reflexes. GBS is a heterogeneous condition with several variants including forms characterized by a primary axonal injury, such as acute motor and sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN), which can leave mid- to long-term sequelae (16, 17).

Acute myelitis is also known as a neurological complication of viral infections, which may be due to direct viral invasion or autoimmune response triggering. Little is known about the causal relationship existing between SARS-CoV-2 infection and acute myelitis, though several cases of myelitis have been reported in association with COVID-19 to date (13, 18, 19).

Neurophysiological investigations represent a fundamental tool in the early diagnosis and follow-up evaluations of both peripheral nervous system and spinal cord diseases.

Non-pharmacological strategies such as neurorehabilitative intervention could ameliorate the neurological impairment of COVID-19 patients with neurological complications. It is likely that physical therapy, when initiated in the early phases of the disease and continued in the subacute and outpatient settings, could improve the clinical outcome and quality of life of these individuals, minimizing the neurological burden and providing a better prognosis (20, 21). However, limited evidence is available on the benefit of physical therapy in the early phases of the disease, and the therapeutic effectiveness of an intensive and prolonged interdisciplinary neurorehabilitation program in patients with SARS-CoV-2-related PINS still has to be demonstrated (22, 23).

In this paper, we report a case series of five patients who developed PINS following COVID-19 infection and underwent an intensive and personalized multidisciplinary rehabilitation program. Clinical and electrophysiological findings at baseline and at 3- and 6-month follow-ups are thoroughly described.

MATERIALS AND METHODS

This is an observational study of five patients with PINS following COVID-19 who were hospitalized at the IRCCS Mondino Foundation Hospital, Pavia (Italy), in March 2020 during the first COVID-19 outbreak in Northern Italy. During the same time frame (March 2020), a total of 107 patients with other neurological conditions were admitted to the Emergency Neurology Unit and other neurological departments of our hospital. Among them, no other patients with myelitis were observed, and just another patient with GBS not associated with SARS-CoV-2 infection was hospitalized. All diagnostic

investigations and treatments were carried out according to clinical needs and independently by the research aims.

In all subjects, COVID-19 infection was confirmed by means of a nasopharyngeal swab, followed by detection of serum IgG antibodies against SARS-CoV-2. No patient had previous history of central or peripheral neurological disease, cranial or spinal surgery, or traumatic head or spinal injury.

Cerebrospinal fluid (CSF) was collected and processed for standard analyses including white blood cell count, level of proteins and glucose, and real-time quantitative PCR (RT-qPCR) for SARS-CoV-2. Chest radiography and, in some patients, MRI scans were also performed at baseline.

After completing the diagnostic assessment and acute neurological treatments in the intensive care unit (ICU), subjects were admitted to the neurorehabilitation unit once they tested negative at nasopharyngeal swab SARS-CoV-2 RT-qPCR testing and were started on a personalized multidisciplinary rehabilitation program (RP). The RP consisted of six individual sessions per week, each lasting 90 min. The RP intervention involved a program of functional exercise with increasing intensity and duration of activity or exercise, dynamically adapted to progressive clinical improvement. More specifically, the program included different exercise modalities, ranging from passive mobilization, neurosensory stimulation, isokinetic muscle strengthening, active mobilization, endurance training, postural control, balance, transfers, and gait training. Subjects gave their written informed consent to all study procedures.

After completing the RP, all patients were discharged at home and returned for a clinical and laboratory follow-up at 3 and 6 months after the onset of neurological symptoms.

All patients underwent an in-depth clinical evaluation by means of the Medical Research Council's scale (MRC scale) for evaluation of muscle strength, Functional Independence Measure (FIM) scale, Barthel index, Tinetti and Hauser scale at baseline and at the follow-up visits. An extensive neurophysiological investigation was also carried out at baseline and at 3- and 6-month follow-ups, with the exception of patient #3 who performed the electrophysiological reevaluation only at 3-month after onset of the neurological symptoms.

The electrophysiological assessment included nerve conduction and electromyography (EMG) studies along with motor evoked potential (MEP) assessment. All investigations were performed by means of a five-channel electromyograph (Synergy, Medelec, UK). The following motor nerve conduction parameters of the four limbs were assessed: distal latency, amplitude of the compound muscle action potential, and conduction velocity of the common peroneal, tibial, and ulnar nerves, as well as F wave latency of the tibial and ulnar nerves. Antidromic sensory nerve conduction parameters of the limbs comprised amplitude of the sensory nerve action potential and conduction velocity of the sural and ulnar nerves. EMG of the tibialis anterior, gastrocnemius medialis, vastus lateralis, first dorsal interosseous, and deltoid muscles was performed bilaterally using concentric needle electrodes. The following EMG parameters were assessed: the presence of spontaneous activity (i.e., fibrillation potentials, positive sharp waves, and complex repetitive discharges), motor unit action potential (MUAP) analysis (i.e., duration and amplitude), and spatial recruitment of MUAPs (i.e., normal, reduced, or early interference pattern). MEPs were obtained by means of a single-pulse monophasic electromagnetic stimulator (STM9000, Ates Medica Device, EB Neuro, Italy) capable of generating a maximal output of 2.4 Tesla. Cortical and spinal hot spots for the abductor hallucis and abductor digiti minimi muscles were stimulated using a 90-mm circular coil (inner diameter of 5 cm). Magnetic pulse intensity, expressed as the percentage of the maximal stimulator output, was set up to obtain the MEP with suprathreshold amplitude size. The following MEP parameters were assessed: cortical and peripheral MEP amplitude, cortical and peripheral motor conduction time, and central motor conduction time (CMCT), defined as the difference between the cortical and peripheral motor conduction time.

The study was approved by the local ethics committee (IRCCS San Matteo Polyclinic in Pavia). Written informed consent was obtained from all subjects involved in the study.

RESULTS

Baseline Evaluations

Demographic, clinical, laboratory, and instrumental findings of the patients enrolled both at baseline and at follow-up examinations are summarized in **Tables 1**, **2**. The main rehabilitation outcomes are reported in **Table 3**.

All subjects were admitted to the neurorehabilitation unit with mild motor signs in the lower limbs and variable sensory involvement (**Tables 1**, **2**, **4**). The baseline electrophysiological study was consistent with a diagnosis of GBS in patients #1, #2, and #3. In particular, according to Uncini's criteria (24), nerve conduction findings were compatible with an acute inflammatory demyelinating polyradiculoneuropathy (AIDP) variant in patients #1 and #2 and with an AMSAN in patient #3. Nerve conduction investigation disclosed signs of a severe and widespread axonal damage in all three subjects. Accordingly, EMG showed very rich spontaneous activity (fibrillation potentials and positive sharp waves) and severely reduced spatial recruitment of MUAPs bilaterally in the tibialis anterior, gastrocnemius medialis, and first dorsal interosseous muscles of all three patients. The spatial recruitment of MUAPs was reduced, albeit to a lesser extent, in the vastus lateralis and deltoid muscles on both sides, while MUAP parameters were within normal limits in all muscles.

Two of the three patients underwent a lumbosacral MRI scan with contrast that showed no signs of myelitis nor thickening or contrast enhancement of the nerve roots. No patient presented a positive RT-qPCR for SARS-CoV-2 on CSF samples. At symptom's onset, chest radiographies were negative for pneumonia in all patients. They were all treated with intravenous immunoglobulin (IVIG) (0.4 g/day for at least 5 days), but patients #1 and #3 presented severe worsening of the motor and sensory deficit within the first days of treatment. Patient #1 required ventilatory support and a tracheostomy due to acute respiratory failure in the context of a severe tetraparesis with axial muscle involvement and *Acinetobacter baumannii* concomitant infection. This patient required a total stay of 56

TABLE 1 | Demographic, and main clinical and laboratory/instrumental findings of the subjects enrolled in this case series.

Patient	#1	#2	#3	#4	#5
Age, years	61	72	57	69	25
Sex	M	F	M	M	F
Diagnosis	Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Acute motor sensory axonal neuropathy (AMSAN)	Myelitis	Myelitis
Early symptoms of COVID-19	Cough, hyposmia and dysgeusia	Fever (up to 39°C), cough, ageusia	Fever (up to 39°C), cough and dysgeusia	Fever and asthenia	Fever (up to 38°C), anosmia and dysgeusia
Need for mechanical ventilation	Yes	No	No	No	No
COVID-19 treatment	None	Antibiotics, LMWH and hydroxychloroquine	None	Antibiotics, lopinavir/ritonavir, LMWH and hydroxychloroquine	LMWH
Latency of neurological symptoms, days	21	8	12	3	15
CSF findings	Normal, SARS-CoV-2 RT-qPCR negative	1st exam: normal, SARS-CoV-2 RT-qPCR negative 2nd exam: albumin-cytological dissociation	Normal, SARS-CoV-2 RT-qPCR negative	Marked pleocytosis with neutrophil prevalence, hyperproteinorrachia and oligoclonal bands, SARS-CoV-2 RT-qPCR negative	Normal (polyclonal distribution of immunoglobulins), SARS-CoV-2 RT-qPCR negative
Brain MRI findings	Not performed	Chronic cerebrovascular disease	Not performed	Normal	Normal
Spinal cord MRI findings	–	No signs of myelitis nor thickening or contrast enhancement of nerve roots	No signs of myelitis nor thickening or contrast enhancement of nerve roots	Multiple small T2-hyperintense cervical and thoracic lesions, mostly affecting the lateral and posterior columns	T2-hyperintensity at the thoracic spinal cord level mainly affecting the T3 and T8-T10 myelomeres
Neurological symptoms at baseline	Impaired walking and sensory loss at the lower limbs which rapidly evolved to tetraparesis with acute respiratory failure	Walking impairment and diffuse paresthesia, gradually evolving in a tetraparesis with sensory deficit in the four limbs	Progressive sensory-motor deficit in the four limbs (sensory symptoms prevalent on motor impairment)	Acute urinary retention, rapidly followed by complete motor and sensory impairment in the lower limbs	Hyposthenia in both legs, paresthesia and numbness with upper level at the breast line and sensation of incomplete bladder emptying
Acute Treatments of the neurological syndrome	IVIG, 1 cycle of 3 days (0.4 g/die)	IVIG, 2 cycles of 5 days each (0.4 g/die) within the first month	IVIG, 1 cycle of 5 days (0.4 g/die)	IVIG, 1 cycle of 5 days (0.4 g/die)	2 cycles of IV methylprednisolone 1 g/day (each of 7 days) with a 3-month interval
Chronic treatments of the neurological syndrome	None	Plasma exchange cycles, 6 times over 14 days	None	None	Low dose of oral prednisone with a tapering scheme over 2 months
Duration of rehabilitation treatment including physiotherapy and occupational therapy, days	120	179	36	128	72
Clinical outcome	Autonomy recovery; persistence of mild distal weakness at lower limbs	Autonomy in self transferring, ability to walk with aids and bilateral support	Autonomy recovery; walking with right ankle-foot orthosis	Autonomy recovery; normal walking but with early fatigue	Autonomy recovery; persistence of distal weakness at lower limbs and gait ataxia

IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin.

TABLE 2 | Detailed clinical features of patients at baseline and at 3- and 6-month follow-ups.

Patient	Baseline				3-month follow-up				6-month follow-up			
	Deep tendon reflexes	**Sensory symptoms and signs**	**MRC scale Upper limbs: R/L**	**MRC scale Lower limbs: R/L**	**Deep tendon reflexes**	**Sensory symptoms and signs**	**MRC scale Upper limbs: R/L**	**MRC scale Lower limbs: R/L**	**Deep tendon reflexes**	**Sensory symptoms and signs**	**MRC scale Upper limbs: R/L**	**MRC scale Lower limbs: R/L**
#1	Absent in the lower and upper limbs, normal plantar reflex response bilaterally	Severe hypoesthesia in the lower limbs till the superior anterior iliac spine	39/35	19/21	Hyporeflexia only in the lower limbs, normal plantar reflex response bilaterally	Moderate hypoesthesia at the lower limbs	24/24	9/9	Areflexia of the Achilles reflexes; DPR normalized in the other districts; normal plantar reflex response bilaterally	Mild hypoesthesia in the lower limbs, till the ankle	42/41	18/18
#2	Hyporeflexia in the upper limbs, areflexia in the lower limbs, silent plantar reflex response bilaterally	Distal hypoesthesia and paresthesia in the four limbs	21/23	6/8	Hyporeflexia in the upper limbs, areflexia in the lower limbs, silent plantar reflex response bilaterally	Slight improvement of the distal hypoesthesia and paresthesia in the four limbs	22/24	6/9	Hyporeflexia in the lower limbs, abnormal plantar reflex response bilaterally	Mild distal paraesthesia in the lower limbs	28/29	13/14
#3	Hyporeflexia of the patellar reflexes, areflexia of the Achilles tendon reflexes, silent plantar reflex response bilaterally	Distal hypoesthesia in the four limbs more prominent in the right lower limb below the knee; distal apallesthesia in the lower limbs	41/41	12/25	Areflexia of the Achilles reflexes, silent plantar reflex response bilaterally	Mild recovery of the hypoesthesia now confined to the right lower limb above the knee and at the left foot; no variation in the distal apallesthesia in the lower limbs	42/38	17/19	NA	NA	NA	NA
#4	Hyporeflexia in the upper limbs, areflexia in the lower limbs, bilateral Babinski sign	Severe hypoesthesia and hypopallesthesia in the lower limbs	40/40	9/6	Hyperreflexia in the lower limbs, bilateral Babinski sign	Mild hypoesthesia in the lower limbs	40/40	21/20	Mild hyperreflexia at lower limbs, bilateral Babinski sign	Normal	40/40	24/24
#5	Hyperreflexia of the patellar and Achilles tendon reflexes, bilateral Babinski sign	Severe hypoesthesia and hypopallesthesia in the lower part of the body with upper level at T4-T5	40/40	16/16	Hyperreflexia of the patellar and Achilles reflexes with ankle clonus; bilateral Babinski sign	Moderate improvement of the hypoesthesia, upper level at T4-T5	40/40	19/20	Hyperreflexia of the patellar and Achilles reflexes with ankle clonus; bilateral Babinski sign	Mild hypoesthesia with upper level T4-T5	40/40	24/24

DPR, Deep Tendon Reflexes; MRC, Medical Research Council Scale for muscle strength assessment. Muscle effort evaluated in the upper limbs (sum score ranging between 0 and 40 for each body side) included: deltoid, biceps brachii, triceps brachii, wrist extension, wrist flexion, finger extension, finger flexion, first dorsal interosseous muscles. Muscle effort evaluated in the lower limbs (sum score ranging between 0 and 25 for each body side) included: iliopsoas, quadriceps femoralis, gastrocnemius, tibialis anterior, extensor hallucis longus mucles.

TABLE 3 | Functional status of the subjects at baseline and follow-ups.

Patient	Barthel index			FIM			Hauser			Tinetti		
	Baseline	3-m FU	6-m FU	Baseline	3-m FU	6-m FU	Baseline	3-m FU	6-m FU	Baseline	3-m FU	6-m FU
#1	0	50	95	10	56	115	9	7	2	0	12	26
#2	30	30	35	44	47	76	9	9	7	0	1	11
#3	60	80	NA	85	115	NA	9	3	NA	6	23	NA
#4	35	70	90	69	105	121	9	3	2	0	18	28
#5	65	90	100	95	108	110	5	5	2	15	17	26

Barthel, Barthel index for activities of daily living (0–100); FIM, Functional Independence Measure index (0–126); Hauser, Hauser ambulatory index (0–9); Tinetti, Tinetti assessment tool, balance plus gait score (0–28); 3-m FU, follow-up at 3 months; 6-m FU, follow-up at 6 months.

days in the ICU and started an intensive rehabilitation program only 2 months after the onset of symptoms.

Patient #3 presented severe worsening of the respiratory muscular performance as well: at first, the possibility of a plasma exchange was evaluated, but in order to avoid a possible worsening of the COVID-19 infection, we chose to perform a second IVIG cycle. The procedure halted clinical deterioration, and the patient was therefore transferred to the neurorehabilitation unit.

Patients #4 and #5 presented with progressive sensory and motor deficits in the lower limbs associated with bladder dysfunction with urinary retention (**Tables 1**, **2**). As mentioned above, no sign of SARS-CoV-2 replication was observed in the CSF, while both patients presented altered MRI signals proving an inflammatory spinal cord involvement. Findings from electroneurography (ENG) and EMG assessment of the four limbs were within normal ranges. Both subjects tested negative for antibodies against AQP4, MOG, GQ1b, or GD1b. MEP investigation in patient #4 revealed an impaired corticospinal conduction deriving from the lower limbs, with asymmetric involvement (predominant on the left side); MEP findings in patient #5 were consistent with a diffuse impairment of the corticospinal tract, predominant when deriving from the right limbs (**Table 5**). After a diagnosis of myelitis was made, adequate treatment with a high dose of IV methylprednisolone (7 g in total) was performed.

Follow-Up Evaluations

At the electrophysiological follow-up, patient #1 presented with improvement of the nerve conduction parameters, especially in the upper limbs with exception for common peroneal nerves. In parallel, EMG showed disappearance of spontaneous activity, enhancement of MUAP recruitment, and neurogenic MUAPs (increased amplitude and duration) as an expression of reinnervation phenomena. From a clinical point of view, the patient globally improved except for mild hypoesthesia persisting in the lower limbs. Independence in walking and in daily living activities was fully recovered within 6 months.

Conversely, nerve conduction findings did not significantly improve in patient #2, with exception of the upper limbs' parameters, and in patient #3. In these subjects, EMG findings confirmed the remarkable axonal impairment, with persistent spontaneous activity in the same muscle districts previously examined (which was enriched by frequent complex repetitive discharges) that also involved the vastus lateralis muscle bilaterally. In both patients #2 and #3, MUAP recruitment did not significantly improve and MUAPs presented with neurogenic features in proximal and distal muscle districts of the four limbs. Nerve conduction findings at baseline and follow-up of all patients are listed in **Table 4**.

Taking into account these findings, since patient #2 presented with no significant lower limb motor improvement at 3-month follow-up, her case was further reevaluated. Also considering the presence of persisting active denervation in both lower limbs, she was therefore treated with six cycles of therapeutic plasma exchange over a 14-day period, with clear benefit. At 6-month follow-up, the patient has recovered short-distance walking ability (12 m) with the support of walking aids.

The clinical course of patient #3 was complicated by the occurrence of a deep venous thrombosis affecting the left leg about 2 months after the onset of neurological symptoms. This determined a reduced mobility of the left lower limb as shown by reduced MRC subscore of the left lower limb at 3-month follow-up (**Table 2**). The patient did not return to the 6-month follow-up, and no further information were available.

Patients #4 and #5 presented with global functional and electrophysiological improvement (**Tables 2**, **3**, **5**). From a clinical point of view, both patients reacquired full independence in daily living activities within 6 months, with persistence of minor gait abnormalities that did not require any aids. However, it is noteworthy that patient #5 presented with transient worsening of the motor deficit, leading to increased disability during the first trimester, as soon as the corticosteroid therapy was tapered. In agreement with clinical findings, signs of active progression of the disease were observed at a whole-spine MRI (increased number of lesions in both cervical and dorsal spinal cord, with tendency to confluence, without areas of pathological spinal enhancement). A second cycle of high-dose IV methylprednisolone was performed, which rapidly led to global clinical improvement. MEP findings of both patients with myelitis improved at the follow-up assessment, although in patient #5, abnormalities were still found (**Table 5**).

TABLE 4 | Nerve conduction findings in subjects with polyradiculoneuropathy.

Nerves	ENG parameters	Patient #1			Patient #2			Patient #3		Normal values
		Baseline	3-month follow-up	6-month follow-up	Baseline	3-month follow-up	6-month follow-up	Baseline	3-month follow-up	
Common peroneal										
Ankle – EDB	DL, ms	R = 12.7; L = 11.8	–	–	–	–	–	R = –; L = 4.0	R = –; L = 4.6	≤6.5
	Amp, mV	R = 0.6; L = 0.7	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = 0.1	R = Abs; L = 0.1	≥2
Below fibula – Ankle	Amp, mV	R = 0.1; L = 0.1	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = 0.1	R = Abs; L = 0.1	≥2
	CV, m/s	R = 19.2; L = 20.3	–	–	–	–	–	R = –; L = 36.7	R = –; L = 34.9	≥44
Tibial										
Ankle – AH	DL, ms	R = 20.7; L = 17.6	R = 13.1; L = 9.4	R = 6.7; L = 6.2	R = 6.4; L = 4.8	R = 7.2; L = 4.7	R = 7.5; L = 4.6	–	–	≤5.8
	Amp, mV	R = 0.3; L = 0.6	R = 0.5; L = 0.7	R = 0.6; L = 0.8	R = 0.4; L = 0.8	R = 0.3; L = 0.4	R = 0.1; L = 0.1	R = Abs; L = Abs	R = Abs; L = Abs	≥4
	F latency, ms	R = Abs; L = Abs	R = 95.8; L = 84.6	R = 95.2; L = 84.0	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	R = Abs; L = Abs	≤52
Popliteal fossa – Ankle	Amp, mV	R = 0.1; L = 0.1	R = 0.4; L = 0.6	R = 0.4; L = 0.8	R = 0.4; L = 0.8	R = 0.3; L = 0.4	R = 0.1; L = 0.1	R = Abs; L = Abs	R = Abs; L = Abs	≥4
	CV, m/s	R = 16.9; L = 17.5	R = 27.5; L = 28.3	R = 29.6; L = 30.4	R = 39.1; L = 39.3	R = 37.8; L = 37.2	R = 35.0; L = 36.7	–	–	≥41
Ulnar (motor)										
Wrist – ADM	DL, ms	R = 8.8; L = 8.7	R = 5.3; L = 5.1	R = 3.5; L = 4.0	R = 4.2; L = 3.6	R = 4.4; L = 3.8	R = 4.5; L = 3.9	R = 2.2; L = 2.5	R = 3.2; L = 2.7	≤3.3
	Amp, mV	R = 0.8; L = 0.6	R = 8.6; L = 6.3	R = 9.7; L = 7.4	R = 1.5; L = 1.6	R = 1.6; L = 1.7	R = 1.8; L = 2.9	R = 8.5; L = 8.9	R = 7.0; L = 8.1	≥6
	F latency, ms	R = 57.2; L = 59.4	R = 40.3; L = 39.4	R = 39.0; L = 37.0	R = Abs; L = Abs	R = 41.8; L = 38.4	R = 40.2; L = 36.7	R = 30.8; L = 30.5	R = 31.9; L = 34.2	≤30
Below elbow – Wrist	Amp, mV	R = 0.8; L = 0.6	R = 8.5; L = 6.2	R = 7.1; L = 7.3	R = 0.7; L = 0.8	R = 1.5; L = 1.6	R = 1.5; L = 2.4	R = 7.0; L = 6.7	R = 5.1; L = 5.5	≥6
	CV, m/s	R = 25.1; L = 24.2	R = 37.5; L = 39.4	R = 42.6; L = 41.9	R = 34.0; L = 35.8	R = 35.1; L = 36.7	R = 35.4; L = 38.8	R = 54.4; L = 59.2	R = 56.0; L = 50.0	≥49
Sural										
Calf – Posterior ankle	Amp, μV	R = 1.5; L = 0.6	R = 1.7; L = 1.3	R = 1.9; L = 1.4	R = 4.4; L = 0.6	R = 1.4; L = 0.4	R = 0.3; L = 0.2	R = Abs; L = Abs	R = Abs; L = Abs	≥6
	CV, m/s	R = 27.4; L = 24.2	R = 30.5; L = 30.2	R = 31.2; L = 31.6	R = 35.7; L = 32.8	R = 36.4; L = 36.0	R = 29.0; L = 35.1	–	–	≥40
Ulnar (sensory)										
Wrist – Digit 5	Amp, μV	R = 4.6; L = 5.8	R = 7.4; L = 7.9	R = 9.8; L = 11.3	R = 1.0; L = 4.2	R = 3.9; L = 4.8	R = 6.7; L = 9.3	R = 6.9; L = 1.6	R = 2.7; L = 0.9	≥10
	CV, m/s	R = 32.9; L = 33.2	R = 33.3; L = 34.4	R = 34.2; L = 34.6	R = 31.9; L = 22.9	R = 32.7; L = 28.0	R = 33.8; L = 34.8	R = 52.2; L = 46.2	R = 41.0; L = 41.9	≥50

ADM, abductor digiti minimi muscle; AH, abductor hallucis muscle; Amp, amplitude; CV, conduction velocity; DL, distal latency; EDB, extensor digitorum brevis muscle; ENG, electroneurography; L, left; R, right. Normative values were defined by examining a group of 30 healthy subjects.

TABLE 5 | Motor evoked potentials findings in subjects with myelitis.

Muscles	MEP parameters	Patient #4			Patient #5			Normal values
		Baseline	3 month follow-up	6 month follow-up	Baseline	3-month follow-up	6-month follow-up	
AH	Cortical Amp, mV	R = 0.4; L = Abs	R = 2.1; L = 1.9	R = 3.4; L = 3.3	R = 0.1; L = 0.2	R = 0.7; L = 0.8	R = 1.0; L = 1.0	≥3.0
	Peripheral Amp, mV	R = 6.4; L = 6.1	R = 5.7; L = 5.9	R = 5.4; L = 5.7	R = 5.2; L = 6.4	R = 6.0; L = 6.8	R = 6.2; L = 7.5	≥4.0
	CMCT, ms	R = 16.9; L = –	R = 15.3; L = 17.3	R = 14.6; L = 16.4	R = 31.7; L = 24.3	R = 27.8; L = 23.1	R = 24.9; L = 17.3	≤16.7
	PMCT, ms	R = 24.3; L = 23.4	R = 23.5; L = 22.9	R = 22.7; L = 22.5	R = 23.9; L = 23.0	R = 24.1; L = 22.9	R = 24.2; L = 22.6	≤29.5
ADM	Cortical Amp, mV	R = 4.4; L = 4.2	R = 4.3; L = 4.3	R = 4.3; L = 4.2	R = 3.1; L = 3.7	R = 4.4; L = 4.7	R = 4.8; L = 5.4	≥4.0
	Peripheral Amp, mV	R = 6.2; L = 6.3	R = 5.9; L = 5.9	R = 5.9; L = 5.8	R = 7.1; L = 8.3	R = 7.3; L = 8.2	R = 7.4; L = 8.8	≥5.0
	CMCT, ms	R = 6.0; L = 5.7	R = 5.3; L = 4.9	R = 4.8; L = 4.5	R = 12.8; L = 11.0	R = 10.6; L = 8.6	R = 8.6; L = 7.4	≤6.7
	PMCT, ms	R = 14.7; L = 14.6	R = 14.4; L = 14.0	R = 14.1; L = 13.6	R = 14.0; L = 14.2	R = 13.6; L = 14.4	R = 13.4; L = 14.6	≤16.5

ADM, abductor digiti minimi muscle; AH, abductor hallucis muscle; Amp, amplitude; CMCT, central motor conduction time; MEP, motor evoked potentials; PMCT, peripheral motor conduction time. Normative values were defined by examining a group of 30 healthy subjects.

DISCUSSION

In this paper, we describe clinical and electrophysiological features of five patients with PINS associated with COVID-19 who underwent an intensive personalized rehabilitation program and were followed up for a 6-month period.

GBS cases associated with SARS-CoV-2 infection have been described so far (13, 14). GBS is an autoimmune syndrome characterized by inflammatory axonal and/or demyelinating neuropathy. It may lead to severe sequelae, disability, or even death when a severe neuromuscular respiratory failure occurs. Depending on the GBS subtype (e.g., axonal vs. demyelinating damage), the outcomes are largely variable, ranging from poor recovery to remarkable improvement (11). When GBS is associated with SARS-CoV-2 infection, the recovery may be complicated by an overlap with severe respiratory symptoms, leading to a worse prognosis. Indeed, patients #1 and #3 presented in the early stages severe worsening of the respiratory performance, requiring urgent ventilatory support; in patient #1, tracheostomy was indeed required and the pulmonary function was further impaired by a severe bacterial lung infection. In this regard, it should be noted that none of the patients showed signs of COVID-19-related pneumonia at chest X-ray, though it is likely that some degree of pulmonary damage might have been detected by a CT scan of the chest, but such an investigation was not performed.

Similarly to other acute neurological conditions, even patients with GBS and myelitis related to COVID-19 may benefit from a neurorehabilitation intervention begun in the early phases after onset of neurological symptoms in terms of fostering recovery and determining a better prognosis.

In this study, all subjects underwent an intensive rehabilitation program, personalized according to their level of disability and progressively incremented after improvement in their performances was observed.

At baseline, all patients with polyradiculoneuropathy presented signs of considerable axonal damage at the electrophysiological assessment that could probably explain the poorer prognosis with respect to the patients with myelitis. The two subjects with AIDP variant of GBS had a different clinical and electrophysiological outcome. In patient #1, both clinical measures and electrophysiological parameters improved at the 6-month follow-up, and the patient reacquired functional autonomy and was able to walk independently with only slight distal weakness persisting in the lower limbs. In patient #2, despite the prolonged rehabilitation intervention (179 days), relevant neurological deficits remained, although the patient reacquired the ability to walk short distances with aids and bilateral support. The electrophysiological assessment confirmed the presence of a remarkable axonal impairment even at the follow-up. Patient #3, affected by an AMSAN GBS variant, presented with a rapid clinical improvement in the first months in the absence of significant amelioration of ENG and EMG parameters at 3-month follow-up. This apparent discrepancy was likely linked also to the relatively short time period from the previous instrumental evaluation. Unfortunately, the clinical

status of the patient was further deteriorated by a deep venous thrombosis in the left leg, which led to reduced mobility.

Within our limited case series, we observed that two out of three GBS patients developed axonal forms of the disease, contrary to what was reported by Filosto et al. (25), who instead reported a higher prevalence of COVID-related demyelinating forms of GBS in a broader case series. However, data from the literature are still too preliminary to understand whether the clinical and prognostic profile of GBS or myelitis related to SARS-CoV-2 infection may present peculiar features.

The two subjects with myelitis showed global clinical improvement after the RP that was in line with the results of MEP assessment at the follow-up.

Major limitations of this study are represented by the small number of cases enrolled and by the clinical heterogeneity of the SARS-CoV-2 infection-related PINS, which involved either the PNS or the CNS. However, no other myelitis and just one patient with GBS not COVID-19-related among 107 patients was hospitalized at Mondino Foundation during the pandemic peak that hit Northern Italy in March 2020. We are also aware that the absence of a control group may have limited this study. However, in this context, the control condition (being no rehabilitation) is considered an unethical option for patients with functional limitations caused by PINS.

Notwithstanding, a novelty of this study is represented by the in-depth description of clinical and electrophysiological aspects of patients with rare neurological manifestations of COVID-19 who underwent an intensive rehabilitation program and were followed up for a relatively long time period of 6 months. Current literature on COVID-19 is mainly focused on clinical manifestations and complications of the SARS-CoV-2 infection in the acute phase, while evidence regarding long-term outcome is still lacking (22, 26, 27). To our knowledge, this is the first report to suggest the important role of neurological rehabilitation intervention in COVID-19 patients with neurological impairment.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the IRCCS San Matteo Polyclinic in Pavia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA, DM, and MT: drafting of manuscript. EA, CT, and GC: study conception and design. MA, DM, MT, IC, FV, and GM: acquisition of data. MA, DM, MT, and GC: analysis and interpretation of data. All authors critical revision.

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Telemedicine and Virtual Reality at Time of COVID-19 Pandemic: An Overview for Future Perspectives in Neurorehabilitation

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In catastrophic situations such as pandemics, patients' healthcare including admissions to hospitals and emergency services are challenged by the risk of infection and by limitations of healthcare resources. In such a setting, the use of telemedicine interventions has become extremely important. New technologies have proved helpful in pandemics as a solution to improve the quality of life in vulnerable patients such as persons with neurological diseases. Moreover, telemedicine interventions provide at-home solutions allowing clinicians to telemonitor and assess patients remotely, thus minimizing risk of infection. After a review of different studies using telemedicine in neurological patients, we propose a telemedicine process flow for healthcare of subjects with chronic neurological disease to respond to the new challenges for delivering quality healthcare during the transformation of public and private healthcare organizations around the world forced by COVID-19 pandemic contingency. This telemedicine process flow represents a replacement for in-person treatment and thereby the provision equitable access to the care of vulnerable people. It is conceptualized as comprehensive service including (1) teleassistance with patient counseling and medical treatment, (2) telemonitoring of patients' health conditions and any changes over time, as well as (3) telerehabilitation, i.e., interventions to assess and promote body functions, activities, and consecutively participation. The hereby proposed telemedicine process flow could be adopted on a large scale to improve the public health response during healthcare crises like the COVID-19 pandemic but could equally promote equitable health care independent of people's mobility or location with respect to the specialized health care center.

Keywords: telemedicine, healthcare, virtual reality, neurorehabilitation, COVID-19

INTRODUCTION

On 20 March 2020, the World Health Organization (WHO) declared the pandemic state due to the spread of SARS-CoV-2 (1). In December 2020, more than 72 million subjects had been diagnosed with COVID-19 over the world, and more than 1.5 million of them had died (2). Due to the lack of an effective medical treatment to fight against the SARS-CoV-2, the healthcare measures mainly focused on symptomatic treatment, social distancing, use of device for individual protection, and the mandatory quarantine after being in close contact with an infected person (2). In this setting, medical visits, non-urgent treatments, and non-urgent medical issues, particularly for vulnerable subjects such as persons with neurological disorders, were initially interrupted and then re-assumed but frequently with a reduced scope. These measures have inevitably created long waiting lists and delays on medical visits, thus ultimately affecting patients' quality of life. Nevertheless, some preliminary efforts for maintaining the standard of care in the field of neurorehabilitation have been proposed (3, 4). Notably, the pandemic has also posed ethical questions for the healthcare system and the clinicians themselves (5). For instance, doctors had to face the dilemma of who can be treated at the hospital or at home, or who can be admitted to the limited number of beds in the intensive care units (ICU). Ultimately, in some areas, the most difficult question became how to fairly distribute scarce life-supporting clinical resources with implications for COVID-19 survivals. People with a severe chronic neurological condition who depend on a caregiver for their needs and/or to carry out their daily life routine had to face a difficult situations during the pandemic (5). COVID-19 is particularly lethal for the elderly with pre-existing conditions such as neurodegenerative and neuropsychiatric disorders, as they are a vulnerable population needing continuous supervision (6–8).

In times of stressed healthcare resources, the public health guidelines endorse the priority of treatment to those who are at short-term risk of death (9, 10). Moreover, the argument exists that young people should have priority over elderly people, even though whether and how this rule should be implemented is still controversial (10, 11). It must be noted that only a minority of people testing positive for SARS-CoV-2 become severely ill (12). Most people affected by COVID-19 present with mild symptoms and recover over a few days or weeks. From a healthcare point of view, this situation demands new ways to monitor the clinical situation of a large number of subjects at home. In addition, COVID-19 persons may develop a post-intensive care syndrome, presenting motor, cognitive, and emotional disorders, requiring an intensive rehabilitation program and a long-term supervision (13, 14). In patients with neurological disorders, the chronic persistence of COVID-19 have led to re-organized neurorehabilitation services accordingly (15, 16). In this regard, the use of new telecommunication technologies integrating telemedicine systems represents an alternative solution to facilitate the exchange between the healthcare providers and the patients (17, 18). Recently, some investigations reported the effectiveness of telemedicine services in remotely assisting, monitoring, and treating COVID-19 subjects or other diseases (17, 19–27). Indeed, a well-organized network could have the potential to reduce case fatality or at least provide a better management and supervision of the clinical conditions of vulnerable patients, such as those with neurological disorders, during the COVID-19 pandemic (28).

In this perspective article, we propose a telemedicine process flow representing a viable alternative to respond to the new challenges for patient care forced by the transformation of public and private healthcare organizations due to the COVID-19 pandemic. This network will represent a replacement for in-person treatment, providing equitable access to care for vulnerable people, including subjects with chronic neurological disorders. Such a network, which can be time- and cost-saving in normal situations, may feature two important added values: (1) safety and (2) access to care for a wider number of subjects.

TELEMEDICINE AT THE TIME OF COVID-19

In the '70s, Thomas Bird introduced the term "telemedicine," meaning "healing at a distance," which implies the delivery of healthcare services by using telecommunication technologies (29–31). Specifically, telemedicine interventions aim to facilitate healthcare treatment, limiting or avoiding hospitalization (29). More recently, WHO described "telemedicine" or "e-Health" as the use of technology related to informatics and telecommunication, i.e., information and communication technologies (ICT), directed to provide a positive effect in the patient's health status (32). The main goals of telemedicine are to (1) improve the access to health care for rural areas, (2) give the physicians better access to tertiary consultation, (3) allow physicians to conduct remote examinations, (4) reduce health-care costs, (5) provide health-care services to a larger geographic region and or population, (6) reduce the need to transfer patients to the care centers, and (7) improve patient care (33).

During the COVID-19 pandemic, telemedicine represents an additional solution for healthcare services, allowing to deliver them directly at patient's home, reducing risks of possible infections, and enabling virtual triage to mitigate the negative psychological effects of social isolation (34). Then, with the current limitations in assisting patients at the hospital, the use of new telecommunication technologies by means of integrating telemedicine systems into the clinical routine may facilitate the maintenance of the remote relationship between healthcare providers and neurological patients (17, 35, 36). In this framework, the concept of "telemedicine" involves three treatment categories allowing to assist, monitor, and counseling patient remotely: (1) tele-assistance, (2) telemonitoring, and (3) telerehabilitation (37, 38). In the following section, we will discuss the three concepts embedded in the "telemedicine" overarching concept.

Tele-Assistance

The concept of tele-assistance refers to the use of new technologies for patients' counseling at a distance. There are different modalities for providing tele-assistance: video-conferencing, e-mail, on-line chat sessions, forums, telephone

calls, and mobile phone messages (39). A large number of studies have demonstrated the effectiveness of tele-assistance when dealing with patients with chronic disorders, such as cancer (40), diabetes (41), chronic respiratory failure (42), cystic fibrosis (43), brain injury (44), chronic pain (45), and stroke (46). For instance, a recent study demonstrated the effectiveness of tele-assistance at improving quality of life in people suffering from neuromuscular diseases (39). In this study, 24 participants with neuromuscular diseases were assisted through video-conferencing sessions in an on-line psychosocial program lasting 3 months. Participants reported benefits in some psychosocial variables as "getting along with people," "psychosocial domain," and "life activities" when compared to a control group (39). Others used a tele-assistance integrated care intervention to monitor patients with amyotrophic lateral sclerosis by using telephone calls, showing important time- and cost-saving benefits (47). One of the most useful features of tele-assistance is the possibility to support patients comprehensively from symptom onset to medical treatment delivery. For instance, a tele-assistance protocol—consisting in phone and video-conferencing connection between the ICU ambulance and the clinicians at the hospital—reduced the waiting time from symptom onset to treatment delivery in patients with stroke (48). This approach could be particularly useful at the time of the COVID-19, allowing the clinicians to assist and counsel patients at a distance, sending the clinical staff for the treatment delivery directly at their homes if and when necessary, thus avoiding the presence of the patients at the hospital.

Telemonitoring

The concept of telemonitoring is defined as the use of information provided by the technology to monitor the patient's health state at a distance (49, 50). Telemonitoring systems are promising approaches able to reduce clinical complications in chronic patients (49), as in case of neurological disorders. For instance, it has been effectively used in patients with neuromuscular diseases (51, 52) and multiple sclerosis (MS) (53). Telemonitoring systems consist in the biometric tracking and transmission to the clinicians of physiological and/or behavioral data of the patients (e.g., heart rate, breathing rate, gait pattern, motor functions, etc.) in synchronous or asynchronous videoconferencing (54). Telemonitoring has also been proposed to deliver new data necessary for differential diagnosis or to stage illnesses in a health telematic network (55). Recently, telemonitoring has been used in patients with confirmed or suspected COVID-19 remotely, allowing for the timely identification of worsening symptoms (56). This approach seems particularly useful for telemonitoring COVID-19 patients with other chronic or high-risk pathologies (e.g., multiple sclerosis, Parkinson's disease, and myasthenia gravis) as it would limit the number of hospitalizations, optimize healthcare resources, and reduce the risk of virus transmission.

Telerehabilitation

Telerehabilitation (TR) is a young telemedicine subfield consisting in the use of new telecommunication-based practices for controlling and conducting rehabilitation at a distance (57). TR can be used in all those situations in which the patient and the therapist cannot be in the same location. TR allows to begin the rehabilitation process as soon as possible after hospital discharge and increases the care access to individuals who are home-forced or geographically remote from their healthcare service (58–60). Hence, TR-based systems represent solid solutions to treat patients with an alternative way compared to the traditional face-to-face approach (58), providing benefits for the healthcare system and patients in terms of cost-effectiveness and feasibility for large-scale implementations. To this end, TR can use different types of technologies, such as sensor-based technology, tele/video-conference, specific *ad hoc* software, or virtual reality (61). Moreover, it has been shown that through telerehabilitation systems it is possible to foster patient motivation and participation in their own rehabilitation process (62), thus improving their well-being (63). TR may be useful for the treatment of motor, cognitive, or psychological deficits. Preliminary evidence indeed suggests its application in stroke, cerebral palsy, traumatic brain injury, multiple sclerosis (MS), and Parkinson's disease (PD), in particular as for treating motor- and speech-related impairments (54–58). TR has also been used for cognitive deficits (64) associated to neurological diseases, such as stroke, MS, brain tumors, Alzheimer's disease, and mild cognitive impairment (60–63, 65, 66).

In line with the necessary adaptation of healthcare services to the COVID-19, TR technological solutions are increasingly considered as potentially effective options for continuing the rehabilitation process at a distance (45, 67–70). Currently, many efforts are now focused on the treatment of subjects recovering from COVID-19 (71–74), but it seems extremely important to implement TR protocols also in non-COVID subjects in various settings of neurological care, in order to provide a continuity of care during this pandemic contingency and possibly in the future (75–78). During the COVD-19 pandemic, we have tested an innovative TR approach for the remote treatment of cognitive deficits in neurodegenerative diseases (79, 80) called HomeCoRe (Home Cognitive Rehabilitation) (81). HomeCoRe is a patient-tailored intervention stimulating many cognitive abilities, which is the home-based version of a previously tested computer-based cognitive training program (CoRe) (82–85), devised for the hospital setting. The system proved useful for providing continuity of care after hospital discharge in a condition of safety and distance and thus can be incorporated into clinical routine protocols.

TECHNOLOGICAL SOLUTIONS FOR TELEMEDICINE

Even though telemedicine interventions clearly have limitations compared to a hands-on approach in medicine (86, 87), the development of new technologies has also advantages over face-to-face health care, e.g., it allows the clinicians to follow the patients in a synchronous or asynchronous way. Synchronous telemedicine refers to the intervention performed in real time through a video call that can be

conducted through a smartphone or a webcam connected to the computer (88). Asynchronous telemedicine interventions refer to the "store-and-forward" technologies, which allow monitoring and collection of physiological and/or behavioral data through wearable or implantable devices connected to an online or virtual platform and then sending the information to a clinical center for review and consultation (88, 89). The most common technological solutions used to provide telemedicine interventions are smartphones, tablets, and wearable sensors (90), including digital applications for self-exercises or monitoring the behavioral or physiological state of the patients (91). However, in the last 20 years, some telemedicine interventions have integrated the use of virtual reality (VR) platforms to deliver personalized rehabilitation training or clinical interventions at a distance (92–94). In some instances, VR can provide full-immersed virtual environments where the patient can feel present (being there) inside the virtual environment (95, 96). In the proposed process flow, VR can be used as an advanced communication interface, in which the patient can interact with different sensory information coming from different modalities, while performing specific rehabilitation tasks within the VR environment. VR systems enable a more intuitive mode of interacting with information, for the clinicians and the patients (63, 92, 97–100).

One of the main advantages of VR is that, through the use of virtual avatars, it is possible to induce virtual body ownership illusions toward the virtual body (physical possession of the virtual body) (101). During the last years, some investigations attempted to use virtual body ownership illusion for rehabilitation purposes in chronic patients (102–111). Some investigations proposed the integration of virtual body ownership illusions within a VR training for telemedicine purposes (100, 112). However, to the best of our knowledge, a comprehensive integrated telemedicine platform that provides synchronous and asynchronous interventions by means of VR, virtual body ownership illusions, and wearable sensors for real-time telemonitoring has neither been created nor tested. In the next paragraph, we propose an integrated telemedicine system for assisting, monitoring, and treating subjects with chronic neurological diseases during this pandemic situation and beyond.

A NEW TELEMEDICINE NETWORK FOR NEUROREHABILITATION DURING COVID-19 PANDEMIC

Telemedicine services have the potential to provide medical service at a distance and in some instances even to save lives,

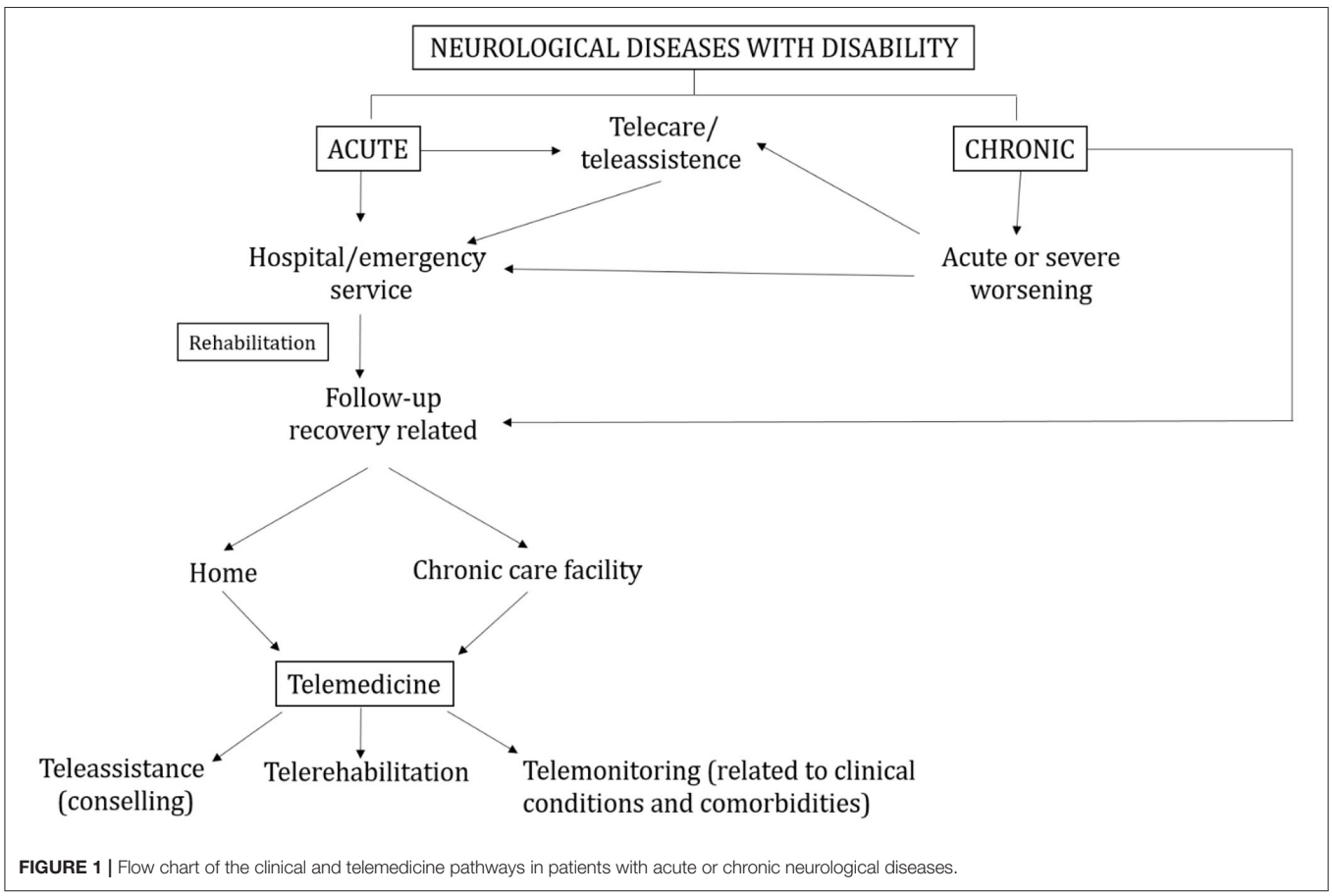


FIGURE 1 | Flow chart of the clinical and telemedicine pathways in patients with acute or chronic neurological diseases.

while allowing patients and clinicians to be in touch safely (113). For this reason, many public health systems worldwide have been seeking for qualified and certified digital medical services to provide a continuity of care at a distance (114). However, most of the countries were unprepared for managing patients with a modern digital approach (113, 115–117). To facilitate the process, at the beginning of 2020, the American Medical Association wrote a telehealth implementation playbook with the definitions of "telehealth" or "telemedicine" as follows: (1) real-time video-conferencing between the patients and the clinicians being in different locations; (2) image and data collection stored and forwarded for the later data interpretation; (3) remote patient's monitoring through the use of mobile health tools, wearable sensors, and devices; and (4) virtual checks through phone calls, messaging, or videoconferencing (118). It must be noted that the definition did not include motor or cognitive rehabilitation based on digital platforms during and beyond the COVID-19.

Based in the above-commented literature and after a review of different studies using telemedicine for remote monitoring and intervention in patients with neurological disorders, here, we propose a telemedicine process flow for remotely managing patients with neurological disorders by including the following components: (1) tele-assistance or patient counseling: weekly or monthly videoconferencing with a health care provider that is tailored for the patient disorder; (2) telerehabilitation: reminder and performance of physical, communicative, and/or cognitive rehabilitation assessment and training through the digital platform; (3) telemonitoring: remote monitoring of the behavioral or physiological responses through the wearable sensors connected to the digital platform; (4) interpretation of stored data by the clinicians; and (5) virtual follow-up: virtual checks between the patients and the healthcare provider for adjusting the healthcare routine based on data interpretation. All these components will create a closed-loop telemedicine process flow, where the clinicians are enabled to visit and monitor a large number of patients with a virtual face-to-face approach through videoconferencing, thus reducing the need of transportation (of people with mobility restrictions) and avoiding the risk of infection on both ends in case of particular emergencies (**Figure 1**). Moreover, the telemedicine process flow can facilitate the active involvement of both the patients themselves and their caregivers in the healthcare process, which is a crucial element when dealing with telemedicine solutions for managing vulnerable populations in need of continuous supervision. The proposed telemedicine process flow would also enable clinicians to detect early sign or symptoms of COVID-19. The telemedicine process flow should be based on easy-to-use and accessible technology such as smartphones or tablets, integrated with a VR platform to conduct the healthcare routine. The same devices could also be used for telemonitoring patients' physiological or behavioral responses. Even though the proposed telemedicine intervention would be very helpful for managing patients during the COVID-19 pandemic, this telemedicine process flow can be also applied in normal circumstances avoiding or reducing patients' need for transportation or hospitalization and allowing clinicians to follow their patients at a distance, where in-person evaluations can be also considered as a complement of the telemedicine intervention. This could implement patients' engagement and activation (119).

LIMITATIONS

Even though the proposed telemedicine intervention can be an optimal solution for monitoring and treating patients at a distance during a pandemic situation, the proposed telemedicine process flow still presents some limitations. A limitation is the availability of easy-to-use technology to deliver tele-consultations or for monitoring the patient's behavioral or physiological responses. Such limitations have been also suggested in earlier studies (36). Moreover, the performance of the training routine alone can represent some risk for the patients such as patient's falls or a bad performance of the exercises. Further, still, there is a lack of standardized tools to be used for virtual reality training and remote monitoring.

CONCLUSION

The COVID-19 pandemic has created new challenges to patient care, imposing adaptation of healthcare facilities. ICT can be extremely useful in this adaptation process and also to maintain people connected with the world (120). These adaptations should be extended to the delivery of care for neurological diseases. Here, we proposed a telemedicine process flow for healthcare of subjects with chronic neurological disease. In the future, this telemedicine process flow could be implemented and applied on a large scale not only to improve the public health capacity and to allow clinicians to deliver good quality care in case of particular emergencies such as COVID-19 but also to provide equitable health care for patients with mobility restrictions or living remotely from specialized health care centers. Even though the proposed telemedicine process flow could lead to an improvement of the public health management, some limitations should be considered.

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

GS, MM-G, and SB contributed to the conceptualization of the manuscript and bibliographic review. MM-G, SB, and RD contributed to the writing. GR and OR contributed to the bibliographic review and writing of the manuscript. LG contributed to the bibliographic suggestions and the revision of the manuscript. CT, GS, and TP contributed to the supervision of the manuscript. All authors approved the final version of the manuscript for submission.

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The Challenge of Reorganizing Rehabilitation Services at the Time of COVID-19 Pandemic: A New Digital and Artificial Intelligence Platform to Support Team Work in Planning and Delivering Safe and High Quality Care

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Introduction: The COVID-19 pandemic has posed great challenges in inpatient rehabilitation services, not only to implement the preventative measures to avoid the spreading of the virus in a highly interactive, multidisciplinary setting but also to create a rehabilitation pathway for post-COVID-19 patients. The aim of this retrospective study was to describe the role of a digital and artificial intelligence platform (DAIP) in facilitating the implementation of changes in a rehabilitation service during the COVID-19 pandemic.

Materials and Methods: We gathered qualitative and quantitative descriptors of the DAIP, including measures to assess its efficiency in scheduling therapy sessions, and staff satisfaction using two simple numeric rating scales and the System Usability Scale. We describe how the volume of activity and the quality of care of our rehabilitation service have changed when the DAIP was implemented by comparing the pre-COVID-19 and the pandemic periods for patients' [sex, age, co-morbidities, diagnosis, and Functional Independence Measure (FIM) gain] and service's (bed occupancy, patients' length of stay, and staff capacity) characteristics.

Results: Bed occupancy and the impact of rehabilitation on patients' outcome remained stable between the two periods. The DAIP provided a qualitative support for goal setting from remote; 95% of the planned sessions were delivered; the time for scheduling and registering sessions dropped by 50%. Staff satisfaction was about 70% for the easiness and 60% for the usefulness, and the mean "usability" score was close to the cut off for sufficient usability (mean score 65 where 68 is the cut off).

Conclusion: By applying the DAIP to rehabilitation treatment, it was shown that the management of rehabilitation can be efficiently performed even in the COVID-19 pandemic. Staff satisfaction reflected a good acceptance of the changes considering the turbulent changes and the stress burden occurring at the time of the pandemic.

Keywords: COVID-19, centers rehabilitation, goal-directed therapy, staffing and scheduling, artificial intelligence

INTRODUCTION

The global COVID-19 pandemic has determined a great pressure on medical resources worldwide and transformed the organization of health services particularly in countries where the virus spread has been more intense during the two waves of the outbreak. Understandingly, the priority of health care reorganization so far has been on acute care services rather than on the post-acute rehabilitation (1).

Rehabilitation services had to face the challenge of proving the usual care under the increased pressure from the acute sites and of developing dedicated rehabilitation pathways for COVID-19 survivors (2, 3). In fact, the rehabilitation pathway starts from the early acute care and continues in the post-acute and long- term phases based on the complexity of patients' needs and as an integral part of patient's management from hospital to the community setting. Inpatient rehabilitation services had to introduce dedicated pathways for COVID-19 survivors in the post-acute phase, remaining with the more severe physical, emotional, and cognitive sequelae of the viral infection. Although, initially, these pathways have been modeled on the principle of respiratory rehabilitation in COPD and post-ITU syndrome (4), evidences are growing supporting the efficacy of rehabilitation interventions more specifically tailored for post-COVID-19 patients (5–9).

Furthermore, in order to implement COVID-19-related safety measures and to copy with a potentially reduced staff capacity, rehabilitation services have considerably modified their activity, struggling to maintain the same level of service both in terms of the capacity and the quality of care delivered (2, 10). Specific protocols of treatment have been put in place for managing the risks related to the spread of the infection, such as the regulation of personal protective equipment (PPE), disinfection and sterilization protocols, and social distancing between staff members and between patients during therapy sessions, which had to be adapted to the very specific characteristics of rehabilitation settings.

First of all, rehabilitation services provide a multi-disciplinary treatment. This means that many different professionals (including doctors, therapists, nursing staff, and psychologists) interact with single patients and as a team on a daily basis. Group therapy (more patients supervised by one or more therapists) is also an integral part of rehabilitation protocols. The team model itself is based on a highly interactive and coordinated work with regular meetings to set patient-centered goals and discuss patients' progression, as by the definition of an individual rehabilitation program (IRP). Secondly, a direct and prolonged contact between patients and operators is expected, including hand-on or close-distance interventions to support patients in activities such as assisted exercises and ADLs (like dressing, toileting, and feeding) or mobility (like transfers or assisted walking). Furthermore, the use of facilities, equipment, and devices deserves attention in terms of social distancing and disinfection.

The Italian Society of Neurological Rehabilitation (SIRN) has made recommendations (2) to guide activities in rehabilitation units, including the suspension of all meeting activities, replaced by telephone or email and the delivery of rehabilitation activities in patients' rooms whenever possible or, in case of activities taking place in the gym, maintaining at least a 2-m distance between patients.

The change of patients' flow and characteristics together with the safety measures to be introduced in a very particular setting have all posed a particularly challenging reorganizational task for rehabilitation services.

Digitalization and artificial intelligence (AI) systems have shown some promising solutions not only to battle the virus (11) but also to face the organizational difficulties in delivering health care at the time of the outbreak, including systems to prevent the spread of COVID-19 (12), to generate knowledge about the efficacy of certain drug treatments (13), to process COVID-19 related images (14), or to manage the backlog of surgical waiting lists (15). However, there is no digital or AI-based application described in the literature to support rehabilitation services reorganization during the pandemic.

This paper describes how the adoption of a digitalization and artificial intelligence platform (DAIP) could facilitate the implementation of changes in a rehabilitation service during the COVID-19 pandemic while maintaining high-quality standard of care.

In particular, we describe how this DAIP (1) could support the communication between staff for sharing patients' assessment, goal setting, and action plan from remote, (2) could optimize the allocation of therapy sessions (when, where, and how many patients and therapists at the same time), and (3) could be accepted by the staff.

MATERIALS AND METHODS

Project Design

This is a retrospective observational study.

Setting and Inclusion Criteria

This project took place in the 67-bed ICS Maugeri Rehabilitation Unit in Genoa admitting patients discharged from local acute hospital units requiring multidisciplinary rehabilitation to people affected by neurological and musculoskeletal disorders or, more recently, to COVID-19 survivors remaining with physical, cognitive, and emotional difficulties. The rehabilitation team includes rehabilitation medicine physicians, nursing staff, psychologists (PSY), and therapists. The therapy disciplines range from physiotherapy (PT), occupational therapy (OT), speech and language therapy (SLT), and psychology. The treatment is delivered either in patients' rooms or in therapy-dedicated spaces including one main gym; a second small gym; and single rooms set up for OT, SLT, and PSY.

Data were gathered during two observation periods: May to November 2019 (pre-COVID-19) and May to November 2020 (during the COVID-19 pandemic following the DAIP implementation).

For these two periods, all patients admitted for rehabilitation to our service and the related team activities were included.

Data Availability

The data associated with the paper are not publicly available but can be obtained from the corresponding author on reasonable request.

Ethics

All data in this study were collected retrospectively and derived from data and outcome measures used in the routine clinical practice and service evaluation of our rehabilitation service. Patients admitted to ICS Maugeri gave their written consent to the management of their confidential data. The ICS Maugeri informed consent for the treatment of confidential data includes their use for research purposes and it is available to the public online (16).

Digital and Artificial Intelligence Platform

The DAIP, which was newly developed and introduced from May 2020, is made of two main software (Priamo and Q-Rehab), which represent the platform for the management of the two key sequential steps of the rehabilitation pathway from the definition of the IRP to its delivery, by scheduling and recording of therapy activities, as represented in **Figure 1**. The additional value of the DAIP during the COVID-19 pandemic was to support the communication between staff for sharing patients' assessment, goal setting, and action plan from remote (Priamo) and to optimize the allocation of therapy sessions (Q-Rehab) respecting COVID-19-related safety measures when establishing when, where, and how many patients and therapists at the same time.

Priamo was developed by a partnership between the Biomedical Computering System and ICS Maugeri, which started in September 2019. Staff training in our rehabilitation service included a half-day introduction course for all staff, three or four one-to-one 1-h training sessions to a couple of champions selected among doctors and therapists, and monthly drop-in sessions for the first 5 months. Training was arranged and delivered by a dedicated rehabilitation processes team by Maugeri and supported by peer-to-peer support by the champions.

This software is an interactive multidisciplinary platform, allowing patients' evaluation based on the bio-psycho-social model of the International Classification of Functioning framework (17) and the assignment of coherent goals (18–20) for therapy treatment that are established collaboratively by the team. This creates the structure of the IRP. The platform suggests goal areas based on the selection of patients' diagnosis (a list of the main musculoskeletal and neurological pathologies and post-COVID-19) and on the specific impairments and functional limitations that have been identified. Although the system encourages to go through pre-selected lists of functional limitations and matched goals, it allows the flexibility to set up a highly individualized program.

Following the first week of in-depth multidisciplinary assessment and goal negotiation with the patients, each therapist can suggest new goals or define them more in details sharing the same platform. Priamo also includes a weekly goal revision, in the form of an open space where the different members of the treatment team can update the progression or barriers on goals and suggest actions, which are then summarized by the supervising doctor. Priamo is thought to be a support tool for the weekly multidisciplinary meeting; however, during the pandemic, as regular team meetings had to stop, it was completed from remote.

The introduction of the post-COVID-19 rehabilitation meant generating a new dedicated pathway available on Priamo for these patients, based on the best scientific knowledge and expert consensus (3, 4, 21) available so far. Therapy treatment ranges from PT to improve exercise tolerance, endurance, balance, and respiratory function; OT to improve independence in ADL and access to equipment (22); SLT for improving swallowing (23); and psychology to address the psychological and cognitive needs (24–26) of these patients.

The second software (Q-Rehab) is an application based on artificial intelligence algorithms to process and schedule rehabilitation activities into a daily timetable. Q-Rehab was born in January 2019 from a collaboration between Surgi-Q, an EIT Health Headstart start-up, and ICS Maugeri, aiming to develop a novel approach to plan such a complex and multi-professional set of treatments as neurorehabilitation requires. Two therapist coordinators from our rehabilitation service have worked alongside with the software engineers for the development of the software and the provision of staff training. This included one introduction session for all staff, followed by one-to-one 1-h induction for all therapists.

Besides the AI module, the application currently includes a registration and authentication process integrated with ICS Maugeri's overall system, a local database for storing and retrieving the scheduling data, and a graphical user interface to easily visualize and modify patients' timetables and to insert the operator and patient data necessary to the scheduling process. The automated timetable can be manually modified by the therapist coordinator based on specific needs using the drag and drop function enabled in the graphical interface. The AI module uses a programming paradigm developed in the field of non-monotonic reasoning and logic programming. The algorithms operate on constraints and preferences, which have been identified by a joint work between the software engineers and the therapists of the team. The constraints take into account governance quality standards (i.e., a minimum time of daily therapy treatment, a fair number of patients assigned to a therapist based on his/her working hours, etc.) that are rehabilitation-specific as well as COVID-19-related safety recommendations. These included a maximum number of patients per space (i.e., to guarantee social distancing in the gym and avoid sharing of equipment) or patients to be treated in their own room (i.e., requiring isolation and to be treated with appropriate PPE). The algorithms allow taking into account some preferences, once the constraints are met, such as the preferred time by patients and the inclusion of as many supervised sessions as possible.

It is the role of three therapy coordinators to input and fill in the data into the system to create a daily dashboard available for staff and patients (**Figure 2**). Each treating therapist has to confirm if the planned activities have taken place; these are

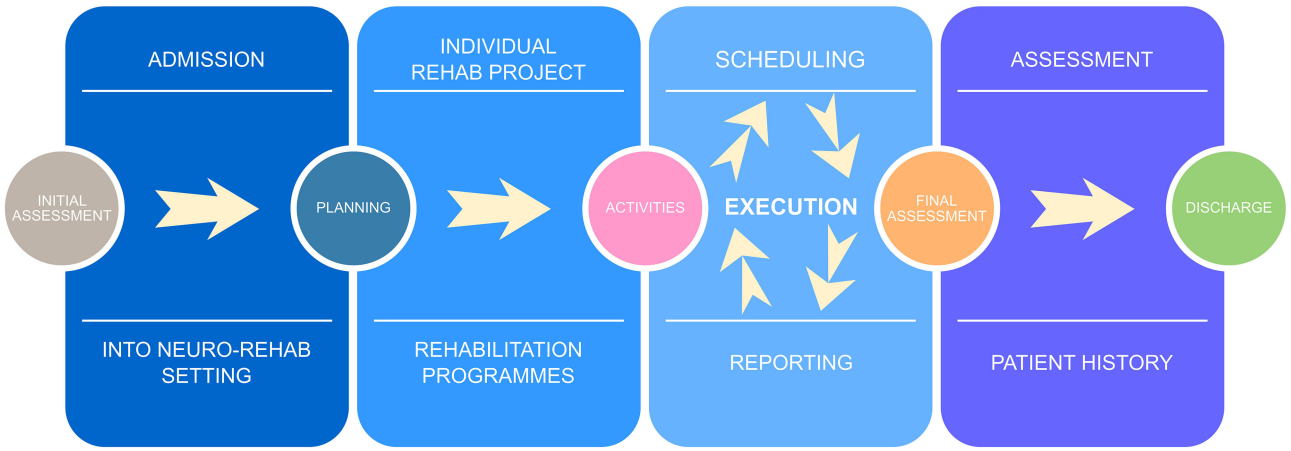


FIGURE 1 | Key steps of the rehabilitation treatment.

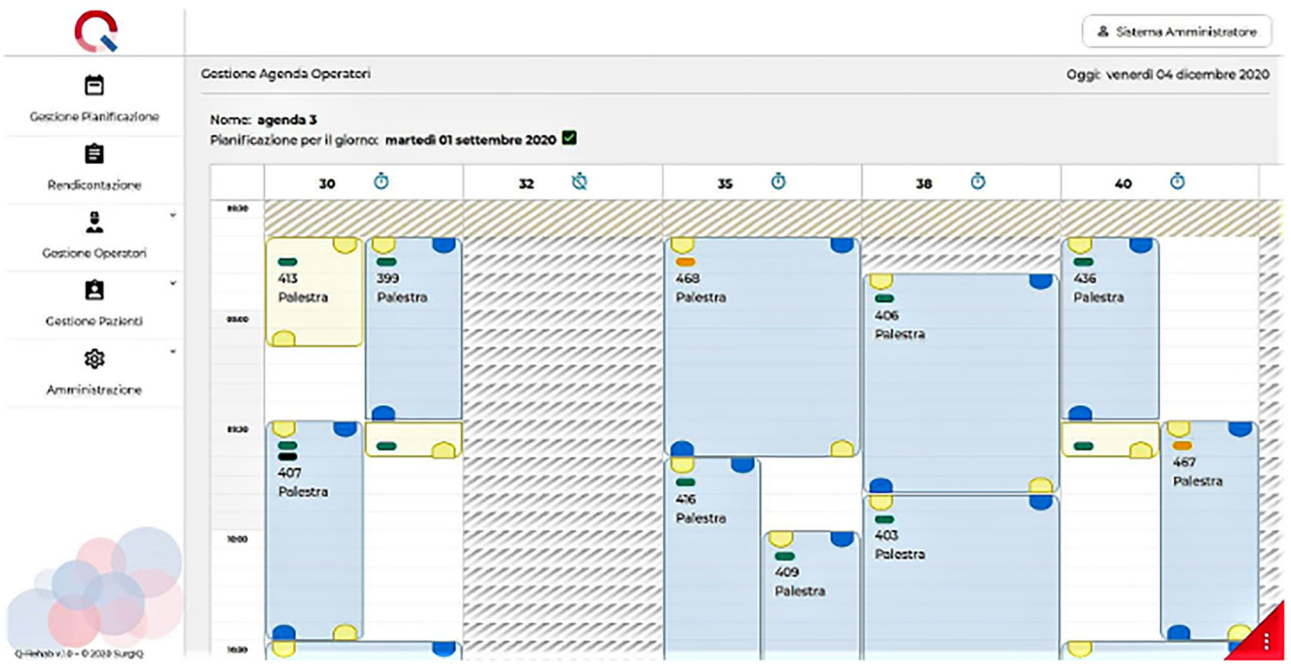


FIGURE 2 | Daily agenda as provided by Q-Rehab. Each column corresponds to a therapist's schedule, with planned sessions represented by colored rectangles (blue for one-to-one sessions and yellow for supervised sessions).

registered by the system and can be displayed as a summary of planned and delivered activities.

Outcome Measures

We collected patients' general characteristics, such as sex, age, and length of stay (LOS). Clinical measures included the diagnosis (neurological, musculoskeletal, or post-COVID-19), the number of comorbidities, the level of disability (Functional Independence Measure, FIM, at admission and discharge), and the impact of rehabilitation (FIM gain) (27).

We also collected measures of the volume of activity of our service as well as the number of hours worked by the staff members of the different therapy disciplines.

For the period May–November 2020, we tested the efficiency and staff satisfaction for the DAIP.

Three variables of efficiency have been taken into account to evaluate the usefulness of the DAIP.

The first one was the total minutes of therapy sessions delivered to patients either by individualized ("one-to-one" sessions) or supervised practice (one therapist supervising more patients at the same time) and how this has changed month

by month (coefficient of variation, defined as the ratio of the standard deviation to the mean).

The second was the ratio between the minutes of planned and delivered sessions, as reported in the database entries and directly calculated by the Q-Rehab software, which is a component of the DAIP. The latter is the time needed to schedule therapy sessions using the Q-Rehab software in comparison to manual scheduling. This variable was calculated as the average time per day spent by 15 therapists during two consecutive weeks using the manual scheduling method (in November 2019) and the Q-Rehab method (in June 2020). The time to schedule therapy sessions took into account the total minutes utilized from registering the data of the patients until the production of the final dashboard.

Considering the impact of the DAIP on staff, either in terms of their routine work and mindset, we measured staff satisfaction for the DAIP. In November 2020, we administered to all staff a 0–10 numerical rating scale (NRS), asking to rate the easiness and the usefulness of the DAIP (where 0 was not at all satisfied and 10 was 100% satisfied) and the System Usability Scale (SUS) (28). The SUS was originally created by John Brooke in 1986. It provides a "quick and dirty" reliable tool for measuring the usability of a wide variety of products and services, including hardware, software, mobile devices, websites, and applications. It consists of a 10-item questionnaire with five response options ranging from "strongly agree" to "strongly disagree;" the responses can be converted into a total score, indicating a not sufficient (0–68), sufficient (68–74), good (74–80), or excellent (>80) usability.

Statistical Analysis

Data are summarized as means and standard deviations (SD) and frequencies and percentages for quantitative and qualitative variables, respectively. Ordinal data are presented as medians and interquartile range (IR). Comparisons between figures observed in 2019 and 2020 were assessed by means of unpaired Student's *t*-test or chi-square test, as appropriate. Non-parametric statistics, namely, Mann–Whitney *U*-test, was applied to test the differences in the number of comorbidities between patients hospitalized in the 2 years. Missing data occurred in <1% of FIM evaluations; thus, no imputation of missing data was considered.

Statistical significance was set at 0.05. SPSS statistical software was used to perform the analyses.

RESULTS

Patient and Service Characteristics Pre-COVID and During COVID-19 Pandemic

Patient characteristics in the two periods, pre-COVID-19 and during COVID-19 pandemic, are displayed in **Table 1**. In 2019, 34.8% of patients were admitted with a neurological diagnosis [of which 43% were stroke, 16% spinal cord injury (SCI), 14% Parkinson's disease, 9% multiple sclerosis (MS), and 18% other diagnosis] and 65.2% with a musculoskeletal diagnosis (of which 45% were fractures and polytrauma, 27% knee and 21% hip arthroplasty, and 7% others). In 2020, 41.6% were admitted with a neurological diagnosis (of which 60% were stroke, 13% SCI, 5% traumatic brain injury, 2.5% MS, and 19.5% others), 51.5% with a musculoskeletal diagnosis (of which 47% were fractures and polytrauma, 26% hip and 19% knee arthroplasty, and 8% others), and 7.2% post-COVID-19.

There was no statistical difference between the two periods for sex, age, and number of comorbidities (**Figure 3**). Bed occupancy was >90% in the two periods, achieving the target for our service.

In the period of May–November 2020, we admitted 19 patients for post-COVID-19 rehabilitation. The flow of post-COVID-19 patients into our rehabilitation service reflected the post-acute timing of the two waves of the outbreak (**Figure 4**). During this period, the total number of patients admitted was lower, the mean LOS was longer, the mean admission FIM was lower, and the mean FIM gain was larger. Although there was no statistically significant difference in staff capacity, the total number of hours for nursing, PT, and SLT was less in May–November 2020, while it increased for OT and psychology (**Table 2**).

Allocation of Therapy Sessions by Q-Rehab

The total daily minutes of delivered therapy sessions remained fairly constant (mean 3,899 min; SD 371) throughout the period of the COVID-19 pandemic, even considering an initial drop in May 2020. A slight increase of the ratio between supervised and "one-to-one" sessions in July and August 2020 is notable in **Figure 5**. As shown in **Figure 6**, there has not been a considerable discrepancy between minutes of reported and planned sessions. In particular, the ratio between these two quantities has been >0.95 for the 95% of the considered time span.

The mean time per day needed to schedule and record patient therapy sessions by 15 therapists using the manual method was 153 and 35 min, respectively, for scheduling and recording, while using Q-Rehab, it dropped to 78 and 15 min, respectively. The time percentage saved by the software is represented in **Figure 7**.

Staff Acceptance of the DAIP

The two NRS and the SUS were administered to all the operators directly involved in the use of the two software (medical staff for Priamo; therapists and psychologists for both Priamo and Q-Rehab) and returned by four doctors (66%), eight PT (57%), two PSY (66%), two SLT (100%), and zero OT (0%). The mean NRS score (SD) for the easiness/usefulness of Priamo was, respectively, 7.1 (2.4) and 6.25 (1.4), while the mean NRS score (SD) for the easiness/usefulness of Q-Rehab was, respectively, 7.25 (1.5) and 5.9 (2.6) (**Table 3**). The SUS mean total score (SD) was 65.6 (13) for Priamo and 65.8 (11.9) for Q-Rehab.

DISCUSSION

Our rehabilitation service faced a challenging time to remodel itself and adapt to the new patients and service needs during the COVID-19 pandemic. New governance rules and operational policies to protect patients and staff against the spread of the virus had to be implemented and put in place from the start of the pandemic. Moreover, COVID-19 survivors with high rehabilitation needs started to be admitted to our rehabilitation

TABLE 1 | Comparison of patients' characteristics in the two periods.

	May–November 2019	May–November 2020	*p*-value
Total of patients	351	262	<0.001
• Neurological, *N* (%)	122 (34.8)	117 (41.6)	
• Musculoskeletal, *N* (%)	229 (65.2)	145 (51.5)	
• Post-COVID-19, *N* (%)	0	19 (7.2)	
Males, *N* (%)	122 (65.2)	110 (42.0)	0.07
Females, *N* (%)	229 (34.8)	152 (58.0)	
Age, mean (SD)	73.2 (11.4)	73.2 (11.9)	0.97
FIM admission, mean (SD)	79.0 (21.3)	72.8 (20.4)	<0.001
FIM discharge, mean (SD)	98.1 (23.7)	95.5 (23.8)	0.18
FIM gain, mean (SD)	19.1 (10.7)	22.5 (12.1)	<0.001
N of comorbidities, median (RI)	3 (1)	3 (1)	0.37
LOS	26.7 (16.3)	32.4 (19.7)	<0.001

FIM, Functional Independence Measure; LOS, length of stay. FIM gain = FIM discharge – FIM admission.

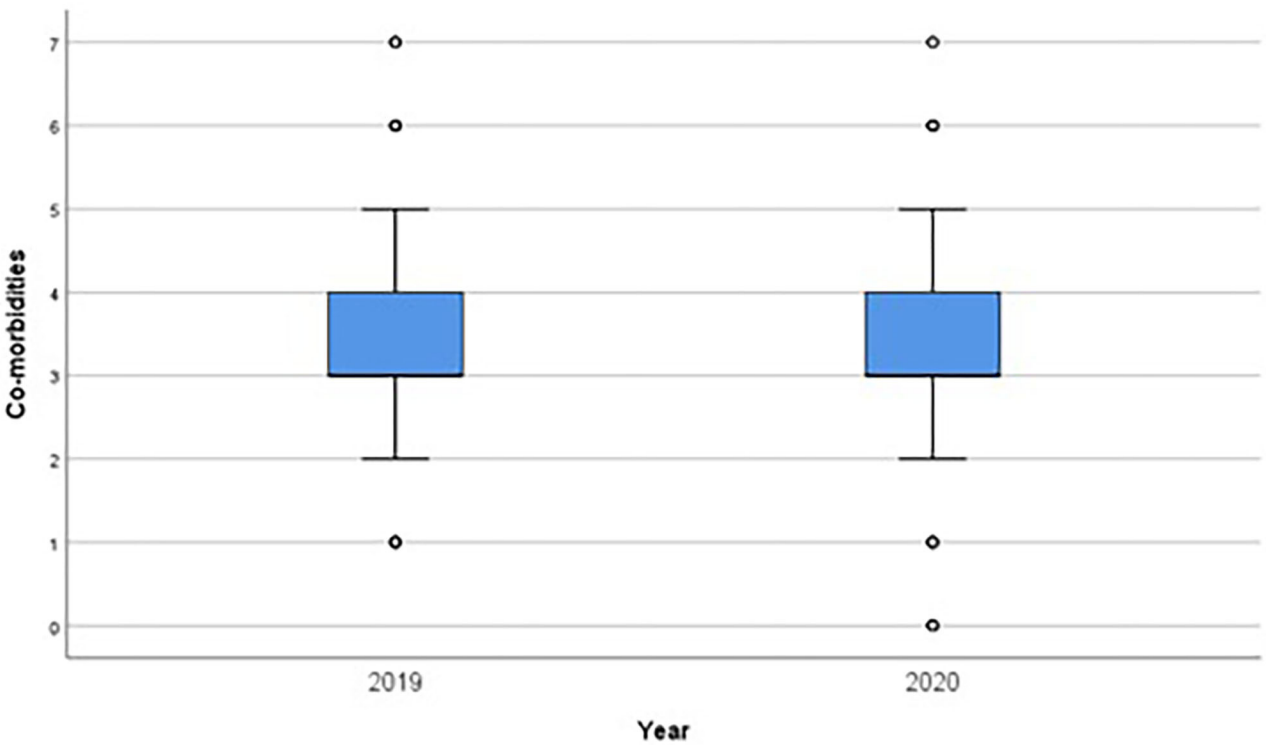


FIGURE 3 | Number of comorbidities in 2019 and 2020.

service in May 2020, for whom an *ad hoc* rehabilitation pathway had to be set up, based on the newly developed international expert recommendations and guidelines (3–10). Progressive learning and changes continue to occur to face the rehabilitation pandemic as unfortunately the virus has not been defeated yet (1, 29, 30).

This paper describes how the adoption of a DAIP helped our rehabilitation service to maintain the high-quality level of care provided by our service (patient outcome) by offering the infrastructure for the team planning and actioning of the IRP while accommodating for the change in the type of the patients being admitted and the new COVID-19-related safety measures.

The DAIP and its implementation have been prepared for a long time before the pandemic, aiming for a quality improvement of our service. The DAIP's additional value during the pandemic was to implement the post-COVID-19 rehabilitation pathway and to schedule and register therapy sessions automatically in a safe and efficient way.

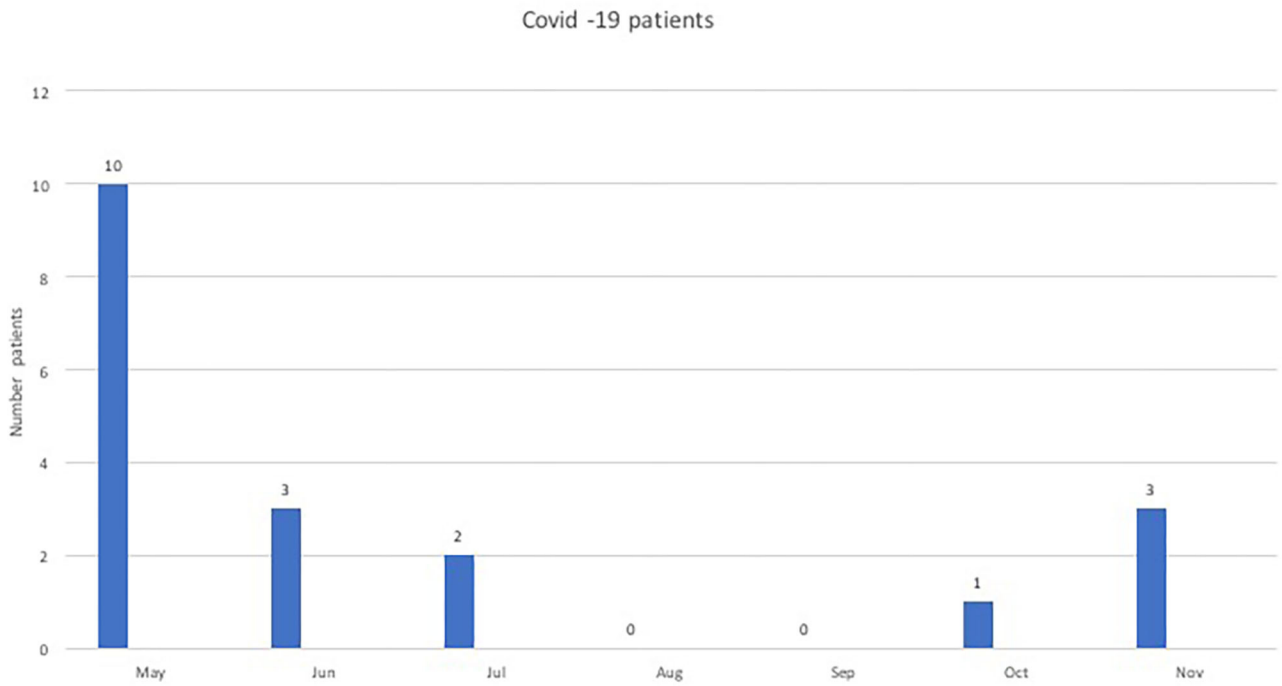


FIGURE 4 | Post-COVID19 patients admitted for rehabilitation.

TABLE 2 | Volume of activity and staff capacity in the two periods.

	May–Nov 2019	May–Nov 2020	*p*-value
OBD *service target*	**>90%**	**>90%**	
Hours nursing, average/month (SD)	3,357 (142)	3,307 (136)	0.52
Hours medical, average/month (SD)	1,327 (94)	1,354 (83)	0.57
Hours PT, average/month (SD)	1,783 (169)	1,669 (116)	0.17
Hours OT, average/month (SD)	49 (15)	71 (12)	0.01
Hours SLT, average/month (SD)	223 (27)	209 (41)	0.30
Hours PSY, average/month (SD)	379 (76)	412 (57)	0.37

OBD, occupied bed days; PT, physiotherapy; OT, occupational therapy; SLT, speech and language therapy; PSY, psychology; SW, social work.

We have shown that the average FIM gain, which is a standard commonly used index of rehabilitation impact applicable to patients across different diagnoses (27), remained at least similar in the two periods, as the statistical difference is likely not clinically relevant (31). Although this is a rather rough measure of rehabilitation quality, it reflects the core outcome variable of the team's work, i.e., the functional change achieved by patients.

We have also described how the different actors of the scene have changed in the new context, i.e., the type of patients being admitted and a more multi-disciplinary treatment team. In particular, we observed a reduced number of admission of patients with musculoskeletal disorders in 2020, related to the discontinuation of elective surgery during the pandemic. Although they may share a similar medical complexity (similar number of comorbidities) with patients admitted with musculoskeletal disorders, patients with neurological disorders or post-COVID-19 are likely more complex in terms of therapy needs, due to the co-existence of physical and cognitive problems, and generally require a longer stay.

Although not statistically significant, some changes took place in the total hours worked by the different staff disciplines, i.e., less hours for nursing, SLT, and PT and more hours for PSY and OT. These changes may reflect a drop of hours due to sick leave for certain therapy disciplines but at the same time show a progressive shift toward a more multi-disciplinary model of rehabilitation.

We have described the qualitative and quantitative contributions that Priamo and Q-Rehab provided.

The qualitative impact of Priamo was to offer a digital room where the team could virtually meet to formulate the IRP and review patients' progression on goals, thus allowing a multi-disciplinary interaction and team goal setting from remote. This

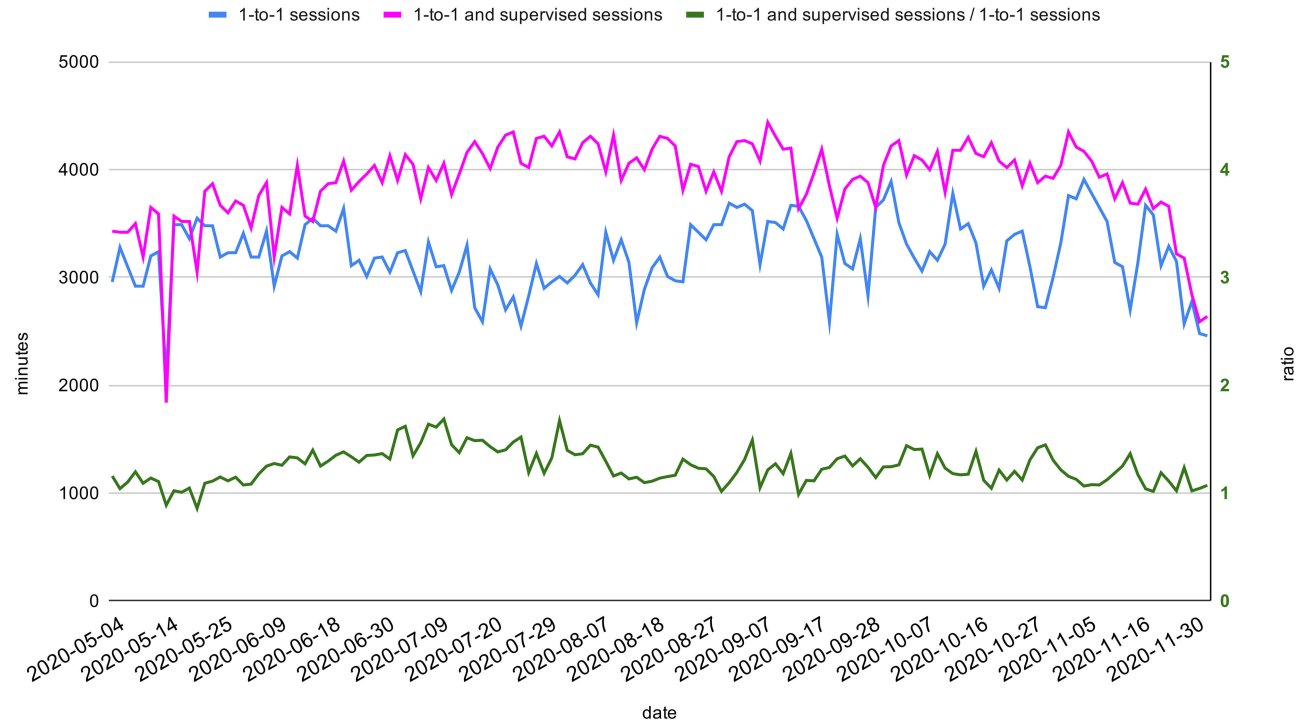


FIGURE 5 | Total daily minutes of therapy sessions. Total daily minutes of one-to-one and minutes of all sessions (both one-to-one and supervised) between May 2020 and November 2020 (light blue and dark blue on the left axis). The ratio between the two aforementioned quantities (pink) is represented on the right axis.

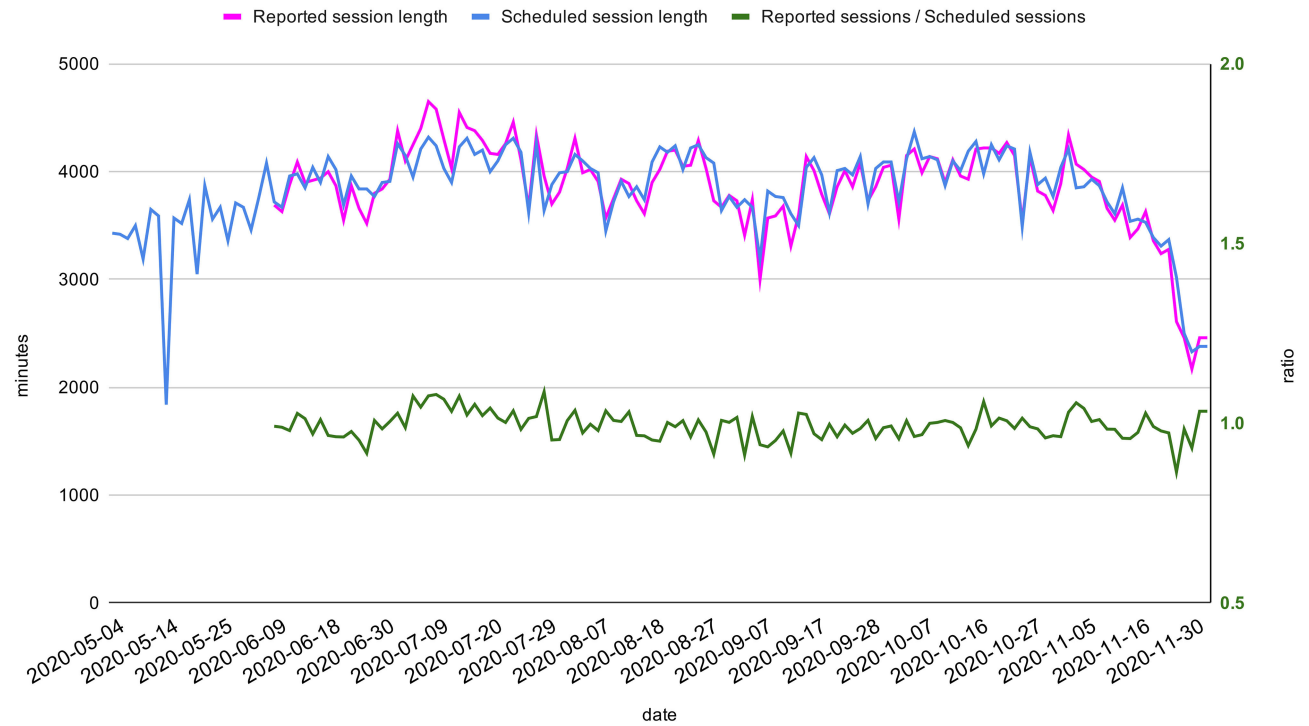


FIGURE 6 | Planned and reported sessions. Total daily minutes of planned and reported sessions between May 2020 and November 2020 (respectively pink and blue, on the left axis). The reporting activity has only started in June. The ratio between minutes of reported and planned sessions (green) is displayed on the right axis.

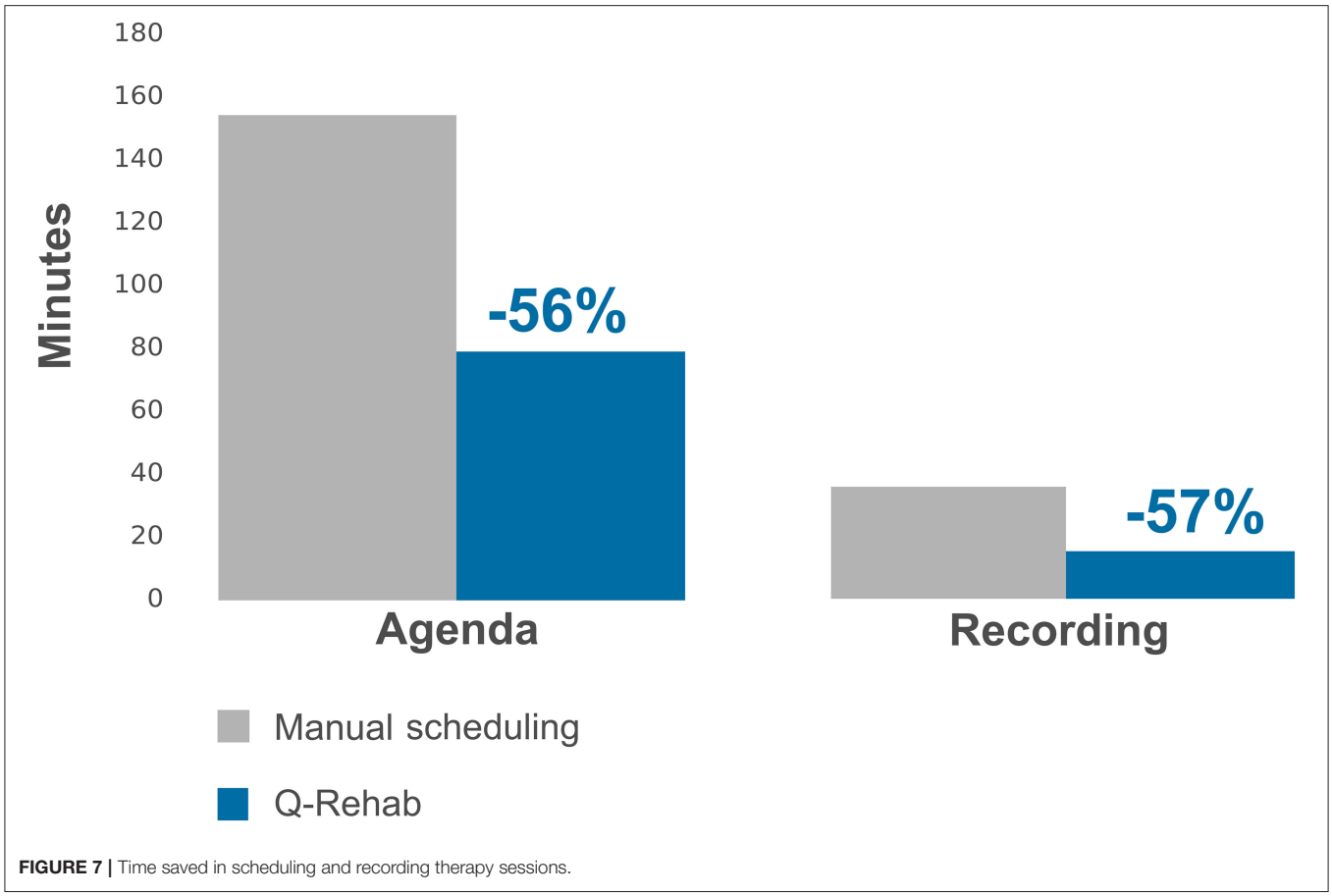


FIGURE 7 | Time saved in scheduling and recording therapy sessions.

reduced the time of direct staff interaction in an apparently easy-to-use intuitive fashion.

Even if we have not quantified the impact of Priamo, for example, on the type of goals being set or their achievement, we have described how it works and staff-related satisfaction. The structure of Priamo is based on the ICF framework for the definition of the IRP following established rehabilitation pathways and producing a consistent goal setting across patients and sound clinical records. Priamo could not substitute the value of multidisciplinary meetings made of people interacting in a physical room, and further communication was still occurring by email, phone, and direct one-to-one talking.

Staff feedback on Priamo showed that it proved to be relatively easy to use (about 70% satisfaction on the easiness) and its "usability" was close to sufficient (SUS mean total score was 65.6, cut-off for usability is 68) with about 65% satisfaction on the usefulness. We suggest that some of the concerns might have come from the limitation of working from remote, reducing the team's direct interaction. An alternative or additional option could have been arranging multi-disciplinary meetings and goal setting via video conference; however, this option was perceived by the team as an excessive burden on staff members, not allowing a real life-like interaction, with expected technical problems and difficulties in updating electronic clinical records in real time.

We tested how Q-Rehab could optimize the allocation of therapy sessions, by measuring its efficiency in different ways. Our results show that the total time of the sessions delivered to patients remained stable during the pandemic and meeting the quality standards for the service.

The slight drop of the total session time in May (**Figure 5**) may suggest the need for an initial adjustment to the new situation, while the "one-to-one" sessions' drop (**Figure 5**) in July and August is more likely related to staff annual leaves during summer, which was well-compensated by the increase of supervised sessions. The high level of adherence to the scheduled agenda demonstrates the excellent reliability and efficiency of the agenda generated by Q-Rehab.

A significant finding was the halving of the scheduling and activity recording time using the Q-Rehab software. The time saved by the therapists in scheduling and recording their activity could have been productively used for wearing PPE, disinfection of equipment, or to update patients' goals and progression, with no subtraction to the patients' treatment time.

From a qualitative point of view, the constraints imposed by the Q-Rehab algorithm establish explicit governance standards in planning the activities to be provided to patients, which can be constantly audited measuring the variance between the planned and delivered activities.

TABLE 3 | Staff satisfaction in the use of the DAIP.

	NRS (0–10) easiness Mean (SD)	NRS (0–10) usefulness Mean (SD)	SUS total score Mean (SD)
Priamo[a]	7.1 (2.4)	6.25 (1.4)	65.6 (13)
Q-Rehab[b]	7.25 (1.5)	5.9 (2.6)	65.8 (11.9)

[a] *Scored by four doctors, eight PT, two PSY, and two SLT.*
[b] *Scored by eight PT, two PSY, and two SLT.*

Staff feedback on Q-Rehab was similar to Primo, showing a relative easiness of use (about 70% of satisfaction) and a "usability" close to sufficient (SUS 65.8). The feedback on the usefulness (about 60% satisfaction) is difficult to interpret but can be related to different staff members using it in different ways (for example, for scheduling or reporting), hence giving different perspectives.

Other perceived barriers either for Priamo or Q-Rehab included the limited number of computers available to therapists and the need to use a different clinical software (on top of Priamo and Q-Rehab) not yet fully integrated. The continuous support by the Maugeri Rehab Processes team and the team champions has been a key enabler to the implementation of the DAIP.

The DAIP implementation was the result of a joint work between informatic engineers and the rehabilitation team, which required a long time for its development, a stepwise introduction until its active routine use in May 2020. Engineer support to the team has been available throughout as well as peer support, for junior members of the staff to be supported by the seniors. In fact, as by the 2019 OECD recommendation (32), the development of digital innovation should originate from a trust-based collaborative work with health professionals to ensure a conscious and lasting adoption of the technology.

No other publication is available to describe a digitally based model to support changes in an inpatient rehabilitation setting during the pandemic.

Our DAIP offers an example of how a DAIP infrastructure has supported our service in a very challenging period. Changes are difficult to be implemented at any time and place both at a personal and organizational level, leading always to a transitional destabilization and requiring a cultural shift. The pressure of the pandemic has added further chaos and complexity to the one that originates from any change occurring within an organization, although the sense of urge might have helped as a drive (33).

Our study presents many limitations. Most of all our observations range across a limited period of time, while changes are still occurring and the second wave of post-COVID-19 rehabilitation admissions might have not achieved its peak as yet.

The implication on patients' outcome has been addressed in general terms, with no reference to the outcome of the post-COVID-19 patients. However, it would have been difficult to interpret and compare the results to our studies due to the limited number of post-COVID-19 patients in our study and in lack of data in the literature about post-COVID-19 rehabilitation outcomes.

Although we have shown how the implementation of the DAIP system has served workflow efficiency, we have not specifically addressed the costs of the implementation as well as the potential savings.

Moreover, staff satisfaction was gathered from a percentage of the team members, and as such, it has not taken into account the collective perspective. A more in-depth understanding of the difficulties that staff members have encountered and the implications for their work and patients' treatment could be gathered by interviews or focus groups. Furthermore, we have not collected measures of patients' satisfaction about their admission and more specifically about the processes regarding their goal setting and the allocation of therapy sessions.

The measures of efficiency that we used present some limitations. First of all, we do not have these data for 2019 for comparison. Only the time spent for scheduling and recording therapy sessions was measured in both periods, manually in 2019 and by Q-Rehab in 2020, showing an increased efficiency due to the use of the software.

Considering the limited time of the observation and the limited volume of the staff–patient sample, we consider our findings to be preliminary and not generalizable or transferrable to other settings.

CONCLUSION AND FUTURE WORK

By applying the DAIP to rehabilitation treatment, it was shown that the management of rehabilitation can be efficiently performed even in the COVID-19 pandemic. This platform has served as a sound infrastructure for the team's work, allowing the rapid implementation of clinical and operational changes and facilitating the interaction between staff members from remote. As facts changed rapidly, we also had to adapt our minds to the changes, although likely with a slower pace and not without difficulties.

In particular, the DAIP provided a qualitative support for goal setting from remote together with an efficient way of planning and recording therapy sessions. Its implementation was generally well-perceived by the staff. Importantly, the processes supported by the DAIP can be easily audited against quality standards.

We envisage further developments of the DAIP during the COVID-19 and post-COVID-19 pandemic, starting from a more in-depth team feedback and from acquiring patients' feedback and considering how the time saved in certain processes could be reallocated to meet the needs still unmet and its implications on costs.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was not

provided because this study is based on retrospective data which are routinely collected by our Service. All patients admitted to our Service sign a consent to agree to the use of their personal data for research purposes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: GP and GG declare their conflict of interest for their business involvement as data scientists at SurgiQ Srl and developers of Q-Rehab.

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

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frontiers in Neurology

CASE REPORT
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Case Report: Behavioral Unresponsiveness in Acute COVID-19 Patients: The Utility of the Motor Behavior Tool-Revised and ^{18}F-FDG PET/CT

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Along with the propagation of COVID-19, emerging evidence reveals significant neurological manifestations in severely infected COVID-19 patients. Among these patients admitted to the intensive care unit (ICU), behavioral unresponsiveness may occur frequently, yet, there are still only a few cases reported and with rare descriptions of their motor behavior after pathological awakening. Several hypotheses regarding central lesions in these patients are conceivable. Here, we describe two acute SARS-CoV-2-infected patients who developed neurological symptoms evoking the condition of clinical cognitive motor dissociation (CMD). This diagnosis could be confirmed first by clinical observation of a dissociation between preserved cognitive abilities and lack of initial motor interaction and second, by performing ^{18}F- FDG PET imaging. Accurate diagnosis led to an appropriate neuro-rehabilitation regimen with long-term neuro-rehabilitation leading to an improved outcome for both patients.

Keywords: COVID-19, SARS-CoV-2, neurological complications, unresponsiveness, PET, ^{18}F-FDG

INTRODUCTION

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is not only restricted to the pulmonary system. Cardiac, thromboembolic, hepatic, renal, gastrointestinal, ocular, endocrine, dermatological, and direct deleterious effects on the central and peripheral nervous systems have been described (1, 2). A retrospective study of 214 COVID-19 patients from China detailed various neurological manifestations in approximately one third of the cases, including acute cerebrovascular disease and impaired consciousness (3). The same study revealed that neurological manifestations in the ICU carried a poor prognosis. In a French case series of 58 consecutive severe acute-COVID-19 patients, encephalopathy with prominent agitation, confusion, and corticospinal tract signs were observed in almost two-thirds of the cases (4). Furthermore, in the 11 patients of this cohort who underwent perfusion imaging, all revealed bilateral frontotemporal hypoperfusion correlating with significant dysexecutive symptoms such as poorly organized motor responses to command in the follow-up.

In the acute stage, such critical damage to the motor output system confers the risk of underestimating the actual conscious awareness, as the patient may be overtly unable to interact even though his cognitive capacity is preserved. This condition is known as cognitive motor dissociation (CMD) (5) and is identified using functional brain imaging and electroencephalography. Such misdiagnosis may present serious consequences as real severe altered consciousness (i.e., true disorders of consciousness) carries unfavorable prognosis (6). Our group recently demonstrated that this particular condition might be also identified clinically (i.e., defined as clinical CMD, ^{c}CMD) by means of the Motor Behavior Tool (MBT and its revised form, MBT-r) (7, 8). The use of this clinical tool as a complement to the Coma Recovery Scale-Revised (CRS-R) (9) allows the identification of subtle motor behavior undermined by the CRS-R, thereby uncovering patients with residual cognition and differentiating them from patients with real disorders of consciousness (DOC), the former having a better prognosis (10).

Complementary to the clinical evaluation, brain ^{18}F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) (11) is a noteworthy sensitive neuroimaging technique to detect brain function related to residual consciousness (12). Most FDG-PET studies have reported consistent, widespread reduced activity in patients with DOC, mainly in the pre-frontal, pre-motor, parietotemporal association areas, and the posterior cingulate cortex/precuneus, with evidence of impaired effective cortical connectivity between the pre-frontal, pre-motor, and posterior cingulate cortices and the thalamus (13). Very few studies have investigated cerebral metabolism in patients displaying covert cognition detected by paraclinical means, but some results indicated preserved metabolic patterns compatible with the presence of conscious awareness (14, 15). None however, investigated the metabolic activity in CMD identified solely by clinical evaluation.

Here, we describe two cases of acute patients infected with COVID-19 who developed neurological symptoms evoking the condition of clinical cognitive motor-dissociation (CMD). Both underwent brain ^{18}F-FDG PET and required a long-term neuro-rehabilitation.

METHODS

The clinical and ancillary test descriptions were personally retrieved by the authors, who examined the patients. This report was conducted in compliance with the Swiss Federal Act on Research involving Human Beings, which waives ethical approval for case reports of less than five patients. Consent of the patient and/or his/her relatives for the re-use of personal data is therefore not required under Swiss Research legislation.

Case Descriptions

Patient 1

A 78-year-old patient without psychiatric or oncologic history was admitted to the ICU with severe acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 infection and needed endotracheal intubation for 25 days. He received hydroxychloroquine for 5 days and after extubation, the sedation was withdrawn. Two experienced physicians clinically assessed the patient at 7 days post-sedation withdrawal as he presented a pathological awakening with absent external responsiveness to stimulation and facial akinesia. According to the French version of the Coma Recovery Scale–Revised (16), he was classified as having unresponsive wakefulness syndrome (UWS) (**Table 1**). However, the MBT-r assessment categorized him as presenting with clinical cognitive motor dissociation (^{c}CMD) with clear, subtle signs of conscious perception not considered by the CRS-R (i.e., attempt at visual pursuit, intentional defense gesture on painful simulation of the breast and an associated grimace). A routine electroencephalogram (EEG) ruled out a non-convulsive status epilepticus. Brain MRI was normal. The lumbar puncture was traumatic with 320 erythrocytes/mm^3, without pleocytosis (<1 cell/mm^3), normal lactate (2.28 mmol/l), a slightly diminished glucose ratio (0.39), the presence of oligoclonal IgG bands, which were identical in the serum and the CSF indicating rupture of the blood brain barrier consistent with systematic infection, negative SARS-CoV-2 and viral/bacterial pathogen PCR and normal ß-Amyloid (-42), hTau and Phospho-Tau (181P) levels. A brain ^{18}F-FDG PET showed diffused hypometabolism of the cortical and subcortical regions of the two cerebral lobes, sparing partially the occipital cortex, the basal ganglia and the cerebellar cortex (**Figure 1**). Patient evolution was marked by a fluctuating hyperactive delirium treated by quetiapine, clonidine and melatonin. He was transferred to the internal medicine ward. His neurological symptomatology gradually improved. He regained voluntary control of his motor responses and followed simple commands, reaching the CRS-R criteria of recovery of consciousness. The overall swift rate of motor interaction recovery along with functional improvement, confirmed the preserved cognition as expected in CMD condition. The patient was transferred to a neuro-rehabilitation clinic, 44 days post-admission with a Glasgow Outcome Scale of three (indicating severe disability). He underwent neurorehabilitation for another 14 days attaining a Glasgow Outcome Scale of 4 (indicating moderate disability) and was able to return home to his wife.

Patient 2

A 61-year old patient without known comorbidities was admitted to the ICU with severe ARDS due to SARS-CoV-2 infection and needed endotracheal intubation for 35 days with extracorporeal membrane oxygenation due to multiple complications. He received hydroxychloroquine and azithromycin for 5 days and one dose of tocilizumab. After 65 days, the sedation was withdrawn and the clinical evaluation 48 h later showed a pathological awakening with reduced behavioral evidence, severe dysfunction of the swallowing pattern with discoordination of the swallow motor circuit, and facial akinesia. According to the French version of the Coma Recovery Scale-Revised, the patient was classified as being in a minimally conscious state minus (MCS-) with no response to the command (**Table 1**), while the MBT-r assessment, considered the patient as presenting with clinical cognitive motor dissociation with the presence of tenuous motor signs (i.e., onset of visual pursuit on the vertical plane, and spontaneous intentional

TABLE 1 | Patient demographics, clinical characteristics, and outcomes.

ID	Sex	Age	Length of sedation (days)	Initial CRS-R diagnosis	CRS-R subscale scores	MBT-r classification	Time to hospital discharge (days)	GOS at discharge
P1	M	78	25	UWS	A2V2M2O2C1Ar2	Clinical CMD	44	3
P2	M	61	65	MCS-	A2V2M3O2C1Ar2	Clinical CMD	105	3

CRS-R, Coma Recovery Scale-Revised; UWS, unresponsive wakefulness syndrome; MCS–, minimally conscious state minus; MBT-r, revised Motor Behavior Tool; GOS, Glasgow Outcome Scale; The subscales for the CRS-R are Auditory Function (A), Visual Function (V), Motor Function (M), Oromotor Function (O), Communication (C), and Arousal (Ar); GOS score of 3 indicates Severe disability.

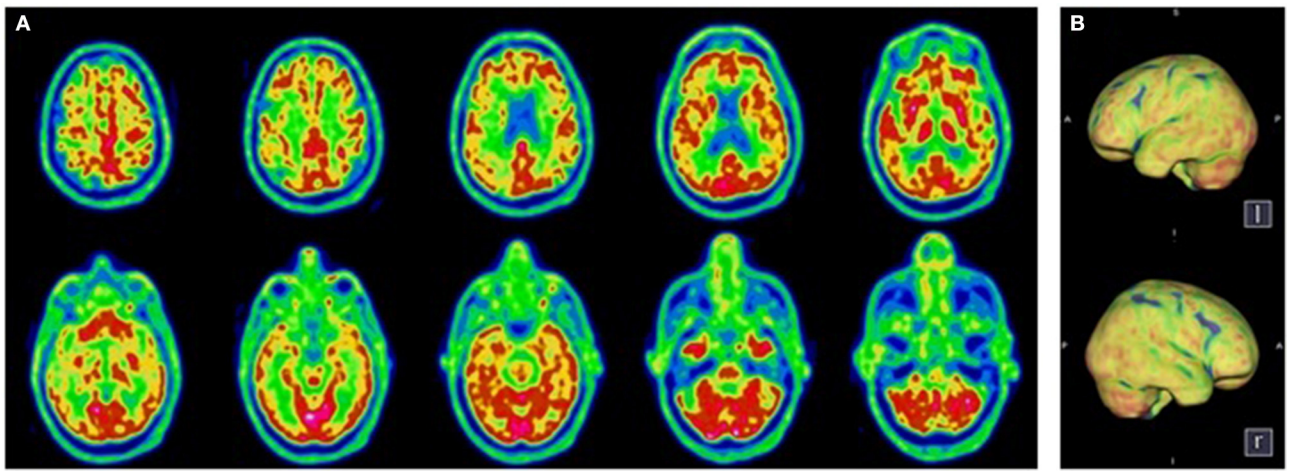


FIGURE 1 | Transaxial **(A)** and Volume Rendered Brain **(B)** ^{18}F-FDG PET. Diffuse cortical hypometabolism. Normal metabolism of the sub-cortical structures and the cerebellum.

distal movements) not taken into account by the CRS-R, yet deemed as indicators of preserved cognitive abilities. A routine electroencephalogram (EEG) ruled out a non-convulsive status epilepticus, showing a moderate encephalopathy. Brain MRI was unremarkable. The electroneuromyography confirmed a critical illness polyneuropathy. A lumbar puncture could not be performed due to bilateral pulmonary embolism. A brain ^{18}F-FDG PET showed a moderate hypometabolism in the frontal, temporal and parietal regions, sparing the motor, and pre-motor cortex (**Figure 2**). The neurological symptomatology improved gradually, the patient regained his ability to display overt motor behavior and responded systematically to commands, thus reaching the CRS-R criteria for recovery of consciousness. The overall functional/cognitive improvement confirmed the preserved cognitive abilities as expected in CMD condition and the patient was transferred to a neuro-rehabilitation clinic, 105 days post-admission with a Glasgow Outcome Scale of three (indicating severe disability). He underwent neurorehabilitation for another 69 days obtaining a Glasgow Outcome Scale of 4 (indicating moderate disability) and was able to return home.

DISCUSSION

The long-term outcomes of patients after severe COVID-19 are still unknown; nonetheless, a new emerging syndrome, Post Covid-19 Neurological Syndrome (PCNS) described by Wijeratne and Crewther shows myopathy and prolonged muscle weakness (17). Intensive care unit survivors have been shown to present a significantly lower health-related quality of life (18). The long stay in the ICU, often complicated by critical illness polyneuropathy/myopathy (19), cannot explain the global akinetic motor pattern observed in the two cases described here. Our patients presented severe swallowing disorders, facial akinesia, absence of oculomotricity and lack of motor interaction to stimulation, without any structural brain MRI signs of inflammatory, vascular, degenerative, or infectious encephalopathy.

The pathogenic mechanism explaining COVID-related neurological disorders and encephalopathy in particular, is the topic of intense discussion (2, 20–23). Indeed, it remains undetermined whether SARS-CoV-2 causes direct brain damages (possibly by affecting the olfactory nerves and migrating retrogradely) or whether the cause is indirect, due to an excessive inflammatory response (cytokine storm) or the trigger of an autoimmune response by the virus (24), but more evidence suggest a migration to the central nervous system via transfer across the blood-brain barrier (20, 23). Despite clear identifiable neurological associations of COVID-19 (25), the effect on motor interaction, which is an overt indicator of consciousness, is still undetermined. Some evidence suggests that coronaviruses may cause damage to the dopaminergic system. Earlier studies in patients with Parkinson's disease showed high anti-coronavirus antibody titers in the cerebrospinal fluid (26) and recently, SARS-CoV-2 was identified in frontal lobe tissue (27) using electron-microscopy. Furthermore, some COVID-19 patients have shown

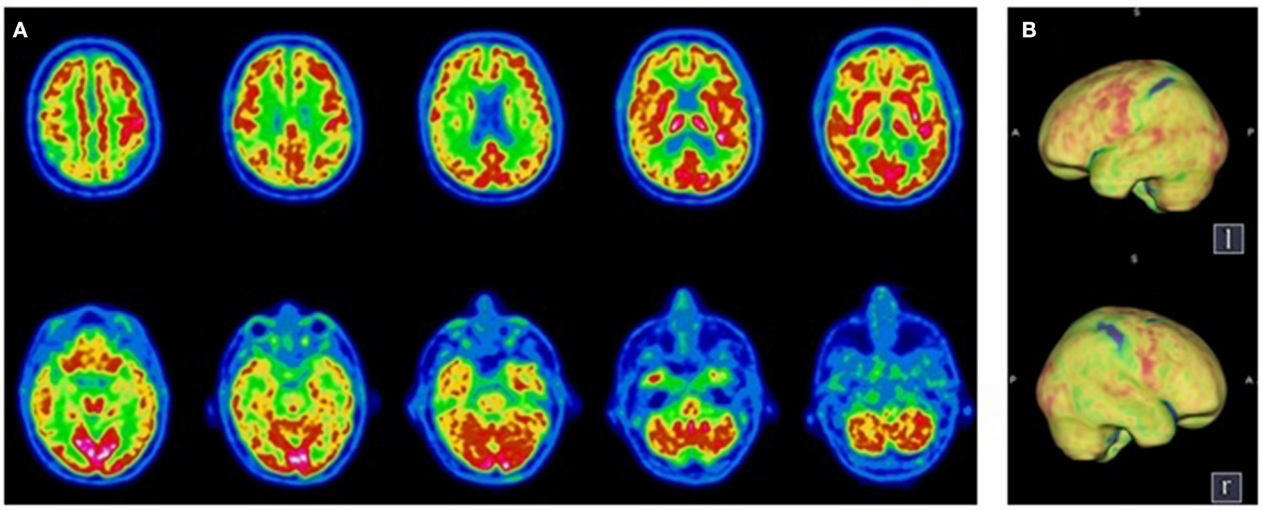


FIGURE 2 | Transaxial **(A)** and Volume Rendered Brain **(B)** ^{18}F-FDG PET. Diffuse cortical hypometabolism predominant in the right hemisphere, with a preservation of the primary sensorimotor areas. Normal metabolism of the sub-cortical structures and the cerebellum.

extended confusion after sedation withdrawal and impaired consciousness (28).

Consistent with these data, our hypothesis is that for the two patients, SARS-Cov-2 induced functional impairment in strategically localized areas of the executive motor network (i.e., frontal, pre-frontal). Indeed, the brain ^{18}F-FDG PET in these patients showed a diffused hypometabolism, sparing the motor and pre-motor cortex but affecting the associative areas responsible for the integration of motor initiation and coordination, explaining the clinical picture.

Regarding prognostic implications, establishing whether a patient has preserved cognition/motor intent is of high significance; patients presenting with clinical CMD are likely to have a better prognosis and superior cognitive/functional outcomes (10), helping to select the most appropriate rehabilitation technique. The outcomes of the two cases described here, which was characterized by a rapid rate of cognitive and functional recovery but enduring executive and attentional disorders, confirmed the initial diagnosis of clinical CMD.

We recommend therefore, using the MBT-r as a simple and economic tool for distinguishing CMD patients from patients with real impairment of consciousness to avoid misdiagnosis in patients awakening from coma after severe COVID-19. This is crucial in the evaluation of COVID-19 patients, where exposure time of care-givers is correlated with the risk of infection (29). In addition to the clinical evaluation with the MBT-r, we recommend ruling out treatable causes by lumbar puncture and brain MRI. It is especially important to rule out stroke since patients with COVID-19 exhibit a higher risk of acute ischemic stroke compared with patients with other respiratory tract infections (30).

In cases of normal MRI results and behavioral unresponsiveness following severe COVID-19, brain ^{18}F-FDG PET may also be used as a more robust technique for confirming the diagnostic hypothesis in selected patients (12). This exam is a complementary tool that can confirm the integrity of the structures responsible for voluntary movement, especially in patients with normal brain MRI or electromyography studies showing motor deficit only. A systematic exploration of all these particular COVID-19 cases using PET might be currently unrealistic due to the number of concerned patients and the theoretical risk of disease contaminating PET imaging departments (31); although we believe that imaging of COVID-19-positive patients can be practiced safely and patients who might benefit from this imaging should not be denied access, as demonstrated by our group (32).

A thorough but practical clinical examination investigating subtle positive signs, such as the MBT-r, complemented by ^{18}F-FDG PET exploration in cases of other unremarkable brain imaging, would have a direct impact on patient care, potentially leading to better therapeutic interventions at an early stage. Indeed, establishing a rapid diagnostic procedure and reliable prognosis outcome is crucial for patients who might benefit from an early treatment (24). Above all, we recommend applying an early and intensive neuro-rehabilitation program for severe COVID-19 patients with behavioral unresponsiveness, which aims at maximizing patient function to achieve the highest possible level of independence (33, 34).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with

the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SV, J-BE, JJ, AP, MM, RD, JP, and KD contributed to the conception and design of the review. SV, J-BE, JJ, and MM contributed to the literature review, drafting the text, and preparing the figures. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.644848/full#supplementary-material

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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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Cognitive and Emotional Disturbances Due to COVID-19: An Exploratory Study in the Rehabilitation Setting

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The coronavirus disease 19 (COVID-19) can cause neurological, psychiatric, psychological, and psychosocial impairments. Literature regarding cognitive impact of COVID-19 is still limited. The aim of this study was to evaluate cognitive deficits and emotional distress among COVID-19 and post–COVID-19 patients who required functional rehabilitation. Specifically, this study explored and compared cognitive and psychological status of patients in the subacute phase of the disease (COVID-19 group) and patients in the postillness period (post–COVID-19 group). Forty patients admitted to rehabilitation units were enrolled in the study and divided into two groups according to the phase of the disease: (a) COVID-19 group ($n = 20$) and (b) post–COVID-19 group ($n = 20$). All patients underwent a neuropsychological assessment including Mini-Mental State Evaluation (MMSE), Montreal Cognitive Assessment (MoCA), Hamilton Rating Scale for Depression, and Impact of Event Scale–Revised (IES-R). A larger part of the COVID group showed neuropsychological deficits in the total MMSE (35%) compared to the post-COVID group (5%), whereas the majority of both groups (75–70%) reported cognitive impairments in the total MoCA. The post-COVID group reported significantly higher score in MMSE subtests of language ($p = 0.02$) and in MoCA subtests of executive functions ($p = 0.05$), language ($p = 0.01$), and abstraction ($p = 0.02$) compared to the COVID group. Regarding emotional disturbances, ∼40% of patients presented with mild to moderate depression (57.9–60%). The post–COVID-19 group reported significantly higher levels of distress at the IES-R compared to the COVID group ($p = 0.02$). These findings highlight the gravity of neuropsychological and psychological symptoms that can be induced by COVID-19 infection and the need for tailored rehabilitation, including cognitive training and psychological support.

Keywords: rehabilitation, pandemic, depression, stress, cognitive function, COVID-19

INTRODUCTION

In December 2019, a new disease, the coronavirus disease 2019 (COVID-19), emerged in China and rapidly spread over the world, resulting in a global pandemic on March 11, 2020.

Scientific literature suggests that COVID-19 is associated with adverse mental health consequences for general population, hospital staff, and patients, leading to dramatic relapses in the healthcare system worldwide (1, 2).

Several studies confirmed high levels of posttraumatic stress disorder (PTSD) symptoms, distress, anxiety, and depression among COVID-19 patients (3, 4). Because of social isolation, perceived danger, uncertainty, physical discomfort, medication side effects, and fear of virus transmission, patients with COVID-19 may experience loneliness, anger, anxiety, depression, insomnia, PTSD, and stigma (5–7), which could negatively affect individuals' functioning and quality of life (8).

However, most of studies have explored mental health and psychological consequences of patients with COVID-19, and there is a lack of scientific studies investigating the effects of COVID-19 on cognitive functions (9–11).

It is well-known that impairment of cognitive function is common following acute respiratory distress syndrome (ARDS) (12, 13). Cognitive impairment following ARDS has been noted to affect most survivors at hospital discharge, and in ∼10% of cases, impairments are persistent at long-term follow-up (12, 14). Neuropsychological impairments may affect memory, attention, and executive functions (14, 15). Furthermore, in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), after recovery from the infection, memory and concentration deficits were found in more than 15% of patients up to 39 months following the infection (5).

It is also noteworthy that the presence of the virus has been found in the cortex and hypothalamus in several SARS patients, as well as edema and neuronal degeneration, lending further support for the theory that coronaviruses may impact the central nervous system (16).

Regarding COVID-19, some studies (5, 10, 17, 18) showed its potential neurological and psychiatric complications, including cerebrovascular events, acute alteration in mental health status (i.e., encephalopathy and encephalitis), and primary psychiatric syndromic diagnoses (i.e., psychosis).

Literature regarding cognitive impact of COVID-19 is still limited. Alemanno et al. (19) analyzed a cohort of 87 COVID-19 patients and showed that ∼80% of these patients, in the subacute phase of the disease, showed significant impairments of cognitive functions, including memory, attention, abstraction, and space and time orientation. They also showed that 1 month after hospital discharge, 70% of these patients still showed signs of cognitive dysfunction. Zhou et al. (11) evaluated the impacts of COVID-19 on cognitive functions in recovered patients using neuropsychological tests; their findings suggested a potential cognitive dysfunction in patients with COVID-19 especially in the sustained attention domain. A French study (20) conducted among inpatients with ARDS due to COVID-19 showed that 15 of 45 patients exhibited a dysexecutive syndrome at discharge.

Therefore, there is the need to better investigate the short- and long-term effects of COVID-19 on cognitive functions in order to provide patients with the best care during the acute phase of the disease and with personalized cognitive training after discharge, when needed.

The aim of this study was thus to evaluate cognitive deficits and emotional distress among COVID-19 and post–COVID-19 patients who required functional rehabilitation and were admitted to COVID-19 or post–COVID-19 rehabilitation units. Indeed, it has been shown that ∼25% of COVID-19 patients need specialized rehabilitation to address cardiorespiratory, motor, and/or cognitive dysfunctions in the subacute phase of the disease (21). Thus, we aimed to explore and compare cognitive and psychological status of patients in the subacute phase of the disease (COVID-19 group) and patients in the postillness period (post–COVID-19 group).

MATERIALS AND METHODS

Population

This was a cross-sectional and exploratory study. The study population consisted of 40 patients admitted to rehabilitation units in order to optimize their functional status prior to discharge and community reintegration. The sample included two groups of patients, according to the phase of their disease: (a) COVID-19 group ($n = 20$) and (b) post–COVID-19 group ($n = 20$).

The majority of sample developed a severe form of COVID-19, with patients needing respiratory support and presenting cardiorespiratory and neurological complications.

The COVID-19 group included infected patients (positive swab) in the subacute phase of the disease (about 10 days after symptom onset), admitted to the COVID-19 rehabilitation unit of the San Raffaele Hospital (Milan, Italy) from May 7 to May 25. Criteria to admit COVID-19 patients in this unit were as follows: positive swab for SARS-CoV-2, stable Sat_{O_2} and respiratory rate (RR), no need for respiratory assistance or no more than 2 L/min, absence of fever, and with areas of dependence at the FIM [Functional Independence Measure evaluation (score <100)] (21).

The second group included post–COVID-19 patients admitted to the post–COVID-19 rehabilitation unit of ICS Maugeri Spa SB Institute (Pavia, Italy) from May 8 to August 11, 2020. Criteria to admit post–COVID-19 patients in this unit were two consecutive negative swabs, no ongoing signs or symptoms of COVID-19 infection, stable Sat_{O_2} and RR, and FIM score <100. The mean time of hospital admission was 25.14 $\pm$ 10.39 days after the last negative swab.

Exclusion criteria included (1) history of mental disorders or current treatment for mental illnesses (e.g., antipsychotics, antidepressants, mood stabilizers, antiepileptics, benzodiazepines, and other drugs that may interfere with the assessment); (2) history of neurological diseases that may affect cognitive status; (3) severe physical illnesses that may interfere with the assessment; (4) history of drug abuse or drug dependence; and (5) hearing or visual impairments.

TABLE 1 | Socio-demographic characteristics of the study-sample.

	Total	COVID-19 group	Post COVID-19 group		
	M (SD)	**M (SD)**	**M (SD)**	**Mann-Whitney U**	***p***
Age	64.13 (11.85)	62.85 (12.35)	65.40 (11.51)	235.00	0.35
Education	11.15 (4.88)	10.65 (5.01)	11.65 (4.82)	217.50	0.64
	% (n)	**% (n)**	**% (n)**	X^2	***p***
Gender					
Male	62.5 (25)	60 (12)	65 (13)	0.11	0.74
Female	37.5 (15)	40 (8)	35 (7)		

SD, Standard Deviation. Age and education are reported in years. "n" = absolute value.

Procedures

All patients underwent a comprehensive rehabilitation program, tailored based on the patients' clinical features and the stage of the infection and in postinfection. The recovery of COVID-19 and post–COVID-19 patients in rehabilitation units aims at improving the respiratory function, counteracting immobilization, and reducing the rate of long-term complications and disability, to improve cognitive functions and promote psychological health, in order to promote quality of life and community reintegration (22, 23).

During the 1st week of admission, all patients underwent an individual psychological and neuropsychological assessment. Neuropsychological assessment was carried out by an experienced neuropsychologist according to standardized procedures. Patients were individually tested, and the full battery lasted ∼30 min. Psychological assessment included the administration of self-report questionnaires. In the COVID-19 rehabilitation units, assessments were performed at patients' bedside to minimize the risks of contagion.

The neuropsychological screening included the Mini-Mental State Examination (MMSE) (24) and the Montreal Cognitive Assessment (MoCA) (25).

The MMSE is the most commonly used test for screening cognitive impairment and consists of a brief 30-point questionnaire. The presence of cognitive impairment was defined by a total score of <23.80 adjusted for age and education in the Italian population (26).

The MoCA is a cognitive screening instrument developed to detect mild cognitive impairment (MCI). It is a simple 10-min paper-and-pencil test and with a maximum score of 30. It assesses multiple cognitive domains including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. As many other studies (27, 28), we used the original cutoff proposed by the author of the test (25), who recommended that a total MoCA score of <26 indicates the presence of cognitive deficits; furthermore, according to the author, one point should be added to the total score in subjects with a low (<12 years) education level.

Depression was assessed using the Hamilton Depression Rating Scale (29), which is a 17-item semistructured interview assessing depressive symptoms. The items are rated on 3- or 5-point scales, and the total score can range from 0 to 53, with higher scores indicative of higher levels of depression. A total score ranging from 0 to 7 suggests no or minimal symptoms of depression, scores from 8 to 17 indicate mild depression, scores from 18 to 25 suggest moderate depression, and scores of 26 or greater are associated with severe depression.

Psychological distress related to the COVID-19 outbreak was assessed using the Impact of Event Scale–Revised (IES-R) (30), which is a validated 22-item self-report that measures the subjective distress caused by a traumatic event. Patients were asked to rate their level of distress using a 5-point Likert scale ranging from 0 ("not at all") to 4 ("often") referring to the previous 7 days. A total score ranging from 0 to 23 indicates the absence of relevant symptoms; from 24 to 32, the presence of mild symptoms; from 33 to 36, the presence of moderate symptoms; and >37, the presence of a severe psychological distress (30, 31).

The present study was approved by the local Scientific Ethics Committee of Maugeri and San Raffaele Hospitals. All participants provided oral and written informed consent to participate in this study.

Statistical Analysis

Categorical variables were expressed as absolute values (percentage), whereas continuous variables were expressed as mean ± standard deviation. The comparison between the two groups of patients was performed using Mann-Whitney *U*-test for continuous variables, whereas categorical variables were compared using the χ^2 test. Bonferroni correction for multiple testing was applied. The significance level was $p < 0.05$ (two-tailed). All the analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL).

RESULTS

The total sample for this study included 20 inpatients admitted to a COVID-19 rehabilitation unit and 20 patients admitted to a post–COVID-19 rehabilitation unit in Northern Italy. The mean age of participants was 64.13 ± 11.85 years. Most patients were males (62.5%) with a mean education of 11.15 ± 4.88 years. There were no significant differences for these sociodemographic

TABLE 2 | Comparison of MMSE subtests between COVID-19 and Post-COVID-19 groups.

MMSE cognitive domains	Range (Min-Max)	Total	COVID-19 group	Post COVID-19 group	Mann-Whitney U	*p*
		M (SD)	M (SD)	M (SD)		
Temporal orientation	0–5	4.38 (1.19)	4.15 (1.49)	4.60 (0.75)	219.00	0.62
Spatial orientation	0–5	4.43 (0.81)	4.25 (0.96)	4.60 (0.60)	242.00	0.26
Retention	0–3	2.90 (0.38)	2.80 (0.52)	3.00 (0.00)	230.00	0.42
Calculation/attention	0–5	3.98 (1.66)	3.45 (2.11)	4.50 (1.14)	249.50	0.18
Memory recall	0–3	2.15 (1.00)	2.00 (1.12)	2.30 (0.86)	227.00	0.47
Language	0–8	7.34 (1.19)	6.83 (1.50)	7.80 (0.52)	257.00	0.02*
Visuospatial	0–1	0.65 (0.48)	0.47 (0.51)	0.80 (0.41)	226.00	0.09
Total score	0–30	25.68 (5.13)	23.80 (6.59)	27.55 (1.79)	246.00	0.22

*M, mean; SD, Standard Deviation. *Significant differences between groups ($p < 0.05$).*

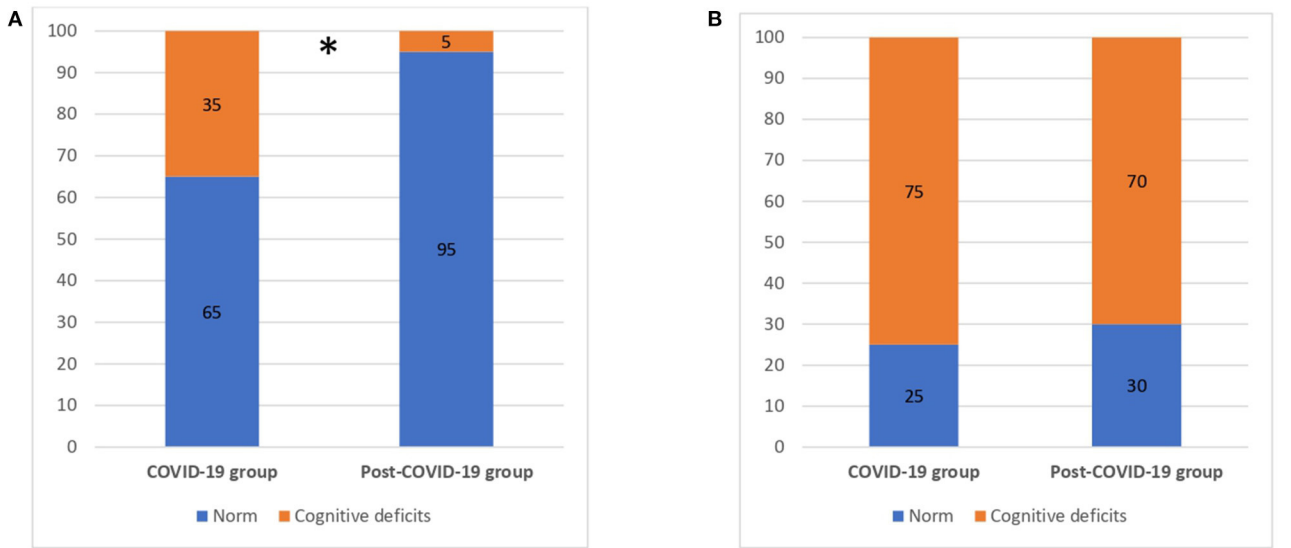


FIGURE 1 | Cognitive deficits for COVID-19 and post-COVID-19 patients. **(A)** MMSE (total score). **(B)** MoCA (total score). MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; numbers are reported as %. *$p < 0.05$.

characteristics between COVID-19 and post–COVID-19 groups. These characteristics are presented in **Table 1**.

Cognitive Assessment

Results from the neuropsychological screening tests showed that 35.0% of the COVID group resulted impaired in the total score of MMSE adjusted for age and education (26) compared to 5% of the post-COVID group ($\chi^2 = 5.625$, $p = 0.02$). We explored any significant differences in cognitive domains of MMSE between the COVID-19 and post–COVID-19 groups (**Table 2**). We found that the post–COVID-19 group performed significantly better in language ($p = 0.02$).

Regarding the MoCA evaluation, 75.0% of COVID-19 patients and 70.0% of the post-COVID patients showed cognitive deficits according to the MoCA total score adjusted for education (25) with no significant differences between the two groups ($p > 0.05$) (**Figure 1**).

Table 3 describes the differences between the two groups in cognitive domains measured by MoCA. The post–COVID-19 group reported a significantly better performance in executive functions ($p = 0.05$), language ($p = 0.01$), and abstraction ($p = 0.016$), compared to the COVID-19 group.

Psychological Assessment

Figure 2 summarizes the results of depression and psychological distress questionnaires in both groups.

Regarding depression, ∼40% of patients, in both groups (57.9%−60%), showed symptoms of mild to moderate depression, with no significant differences between groups ($p > 0.05$). Regarding psychological distress, all of COVID-19 patients (100%) reported an absence of distress. Conversely, 55% of post–COVID-19 patients presented with mild to severe symptoms ($\chi^2 = 15.17$, $p = 0.02$). Results from psychological questionnaires are summarized in **Table 4**.

TABLE 3 | Comparison of MoCA subtests between COVID-19 and Post-COVID-19 groups.

MoCA cognitive domains	Range (Min-Max)	Total	COVID-19 group	Post COVID-19 group	Mann- Whitney U	*p*
		M (SD)	M (SD)	M (SD)		
Executive functions	0–5	3.05 (1.52)	2.50 (1.76)	3.60 (0.99)	271.50	0.05*
Naming	0–3	2.73 (0.68)	2.55 (0.89)	2.90 (0.31)	233.00	0.38
Attention	0–6	4.70 (1.78)	4.30 (2.18)	5.10 (1.21)	230.00	0.43
Language	0–3	1.98 (0.95)	1.55 (0.99)	2.40 (0.68)	297.00	0.01*
Abstraction	0–2	1.23 (0.73)	0.95 (0.60)	1.50 (0.76)	282.50	0.02*
Delayed recall	0–5	1.83 (1.56)	1.60 (1.72)	2.05 (1.39)	239.50	0.29
Orientation	0–6	5.23 (1.51)	4.70 (1.97)	5.75 (0.44)	255.00	0.07
Total score	0–30	21.97(5.42)	20.12 (7.03)	23.55 (2.89)	200.50	0.35

*M, mean; SD, Standard Deviation. *Significant differences between groups ($p < 0.05$).*

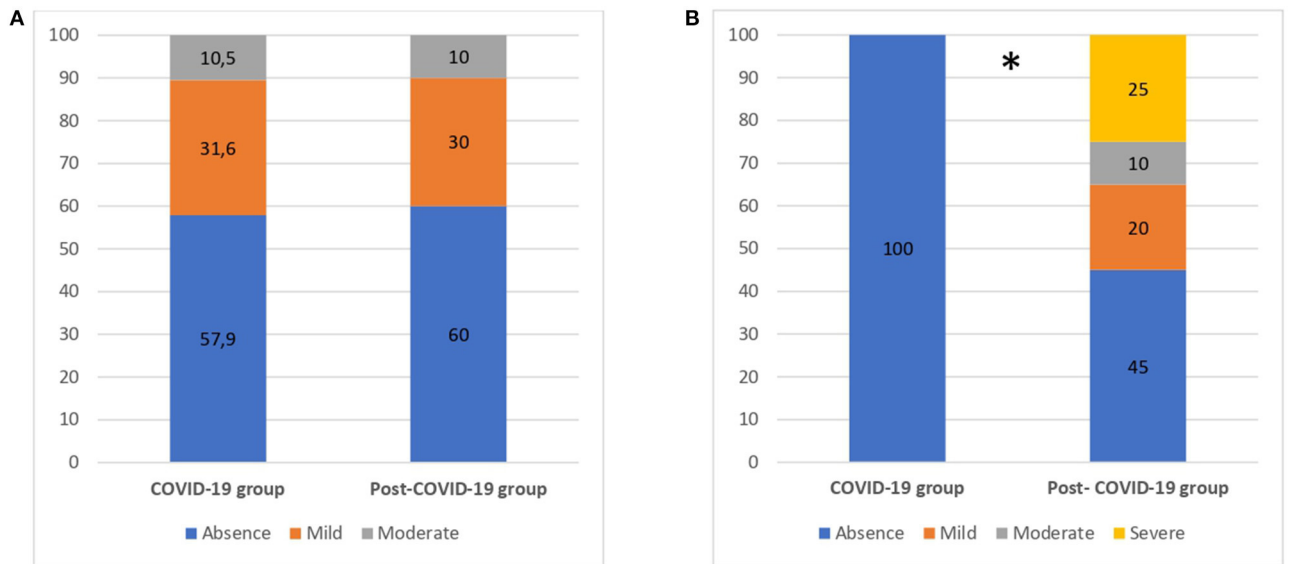


FIGURE 2 | Emotional disturbances for COVID-19 and post-COVID-19 patients. **(A)** Depression. **(B)** Psychological distress. Numbers are reported as %. *$p < 0.05$.

DISCUSSION

These results brought further evidence that patients who recovered in COVID and post-COVID functional rehabilitation units presented with cognitive deficits, confirming the results of Alemanno et al. (19). Specifically, 75% of COVID and 70% of post-COVID patients presented with cognitive deficits according to the MoCA evaluation. These data highlight the gravity of neurological and neuropsychological symptoms that can be induced by COVID-19 infection and how these symptoms can outlast the period of infection. Neurological symptoms and cognitive dysfunctions following COVID-19 infection are likely to result from multiple and interacting causes, notably direct damage by the virus to the cortex and adjacent subcortical structures, and indirect effects as a part of broader systemic illness and psychological distress (5, 9). The hippocampus appears to be particularly vulnerable to coronavirus infections, thus increasing the risk of post-infection memory impairment and acceleration of neurodegenerative disorders (9).

In this study, both groups presented with impairment of cognitive functions, such as executive functions, short- and long-term memory, visuospatial abilities, abstraction, and orientation. However, post–COVID-19 patients, ∼1 month after infection, showed better performance in the language subdomain, compared to COVID-19 patients, showing incomplete recovery in the 1st days following infection. Although partial recovery could be observed, post–COVID-19 patients still presented with significant memory dysfunctions. Such memory deficits have already been reported in post–COVID-19 patients (11, 19, 30, 32). These data sum up with previous evidence showing that SARS-CoV-2 might affect the nervous system, as also shown by symptoms ranging from loss of smell to increased risk of stroke or delirium (16, 20).

TABLE 4 | Comparison of emotional disturbances between COVID-19 and Post-COVID-19 groups.

Psychological factors	Total	COVID-19 group	Post COVID-19 group	Mann-Whitney U	*p*
	M (SD)	M (SD)	M (SD)		
Distress	15.90 (14.43)	9.25 (5.95)	22.55 (17.30)	284.00	0.02*
Depression	8.05 (5.60)	7.95 (5.34)	8.15 (5.96)	189.00	0.99

*M, mean; SD, Standard Deviation. *Significant differences between groups ($p < 0.05$).*

Based on our results, MoCA was more sensitive in detecting cognitive functions impairments, as suggested in previous studies investigating the best tools for MCI diagnosis. Indeed, although MMSE has been widely used to detect cognitive impairments, it would be less efficient than MoCA in detecting MCI (33). MMSE has been further criticized as a poor screening test because of insensitivity to detect visuospatial and executive function impairments (33). MoCA, which includes more testing of cognitive subdomains than MMSE, was thus designed to be more sensitive and may therefore represent a superior screening instrument to detect wide ranges of cognitive impairments.

Regarding the psychological effects of SARS-CoV-2 infection, our data showed that ∼40% of patients of both groups presented with mild depression, with no significant differences between groups. Conversely, both groups differed in the distress evaluation. Post–COVID-19 patients presented with higher levels of distress as measured with the IES-R, compared with the subacute COVID-19 patients. Both these results confirm previous evidence reporting a significant amount of depressed patients as well as signs of PTSD in COVID-19 survivors (34). Psychological distress or signs of PTSD were not observed in COVID-19 patients, most probably because patients were still dealing with the infection and were still in the subacute phase of the disease. Indeed, signs of PTSD are usually reported at a certain distance from the stressful events. In this study, COVID-19 patients were still infectious, within a few days from the symptom onset. Thus, it might have been too early to detect, in this subgroup, signs of PTSD. A recent review and meta-analysis of psychiatric and neuropsychiatric presentations associated with SARS, MERS, and COVID-19 (5) showed that during the acute illness, common symptoms among hospitalized patients included confusion, depressed mood, anxiety, and insomnia. PTSD symptoms are commonly observed among patients in the postillness stage with frequent recall of traumatic memories, insomnia, and emotional lability, as confirmed by our results.

Although such cognitive and psychological effects of COVID-19 infection that are reported in this study still need to be better investigated in higher numbers of patients, our results showed that a high majority of recovered COVID-19 and post–COVID-19 patients present with cognitive dysfunctions.

Several factors might have been responsible for such impairments, including systemic inflammation, cerebrovascular changes, and the risk of developing ARDS, which has been highly associated with long-term cognitive impairment, especially in the domains of executive functions and psychomotor tasks (35). Moreover, such results might also have been related to the acute stress induced by patients clinical conditions, which might have, in turn, been related to the degree of invasiveness of oxygen therapy received in the acute phase of the disease (19).

Our data demonstrate the need to perform detailed investigation of cognitive functions in COVID-19 patients or in COVID-19 survivors in order to provide them with cognitive training and psychological support, as soon as possible. More data are also needed regarding the follow-ups of such patients to define the duration of these impairments. Our data already demonstrated that most patients who recovered in the post-COVID rehabilitation unit 1 month after the end of infection still presented with cognitive deficits, confirming the long-lasting duration of these neuropsychological COVID-19 symptoms. The term "long COVID" has been recently introduced to include those patients still suffering from various symptoms weeks or months after the end of infection (36, 37). Long-term symptoms of COVID-19 infections might thus need long-term rehabilitation, including cognitive training. Various modalities can be proposed to patients after home discharge, including telerehabilitation (37). In the last years, telemedicine and telerehabilitation have been progressively expending its fields of application (38, 39). Nowadays, and especially in response to the COVID-19 pandemic, the field of telerehabilitation must rapidly evolve in response to public health concerns and social distancing directives. Cognitive telerehabilitation refers to intensive home-based exercise under the supervision of a clinician via web (i.e., mobile phone with specific health apps or PC-based exercises), including the possibility to adapt the level of difficulty of the exercises to the patient's performance and the possibility to choose different sets of exercises based on the cognitive deficit These characteristics are fundamental to guarantee treatments in a safe manner, create activities tailored to the patient's needs, and improve social functioning and psychological well-being by also avoiding isolation (37).

In this study, we also found high levels of emotional disturbance related to COVID-19, supporting the idea that, during this pandemic, patients would also benefit from telecounseling and telepsychiatry, which refers to any type of psychological service performed over the internet (i.e., counseling, psychotherapy, psychoeducation) (40). Previous studies reported the psychosocial effects of the COVID-19 pandemic on patients, caregivers, and the general population, demonstrating significant increases of issues related to anxiety, depression, and posttraumatic stress syndrome (2–4, 6–8). For example, in China during COVID-19 outbreak, telemedicine mental health services have been used and prioritized for people who are at higher risk of developing severe health complications related to COVID-19, including COVID-19 patients and their families (39).

Some limitations of this study should be mentioned. First, the low number of evaluated patients limits the generalizability of results and findings; however, this represents that an exploratory study and further research are needed to clearly understand cognitive impairment in COVID-19 patients. Second, this study is cross-sectional, with a single cognitive and psychological

assessment of patients; it is necessary that future studies explore long-term cognitive end emotional consequences of COVID-19 infection using a longitudinal design. Third, to assess cognitive and emotional disturbances, we used standardized instruments characterized by good psychometric properties and widely used for research and clinical purposes, but the lack of a control group with subjects without COVID-19 infection confirmed by negative serologic tests could limit the interpretation of our results.

To conclude, our data showed extended neuropsychological dysfunctions in patients recovered in functional rehabilitation units for COVID-19 (in the subacute phase of the disease) or post–COVID-19 patients. These data confirmed the potential neurological and neuropsychological sequelae of SARS-CoV-2 infection. Moreover, as many patients with SARS need to recover in intensive care units, such traumatic experience might further increase the likelihood that these individuals may experience neuropsychological dysfunctions during and following their hospitalization. Thus, more attention should be given to the investigation of cognitive functions of COVID-19 patients in order to provide them with adequate cognitive training and subsequent follow-ups, even in the long term, in case of long–COVID-19 syndrome.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local Scientific Ethics Committee of Istituti Clinici Scientifici Maugeri Spa SB (protocol number: 2470) and San Raffaele Scientific Institute. Written consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

CP was responsible for writing the paper and experimental design. EF made data analysis and contributed to writing the paper. CV and MM contributed to experimental design, data collection, and the revisions of the paper. EH contributed to literature review, data collection, and writing the paper. FA was the supervisor of all the process of the research and the preparation of the paper, including comments, and revisions. 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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Physical Activity and Health-Related Quality of Life in Adults With a Neurologically-Related Mobility Disability During the COVID-19 Pandemic: An Exploratory Analysis

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Background: During the coronavirus-19 (COVID-19) pandemic various containment strategies were employed. Their impact on individuals with neurological conditions, considered vulnerable to COVID-19 complications, remains to be determined.

Objective: To investigate associations between physical activity and health-related quality of life outcomes in individuals with a neurological condition during government mandated COVID-19 restrictions.

Methods: An e-survey assessing fear of COVID-19, physical activity level and health-related quality of life outcomes (functional disability and pain, anxiety and depression, loneliness, fatigue, and vitality) was distributed to individuals with a neurologically-related mobility disability living in the United Kingdom. Open-ended questions were also included to contextualize barriers and facilitators to engage in physical activity during the COVID-19 pandemic. Gamma-weighted generalized linear models and tree-structured regression models were employed to determine the associations between physical activity and health-related quality of life.

Results: Of 199 responses, 69% reported performing less physical activity compared to pre-pandemic. Tree-structured regression models revealed that lower leisure-time physical activity was significantly associated ($p \leq 0.009$) with higher depression and fatigue, but lower vitality. The closure of leisure facilities and organized sport (27%) was the most commonly cited barrier to engage in physical activity, while 31% of participants mentioned concerns around their physical and mental health as a facilitator.

Conclusion: Our analysis identified homogenous subgroups for depression, fatigue, and vitality based specifically on leisure-time physical activity cut points, irrespective of additional demographic or situational characteristics. Findings highlight the importance of and need to safely promote leisure-time physical activity during the COVID-19 pandemic in this at-risk population to help support health-related quality of life.

Keywords: SARS-CoV-2, exercise, neurological disorders, well-being, pandemic, mental health

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the serious life-threatening coronavirus disease of 2019 (COVID-19). COVID-19 is a respiratory infectious disease that can cause considerable damage to various bodily systems (e.g., lungs, heart, and brain) and may even lead to death (1–3). The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020 and on March 11, 2020, the outbreak was declared a global pandemic (4). Due to its rapidly increasing prevalence and high reproduction rate (i.e., the number of secondary infections generated from one infected individual) (5), unprecedented restrictions were put into place to manage the spread of the disease. For example, during the first lockdown in the United Kingdom (UK), initiated on 23rd March 2020, people were only allowed to leave their home for food supplies and to receive medical treatment, as well as once per day for exercise. Schools were closed and people were instructed to work from home. Individuals with a neurologically-related mobility disability present with a heightened prevalence of comorbidities (e.g., respiratory dysfunction, cardio- and cerebrovascular diseases, systemic immune depression, and chronic inflammation and obesity), which can predispose them to poorer outcomes (e.g., mortality and mechanical ventilation) after developing SARS-CoV-2 (3). As such, those who were deemed vulnerable due to underlying health conditions were advised to shield (i.e., not to leave their home at all).

Even though these aforementioned precautions were deemed necessary to restrict virus spread, these extreme measures have resulted in unintended consequences. There is emerging evidence that the prevalence of mental health problems has increased during the COVID-19 pandemic (6–8). This is particularly evident in those with neurological diseases and associated physical health problems (9), who are often already at increased risk for experiencing mental health issues (10).

Physical activity (PA) is a behavioral factor, which has been shown to improve mental health in the general population, as well as in individuals with neurologically-related mobility disabilities (11, 12). Indeed, higher levels of PA have been related to better mental health during the COVID-19 pandemic (13, 14). However, as a result of the restrictions to contain the spread of COVID-19, opportunities for being physically active have been limited. This is accentuated for those who might rely on exercise facilities (e.g., gyms with accessible equipment) and additional support (e.g., carers, trainers) to be physically active, such as people with a neurologically-related mobility disability. In addition, people who were advised to shield also had less opportunity to go outside for PA. Compared to non-disabled people, a greater percentage of people with a disability indicated that COVID-19 had reduced their ability to be physically active (15), with 44% indicating that they did not feel they had the opportunity to be as active as they wanted to be. This was significantly higher compared to pre-pandemic, but also compared to non-disabled individuals (15).

Given the reported impact of PA on mental health and well-being in other population groups, the aim of this study was to explore the associations between PA and health-related quality of life (HRQoL) in individuals with a neurologically-related mobility disability during COVID-19 restrictions. We utilized free-text questions to also provide context around key barriers and facilitators to performing PA or exercise during initial lockdown restrictions, thereby providing additional insight into the knowledge and practices of participants.

METHODS

Participants and Sample Size

Owing to the exploratory nature of this study, no a-priori sample size was proposed. We sought to purposefully recruit a diverse range of participants with a neurologically-related mobility disability with the following inclusion criteria: individuals aged 18 years or over with a self-reported clinical diagnosis of a neurological condition, resulting in upper and/or lower limb mobility impairments. Ethical approval was obtained from the University of Birmingham Science, Technology, Engineering and Mathematics ethics committee (ERN_20-0689) (18/05/2020). All participants provided informed consent electronically prior to completing the e-survey.

Participant Recruitment

Individuals were recruited through social media advertisements promoted by various charities and organizations for neurological conditions in the UK (see Acknowledgments). Prospective participants received an information sheet, provided informed consent, and completed the 25 min e-survey questionnaire between May 28th and July 25th, 2020. During this time period the following response measures were implemented in the UK: stay-at-home orders for the general population but with partially relaxed measures (ended July 4th), stay-at-home

recommendations for risk groups or vulnerable populations (i.e., the elderly, people with underlying health conditions, individuals with physical disabilities) (ended July 5th), which transitioned into partially relaxed measures (16). Importantly, these data were collected before gyms and leisure facilities reopened and corresponded to a Government Response Stringency Index [GRSI: composite measure based on nine response indicators (17), rescaled to a value between 0 and 100, with 100 = strictest] of 64.4–73.2.

Survey Development and Outcome Measures

An e-survey was created on Online Surveys (formerly BOS) (see **Appendix A**). The open survey was designed, and results were analyzed and reported in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (18), see **Appendix B**. The survey could be completed on any electronic device with internet access. Survey structure and content were informed by a review of current evidence, including existing validated patient reported outcome measures (PROMs) and author expertise (TN, NH, SF, and JV). The survey comprised primarily closed questions with open ended questions for additional information where appropriate e.g., challenges, facilitators, and barriers. The survey was developed to capture the following:

1. general participant demographics (e.g., age, sex, and ethnicity) and current living situation to mitigate the risk of catching COVID-19 [e.g., self-imposed isolation/shielded (considered at-risk), isolation due to government legislation (e.g., working from home or furloughed), practicing social distancing, none of the above or other],
2. clinical diagnosis (neurological condition, time since diagnosis, mobility device used, and additional information where appropriate),
3. the degree of functional disability and pain, assessed via the Health Assessment Questionnaire Standardized Disability Index (HAQ-SDI) (19) and 11-point numerical rating scale (20), respectively,
4. PA and sedentary behavior, determined using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) (21). Briefly, the main outputs from this questionnaire are energy expenditure [metabolic equivalents (METs) h/d] for leisure time physical activities (LTPA), housework and occupational activities, as well as total energy expenditure. These values are obtained by multiplying the average hours per day spent performing certain activities by a MET value indicative of the intensity of each activity. Participants were also asked how their PA levels have changed compared to pre-pandemic. Responses were recorded using a five-point Likert scale (22) to assess to what extent participants agree ("slightly more," "considerably more") or disagree ("slightly less, considerably less") with the question, with a neutral option in-between ("about the same").
5. fear of COVID-19 score, determined via the validated Fear of COVID-19 Scale (23),
6. loneliness, determined via the UCLA Loneliness Scale (24),
7. subjective vitality (eudemonic well-being), quantified via the Subjective Vitality Scale (SVS) (25),
8. symptoms of fatigue, determined via the Fatigue Severity Scale (FSS) (26),
9. the prevalence of anxious and depressive symptoms, assessed via the Hospital Anxiety and Depression Scale (HADS) (27),
10. experiences during the COVID-19 pandemic, open ended questions identifying barriers and facilitators to perform exercise or physical activity and specific challenges encountered at this moment in time.

More detailed information on the validated assessment tools and e-survey used to quantify the above outcome measures can be found in **Appendix C**.

Data Preparation and Analysis

Initially, the type and pattern of missing data was assessed. Briefly, we tested the hypothesis that the missing data is missing at random (MAR) and visually explored the pattern of missing data using the R package finalfit. Visual inspection of the density- and QQ-plots as well as with the Shapiro-Wilk test of normality followed. As data was not normally distributed for any of the variables (**Supplementary Table 1**: density and qq-plots for all variables are located at https://github.com/jutzca/COVID-19_Excercise_Neurological_Conditions/tree/main/Figures), non-parametric tests were employed for the statistical analyses. Information related to participant demographics and neurological condition are presented with descriptive statistics [median, interquartile range (IQR), Q1, Q3, percentages].

To address the question if PA and HRQoL outcomes were associated during the COVID-19 pandemic and consequential measures, Gamma-weighted generalized linear models (GLMs) were employed. The Gamma weights were chosen to account for the skewed data distribution of the independent variables. Separate models were designed for each dependent variable, namely HAQ-SDI, fatigue, anxiety, depression, subjective vitality, pain, and change in PA. Independent variables consisted of: predominant mobility aid used, PASIPD total score and sub scores (e.g., LTPA score, household activity score, and work-related activity score), sedentary hours, GRIS, fear of COVID-19, and loneliness. Covariates included age, sex, neurological condition, and duration of condition. *Post-hoc* pairwise comparisons were Bonferroni corrected to account for multiple comparisons (28).

Additionally, we aimed to divide the initial heterogeneous patient population into successively disjoint and more homogeneous pairs of subgroups with regard to the clinical endpoint of interest. To this end, we performed an unbiased recursive partitioning technique called conditional inference tree (URP-CTREE), which is a tree-structured regression model based on sequential tests of independence between predictors and a specified clinical endpoint (29). Importantly, URP does not assume linearity, considers all possible interactions between the independent variables, handles multicollinearity, and, provides

distinct cut-offs—that is, specific values of a variable that infers a given outcome (29).

Diverging stacked bar charts were used to visualize the Likert scale data. Kruksal-Walis tests were employed to test if there is a difference in distribution of the responses between sexes, neurological conditions, and mobility aid, respectively. Posteriori content analysis was used for data generated from open ended questions (challenges, barriers, and facilitators) involving two researchers (NH, JV). This resulted in additional themes/categories which were quantified with calculation of frequencies (30). Participant quotes are included to further illustrate participants free text responses to these open-ended questions (**Appendix C**).

R Statistical Software Version 3.5.2 for Mac Os was used for the analysis and creating the figures.

RESULTS

Cohort Summary

A total of 199 individuals completed the e-survey. The cohort median age was 56.0 years (Q1–Q3: 44.0–65.0 years), 142 (71.4%) were female, and 188 (94.5%) were Caucasian whites. The most frequent neurological condition was multiple sclerosis ($n = 67$, 33.7%), followed by Parkinson's disease ($n = 36$, 18.1%), and spinal cord injury (SCI) ($n = 32$, 16.1%). Almost half of the participants reported to be in self-imposed isolation/shielding (i.e., considered at-risk) ($n = 99$, 49.7%), while the remainder were practicing social distancing ($n = 66$, 33.2%), were in isolation due to government legislation (i.e., working from home or furloughed) ($n = 25$, 12.6%), or reported none/other measure ($n = 9$, 4.5%). Detailed cohort characteristics and descriptive statistics for HRQoL outcomes are provided in **Tables 1**, **2**, respectively.

Survey Data: Response Rate and Missing Data

The response rate was excellent with only 0.1% ($n = 12$ observations across 10 variables) unanswered questions or parts thereof (**Supplementary Table 2**). Our analysis revealed that the missing data do have a relationship with other variables in the dataset (e.g., strenuous sport hours per day AND strenuous sport score), but the actual values that were missing are random (i.e., MAR) (**Supplementary Figure 1**). As a consequence, we omitted the participants in whom the variable of interests were missing for our analysis as we had sufficient power with complete cases to examine the relationships of interest.

Physical Activity and Sedentary Behavior

As shown in **Figure 1**, 69% participants reported performing less (ranging from considerably to slightly less) PA compared to pre-COVID times and these findings were independent of sex (**Figure 1A**), neurological condition (**Figure 1C**), and mobility aid used (**Figure 1C**). There was no significant difference in the

TABLE 1 | Cohort summary.

	Overall ($N = 199$)
Sex, *n* (%)	
Female	142 (71.4%)
Male	56 (28.1%)
Prefer not to disclose	1 (0.5%)
Age (years)	
Median [Q1, Q3]	56.0 [44.0, 65.0]
Ethnicity, *n* (%)	
Asian/Asian British	2 (1.0%)
Black/African/Caribbean/Black British	1 (0.5%)
Caucasian/White	188 (94.5%)
Mixed/multiple ethnic groups	4 (2.0%)
Other	4 (2.0%)
Condition	
Cerebral palsy	
n (%)	11 (5.5%)
Median duration [Q1, Q3] (years)	32.0 [29.5, 40.2]
Fibromyalgia, chronic fatigue syndrome, CRPS	
n (%)	15 (7.5%)
Median duration [Q1, Q3] (years)	6.25 [5.75, 15.2]
Muscular dystrophy, neuromuscular diseases	
n (%)	22 (11.1%)
Median duration [Q1, Q3] (years)	21.3 [12.3, 30.9]
Multiple sclerosis	
n (%)	67 (33.7%)
Median duration [Q1, Q3] (years)	13.5 [6.75, 24.5]
Parkinson's disease	
n (%)	36 (18.1%)
Median duration [Q1, Q3] (years)	4.75 [2.65, 8.31]
Spinal cord injury	
n (%)	32 (16.1%)
Median duration [Q1, Q3] (years)	9.75 [5.00, 18.0]
Other (stroke, ataxia's, spina bifida, dystonia)	
n (%)	16 (8.0%)
Median duration [Q1, Q3] (years)	15.5 [7.00, 30.7]
Mobility aid, *n* (%)	
Manual wheelchair	35 (17.6%)
Power wheelchair	20 (10.1%)
Mobility scooter	6 (3.0%)
Zimmer frame	12 (6.0%)
Walking sticks	43 (21.6%)
Crutches	10 (5.0%)
None	70 (35.2%)
Other	3 (1.5%)
Situation, *n* (%)	
Self-imposed isolation/shielded (considered at-risk)	99 (49.7%)
Isolation due to government legislation	25 (12.6%)
Practicing social distancing	66 (33.2%)
None of the above	5 (2.5%)
Other	4 (2.0%)

TABLE 2 | Summary of outcomes stratified by neurological conditions.

	Cerebral Palsy (*n* = 11)	Fibromyalgia, Chronic fatigue syndrome, CRPS (*n* = 15)	Muscular dystrophy, neuromuscular diseases (*n* = 22)	Multiple Sclerosis (*n* = 67)	Parkinson's disease (*n* = 36)	Spinal Cord Injury (*n* = 32)	Other (*n* = 16)	Overall (*n* = 199)
HAQ SDI								
Median [Q1, Q3]	1.63 [1.22, 1.75]	1.38 [1.00, 1.88]	2.00 [1.75, 2.25]	1.43 [1.00, 1.94]	0.57 [0.37, 1.14]	1.69 [1.47, 2.16]	1.81 [1.47, 2.00]	1.50 [1.00, 2.00]
Pain								
Median [Q1, Q3]	4.00 [2.50, 5.50]	6.00 [3.50, 8.00]	5.50 [3.25, 7.00]	3.00 [1.00, 6.00]	3.00 [1.00, 5.00]	6.00 [2.75, 7.25]	6.00 [2.00, 8.00]	4.00 [2.00, 7.00]
Fear of COVID 19 SCORE								
Median [Q1, Q3]	19.0 [15.0, 20.5]	18.0 [12.0, 22.5]	16.0 [14.3, 22.0]	19.0 [14.5, 22.0]	16.0 [11.8, 20.3]	17.0 [10.8, 22.3]	17.0 [14.0, 19.3]	17.0 [13.0, 22.0]
UCLA loneliness SCORE								
Median [Q1, Q3]	50.0 [39.0, 52.5]	47.0 [38.5, 51.0]	42.0 [30.8, 53.5]	45.0 [35.0, 56.5]	40.0 [33.5, 45.5]	42.5 [27.8, 54.3]	58.5 [49.3, 62.0]	44.0 [33.5, 55.0]
SVS SCORE								
Median [Q1, Q3]	3.00 [2.67, 3.42]	2.17 [1.59, 2.83]	2.67 [1.75, 3.63]	3.17 [1.67, 4.17]	3.33 [2.13, 3.87]	3.34 [2.12, 4.17]	1.83 [1.59, 2.54]	3.00 [1.67, 4.00]
FSS SCORE								
Median [Q1, Q3]	40.0 [30.5, 53.5]	59.0 [56.0, 62.5]	51.0 [35.5, 58.0]	50.0 [39.5, 58.0]	42.5 [31.8, 46.3]	47.0 [26.8, 62.0]	49.5 [41.8, 55.3]	48.0 [37.0, 58.0]
Global fatigue								
Median [Q1, Q3]	6.00 [4.00, 7.00]	4.00 [1.50, 6.50]	5.00 [3.00, 7.00]	5.00 [3.00, 8.00]	5.50 [4.00, 8.00]	6.50 [3.00, 8.00]	4.00 [2.00, 6.00]	5.00 [3.00, 8.00]
Anxiety SCORE*								
Median [Q1, Q3]	9.00 [6.00, 12.0]	10.0 [6.50, 14.0]	5.00 [4.00, 8.75]	7.00 [5.00, 11.0]	6.50 [5.00, 9.00]	7.50 [2.00, 11.0]	9.50 [7.25, 13.0]	7.00 [5.00, 11.0]
Normal, *n* (%)	4 (36.4%)	5 (33.3%)	13 (59.1%)	37 (55.2%)	23 (63.9%)	16 (50.0%)	4 (25.0%)	102 (51.3%)
Borderline abnormal, *n* (%)	3 (27.3%)	3 (20.0%)	6 (27.3%)	12 (17.9%)	7 (19.4%)	6 (18.8%)	5 (31.2%)	42 (21.1%)
Abnormal, *n* (%)	4 (36.4%)	7 (46.7%)	3 (13.6%)	18 (26.9%)	6 (16.7%)	10 (31.2%)	7 (43.8%)	55 (27.6%)
Depression SCORE*								
Median [Q1, Q3]	6.00 [4.00, 7.00]	9.00 [6.00, 10.5]	6.00 [5.00, 10.0]	8.00 [5.00, 11.0]	5.00 [3.00, 7.00]	7.00 [2.75, 11.0]	10.5 [6.50, 12.5]	7.00 [4.00, 10.0]
Normal, *n* (%)	10 (90.9%)	6 (40.0%)	13 (59.1%)	33 (49.3%)	29 (80.6%)	17 (53.1%)	5 (31.2%)	113 (56.8%)
Borderline abnormal, *n* (%)	1 (9.1%)	5 (33.3%)	4 (18.2%)	16 (23.9%)	5 (13.9%)	6 (18.8%)	3 (18.8%)	40 (20.1%)
Abnormal, *n* (%)	0 (0%)	4 (26.7%)	5 (22.7%)	18 (26.9%)	2 (5.6%)	9 (28.1%)	8 (50.0%)	46 (23.1%)

HAQ SDI, Health Assessment Questionnaire - Standard Disability Index; FSS, Fatigue Severity Scale; SVS, Subjective Vitality Scale, UCLA, University of California Los Angeles.

**Scores across the respective 7 items for anxious and depressive symptoms from the Hospital Anxiety and Depression Scale (HADS) were summed together and the following scoring thresholds utilized to characterize participants: 0–7 = Normal, 8–10 = Borderline abnormal (borderline case), 11–21 = Abnormal (case).*

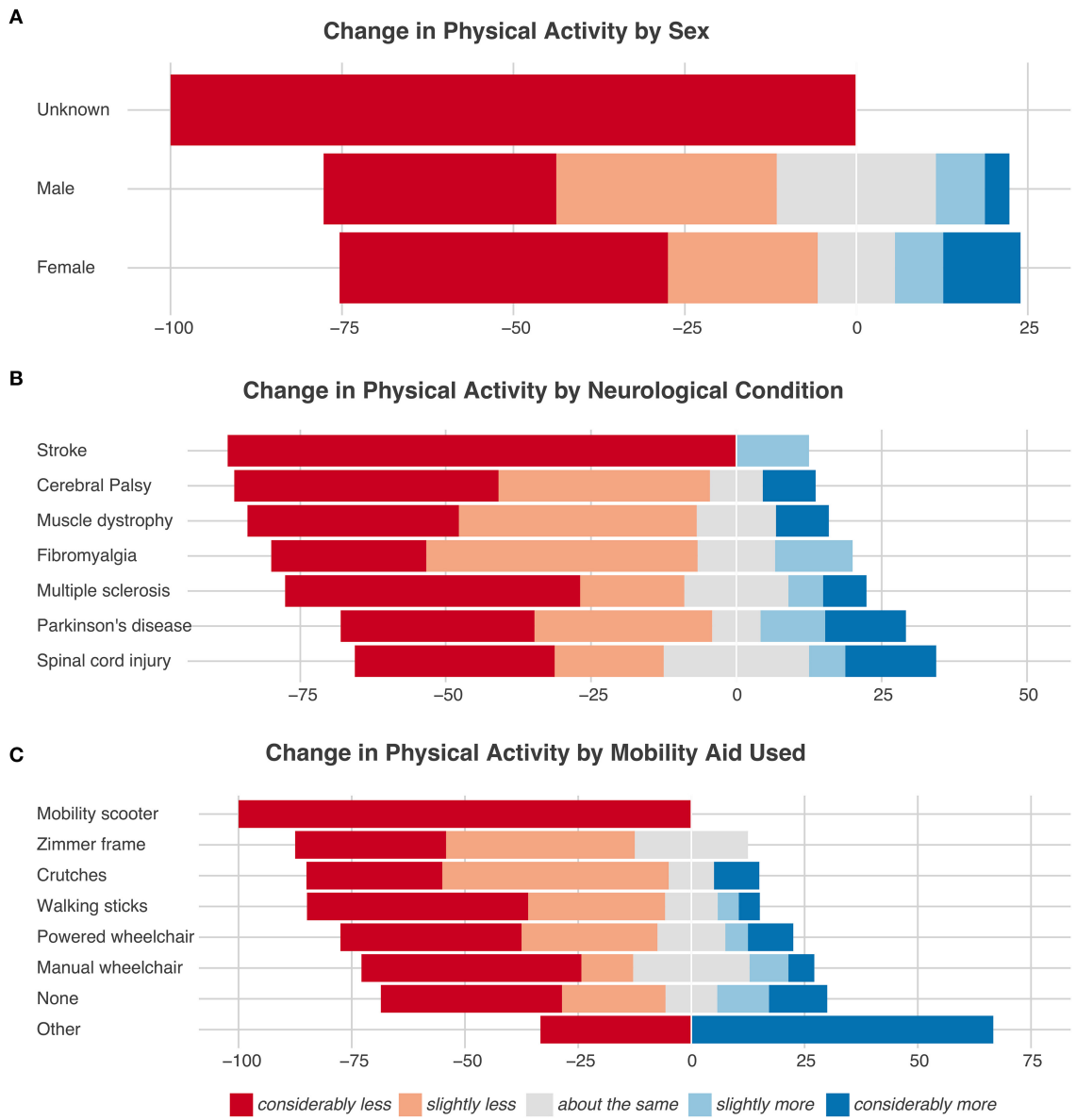


FIGURE 1 | Change in physical activity stratified based on sex **(A)**, neurological condition **(B)**, and mobility aid used **(C)**.

distribution of responses between sexes (chi-squared = 2.80, *df* = 2, $p = 0.25$), neurological conditions (chi-squared = 2.24, *df* = 6, $p = 0.90$), and mobility aid used (chi-squared = 8.22, df = 7, $p = 0.31$). The median daily time spent performing sedentary behaviors was 4.29 [Q1: 2.57, Q3: 4.29] h/day. The median daily time spent performing moderate and strenuous sports were both 0 [Q1: 0, Q3: 0]. Furthermore, participants reported to be walking/wheeling [median = 0.11 (Q1: 0, Q3: 0.75) h/day] or performing light sporting activities [median= 0.11 (Q1: 0, Q3: 0.43) h/day] for a small duration per day. **Table 3** provides an overview of the hours spent per day for all the activities reported.

Impact of COVID-19 on Physical Activity and Health-Related Quality of Life

The GLMs revealed significant associations between HAQ-SDI and the situation, neurological condition, and mobility aid used (**Supplementary Table 3**). Similarly, the degree of pain was associated with the neurological condition and the situation (**Supplementary Table 4**). Moreover, a significant relationship between fatigue and the LTPA score was found (**Supplementary Table 5**). No significant associations were found for depression (**Supplementary Table 6**), anxiety (**Supplementary Table 7**), loneliness (**Supplementary Table 8**) or vitality (**Supplementary Table 9**).

TABLE 3 | Summary of physical activity.

	Overall (N=199)
Sedentary [hours/day]	
Median [Q1, Q3]	4.29 [2.57, 4.29]
0 h, *n* (%)	2 (1.0%)
Walking wheeling [hours/day]	
Median [Q1, Q3]	0.11 [0, 0.75]
0 h, *n* (%)	52 (26.1%)
Light sport [hours/day]	
Median [Q1, Q3]	0.11 [0, 0.43]
Missing	1 (0.5%)
0 h, *n* (%)	93 (46.7%)
Moderate sport [hours/day]	
Median [Q1, Q3]	0 [0, 0]
0 h, *n* (%)	162 (81.4%)
Strenuous sport [hours/day]	
Median [Q1, Q3]	0 [0, 0]
Missing	2 (1.0%)
0 h, *n* (%)	161 (80.9%)
Exercise [hours/day]	
Median [Q1, Q3]	0 [0, 0.25]
0 h, *n* (%)	116 (58.3%)
Light housework [hours/day]	
Median [Q1, Q3]	0.32 [0.11, 1.29]
0 h, *n* (%)	24 (12.1%)
Heavy housework [hours/day]	
Median [Q1, Q3]	0 [0, 0.11]
Missing	1 (0.5%)
0 h, *n* (%)	117 (58.8%)
Home repairs [hours/day]	
Median [Q1, Q3]	0 [0, 0]
Missing	1 (0.5%)
0 h, *n* (%)	160 (80.4%)
Yard work [hours/day]	
Median [Q1, Q3]	0 [0, 0.11]
0 h, *n* (%)	146 (73.4%)
Gardening [hours/day]	
Median [Q1, Q3]	0 [0, 0.250]
0 h, *n* (%)	103 (51.8%)
Caring [hours/day]	
Median [Q1, Q3]	0 [0, 0.32]
Missing	1 (0.5%)
0 h, *n* (%)	134 (67.3%)
Work related activity [hours/day]	
Median [Q1, Q3]	0 [0, 0]
0 h, *n* (%)	173 (86.9%)
PASIPD SCORE [MET h/d]	
Median [Q1, Q3]	7.18 [2.87, 14.9]
LTPA SCORE (MET h/d)	
Median [Q1, Q3]	2.83 [0.61, 6.43]
Household activity SCORE, (MET h/d)	
Median [Q1, Q3]	2.41 [0.61, 6.93]
Work related activity SCORE, (MET h/d)	
Median [Q1, Q3]	0 [0, 0]

LTPA, Leisure Time Physical Activity; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities.

Taking into account interactions between variables, the URP-CTREE illustrates that younger participants (<60 years of age) reported higher anxiety scores (**Figure 2A**), while older participants (≥58 years of age) felt lonelier (**Figure 2B**). Moreover, higher depression and fatigue scores were associated with lower LTPA scores [depression: cut off: ≤2.25 MET h/d (**Figure 2C**); fatigue: cut off: ≤3.66 MET h/d (**Figure 2D**)]. In contrast, higher vitality scores were associated with higher LTPA scores (cut off: <3.26 MET h/d, **Figure 2E**). Higher pain scores (mean = 5.26, $n = 85$) were reported by participants with fibromyalgia, muscular dystrophy, stroke, or SCI compared to those with cerebral palsy, multiple sclerosis, or Parkinson's disease (mean = 3.45, $n = 114$; **Figure 2F**). Moreover, the HAQ-SDI score was the lowest for participants without mobility aids and the highest for participants using any mobility aid AND a household activity score of ≤0.61 MET h/d (**Figure 2G**). Lastly, the PASIPD score was highest for participants who were not using any mobility aids (mean = 2.05 MET h/d, $n = 45$). Participants who used any kind of mobility aid AND had no restriction, self-imposed isolation (i.e., considered at risk), or social distancing reported the lowest PASIPD score (mean = 1.44 MET h/d, $n = 37$) (**Figure 3**).

Challenges, Barriers, and Facilitators: Results From Free Text Data

The response rates to the optional free text questions related to challenges, barriers, and facilitators were high with 99.0% (197/199), 98.5% (196/199), and 96.5% (192/199), respectively. Almost half the participants (n=91/197) reported a lack of "normal life/lockdown" as a challenge during this period, with around a quarter missing or not seeing family ($n = 44/197$). Additionally, "fear/uncertainty" or "isolation" were reported as a challenge by 30 participants.

"Closed gyms/pool/organized sport" was the most commonly reported barrier to engage in PA by participants ($n = 53/196$), with a "lack of motivation" being second ($n = 30/196$). Similar frequencies were reported for barriers relating to "fatigue" ($n = 25/196$), "Leaving home" ($n = 24/196$), "Lack of equipment/space/support" ($n = 24/196$) and "Fear/including hurting/pain" ($n = 22/196$).

In terms of facilitators to engage in PA, almost a third of participants reported factors associated with well-being to be facilitating; "Health (mental and physical)/weight" ($n = 60/192$). Beyond this, similar frequencies were evident for "Nothing/same as ever" ($n = 34/192$), "Family/Healthcare practitioner support" ($n = 30/192$), "Online classes" ($n = 28/192$), and "Leaving the house/fresh air/garden" ($n = 27/192$).

Representative participant quotes to illustrate themes/categories derived from the open-ended questions can be found in **Appendix C**.

DISCUSSION

This study demonstrates the detrimental impact of the COVID-19 pandemic and ensuing restrictions on PA behaviors in a heterogeneous sample of adults with a neurologically-related

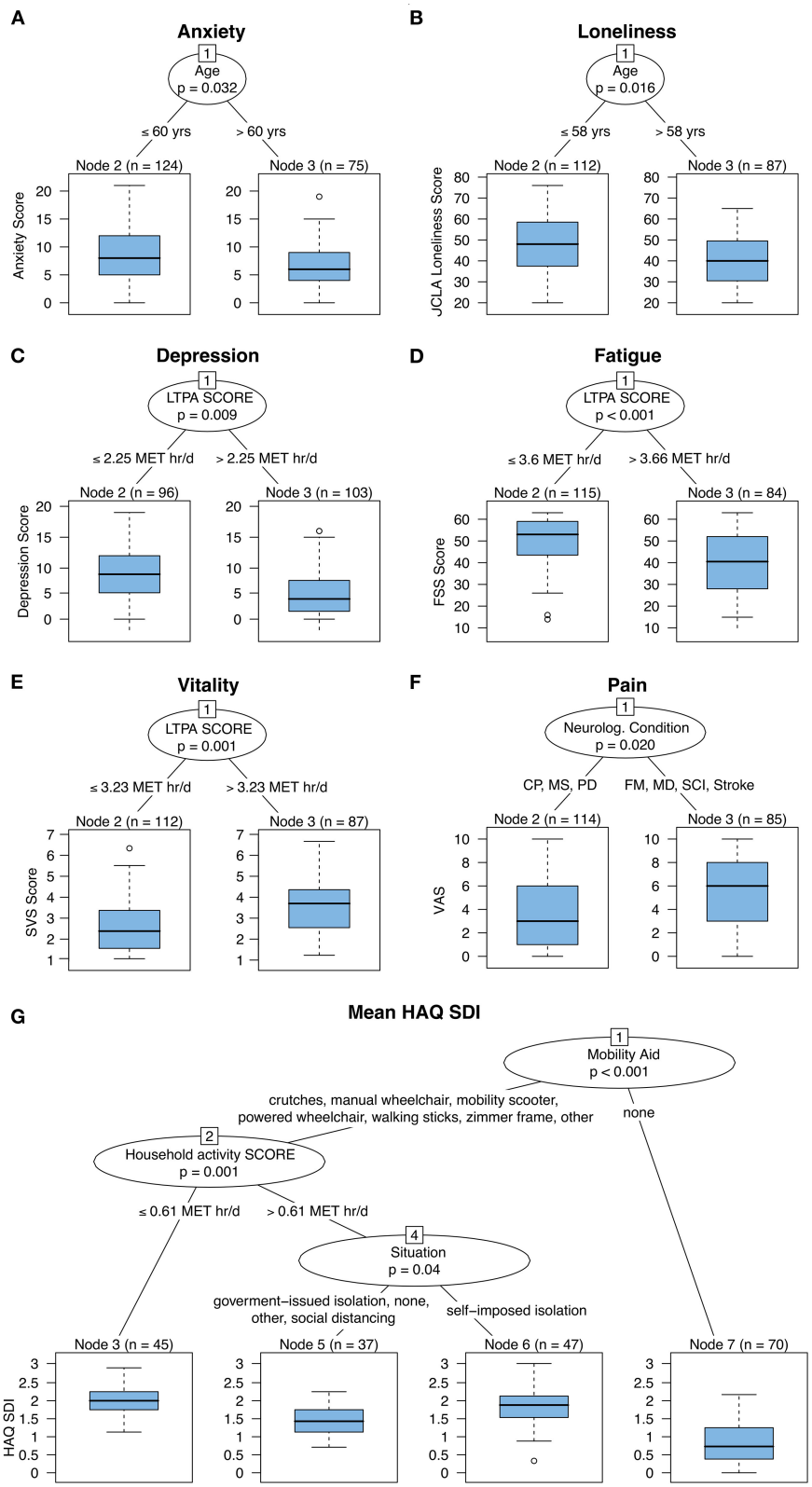


FIGURE 2 | Unbiased recursive partitioning with conditional inference tree (URP-CTREE) for anxiety **(A)**, loneliness **(B)**, depression **(C)**, fatigue **(D)**, vitality **(E)**, pain **(F)**, and HAQ SDI **(G)**. The initial cohort comprises 199 participants with neurologically-related mobility disabilities. Across outcomes, LTPA score and age were

(Continued)

FIGURE 2 | the most common discriminators. CP, cerebral palsy; FM, Fibromyalgia, chronic fatigue syndrome & chronic pain syndrome; FSS, fatigue severity scale; HAQ SDI, health assessment questionnaire standardized disability index; LTPA, leisure time physical activity; MD, muscular dystrophy & neuromuscular diseases; MET, metabolic equivalents; MS, multiple sclerosis; PD, Parkinson's disease; SCI, spinal cord injury; Stroke (other, ataxia's, spina bifida, dystonia); SVS, subjective vitality scale; VAS, visual analog scale.

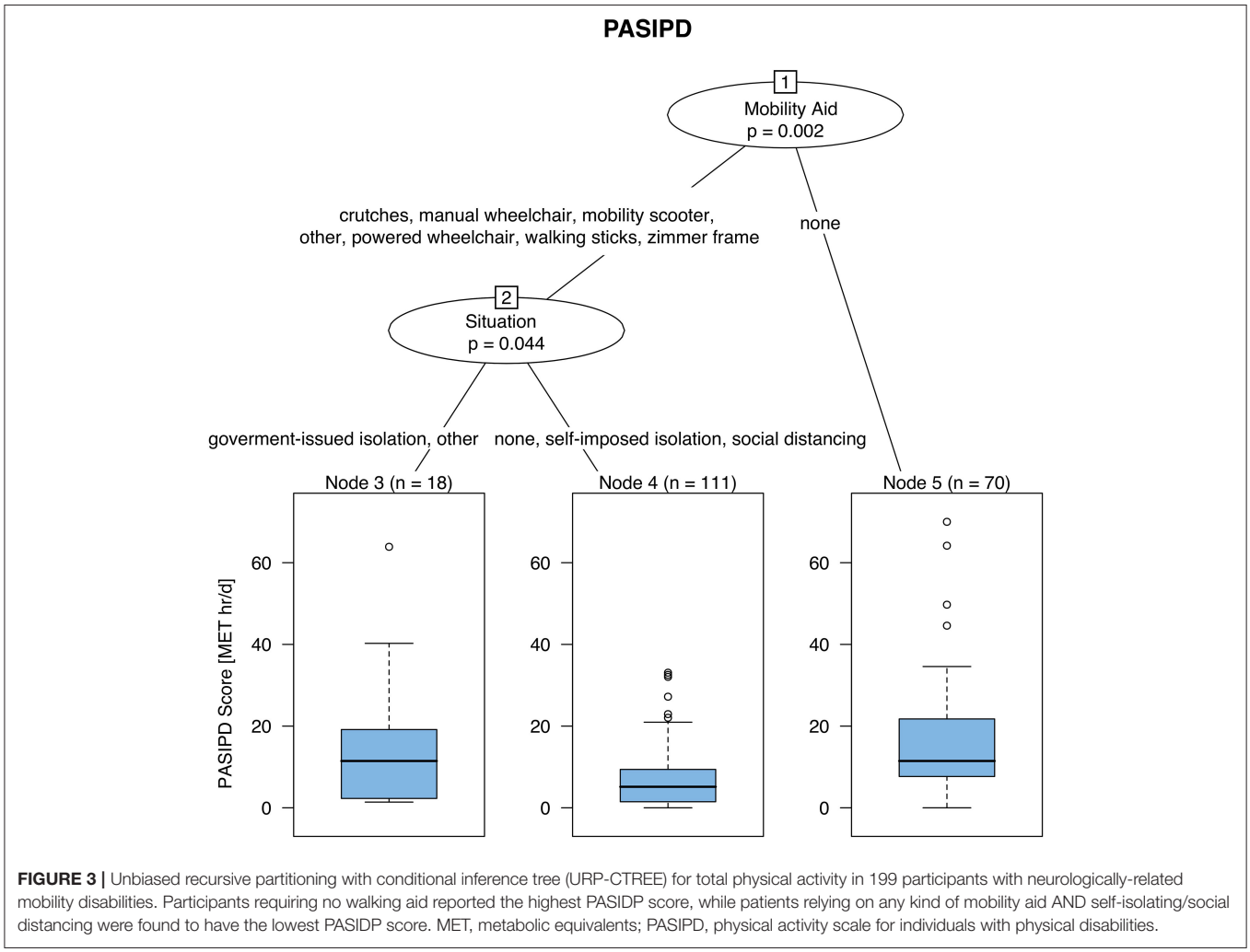


FIGURE 3 | Unbiased recursive partitioning with conditional inference tree (URP-CTREE) for total physical activity in 199 participants with neurologically-related mobility disabilities. Participants requiring no walking aid reported the highest PASIDP score, while patients relying on any kind of mobility aid AND self-isolating/social distancing were found to have the lowest PASIDP score. MET, metabolic equivalents; PASIPD, physical activity scale for individuals with physical disabilities.

mobility disability living in the UK. Our findings attempt to address a key research gap identified by a recent review (31), namely the lack of early research investigating the impact of COVID-19 on individuals with a physical disability. Using a comprehensive battery of valid and reliable PROMs we revealed that LTPA was significantly associated with HRQoL outcomes. Specifically, higher levels of LTPA were related to lower depression and fatigue scores, as well as higher subjective vitality. The closure of leisure facilities and lack of motivation were deemed key barriers to engage in PA/exercise, while concerns around health (both physical and mental) was reported as a key facilitator by approximately a third of participants. Collectively these free text data provided additional insight into the knowledge and experiences of this population during the COVID-19 pandemic.

Self-Reported Physical Activity Behaviors

A scoping review indicated that PA levels in the general population were reduced during the pandemic (32). This is perhaps unsurprising given gyms and swimming pools were closed, and sports or other exercise classes were all stopped. Consequently, the only opportunities for being active were home-based exercise or outdoor PA in the local area, such as walking or cycling. However, individuals with a neurologically-related mobility disability may represent the archetypal patient population of concern during the COVID-19 pandemic. Even before the introduction of government legislation to tackle this pandemic, these individuals reported low levels of PA and multiple obstacles to perform exercise, despite the interest to do so (33, 34). Reported barriers include a perceived low return on physical investment, lack of accessible facilities,

unaffordable equipment, no personal assistance and fears regarding safety and injury (35, 36). Such environmental factors were noted in participants responses to open ended questions (**Appendix C**). Seemingly, COVID-19 restrictions have magnified the environmental and personal barriers commonly experienced by individuals with a disability to perform PA.

Worryingly, sixty-nine percent of our middle-aged cohort reported performing less PA compared to pre-pandemic. Cross-sectional data ($n = 125$) collected during the same time frame in the UK reported that 61% of children and young adults with physical and/or intellectual disabilities were less physically active as a result of lockdown restrictions (37). Outside of the UK, decreased PA was observed in 44% of Parkinson's disease patients in Japan (data collected over a wider timeframe between June and December 2020) (38). The COVID-19 quarantine in Italy significantly decreased total weekly PA levels (quantified via the International Physical Activity Questionnaire Short-Form before and during) in a sample of participants with neuromuscular disease ($n = 149$). The average total PASIPD score (median: 7.18 MET h/day) reported in this current study is less than half that of previous studies (19.40–20.50 MET h/day), which assessed middle-aged individuals with neurological conditions and a similar disability severity outside of a global pandemic (21, 39, 40). A similar total PASIPD score (mean: 7.95 ± 7.91 MET h/day) was reported during lockdown in Spain for twenty individuals with motor-complete SCI (reduced from 26.36 ± 19.09 MET hr/day pre-lockdown) (41). This reduction was mainly explained by a substantial reduction in the LTPA sub-score. Consequently, our results and others highlight that the low levels of PA commonly reported in this population have been further exacerbated by strict lockdown protocols and the closure of non-essential support services.

To provide further context, between 58.3 and 81.0% of our participants reported zero h/day for performing activities above the intensity threshold necessary to improve fitness/health (**Table 3**: moderate or strenuous sport and recreation, exercise for strength and endurance, heavy housework). These data imply that during the COVID-19 pandemic, the majority of individuals with a neurologically-related mobility disability were unable to achieve volumes of moderate-intensity PA (>150 min per week) sufficient to promote substantial health benefits for disabled adults (42). When investigating factors that were linked with the total PASIPD score reported at this time (**Figure 3**), the URP-CTREE split was initially for mobility aid usage followed by COVID-19 living situation. Consequently, participants who used any kind of mobility aid and considered themselves at-risk (i.e., self-imposed isolation/shielded), no restriction or practicing social distancing reported the lowest total PASIPD score. It is therefore intuitive to propose that individuals with the greatest mobility impairment or disability severity and greatest perceived vulnerability, irrespective of other factors (e.g., age, specific neurological condition, sex), require extra support to perform PA during this challenging time.

Physical Functioning and Health-Related Quality of Life

The median HAQ-SDI scores of our cohort (1.5) indicate the presence of disability (>1). Perhaps unsurprisingly, the HAQ-SDI score was lowest for participants without mobility aids but highest for individuals who used any mobility aid and performed less household PA. A subjective worsening of neurological symptoms has been reported in individuals with Parkinson's disease (38, 43) amyotrophic lateral sclerosis (ALS) (44) and cerebellar ataxias (45) as a result of COVID-19 restrictions, increasing the socio-economic burden of these neurological conditions (46). Indeed, the restricted access to healthcare services (rehabilitation, community and home-based support) during the pandemic (31) for disabled individuals may detrimentally impact mobility and function. In ALS patients during the pandemic, a greater mobility impairment and rehabilitation therapy suspension were significant predictors of anxiety symptom severity (44). Thirty-one percent of participants cited concerns around "Health (mental and physical)/weight" as key motivators/facilitators to be physically active, whereas, others voiced concerns about their rapidly declining physical status ("I have declined physically quite rapidly and the exercises I could do at home at the beginning of the lockdown are now impossible" P101). This is particularly worrisome as individuals with neuromuscular disabilities were already predisposed to severe deconditioning (e.g., reduced strength and fitness) and significant health risks (e.g., increased sarcopenia, obesity, and cardiometabolic disease risk factors) due to low rates of PA (35). It is apparent that COVID-19 confinement strategies can further compound these aforementioned health risks (47, 48) and the presence of these comorbidities may also increase the risk of poorer outcomes after developing COVID-19 (3). The pandemic-related declining fitness and functional status should be closely considered by practitioners when resuming rehabilitation and exercise interventions in individuals with neurological conditions.

Psychological Well-Being

A survey from Activity Alliance showed that compared to non-disabled people, people with a physical disability were significantly more likely to be anxious, feel lonely, be less happy and generally more negative about the future during COVID-19 (15). Different factors have been shown to contribute to negative mental health, such as reduced social interactions, concerns about contracting the disease, as well as concerns about not being able to access appropriate healthcare when needed (49, 50). Indeed, participants reported missing or not seeing family (22%) and "fear/uncertainty" or "isolation" (both 15%) as being especially challenging during the COVID-19 pandemic. Despite being considered a vulnerable cohort, the fear of COVID-19 score was not higher than those reported in the general population (17 vs. 15.6–18.3) (51). Our analyses also indicated fear of COVID-19 score was not associated with any HRQoL outcomes. In line with previous reports, our analysis uncovered that younger participants reported higher anxiety scores while older participants felt lonelier (52, 53). It is possible that older adults were less affected by personal and emotional problems during this time (i.e., perhaps retired, therefore less concerned about job security and financial worries). The increased loneliness may be due to older adults shielding for a longer period of time and therefore not experiencing direct contact with family members or friends. Additionally, older adults may be less likely

to successfully utilize digital technology (such as online social media and video chat platforms), which may increase social connectedness and mitigate loneliness (54).

A systematic review unequivocally stated that the COVID-19 pandemic and ensuing containment strategies has caused psychological distress (55). However, conflicting data suggest no worsening in symptoms of anxiety or depression in individuals with a neurological condition as a result of COVID-19 restrictions (56, 57), implying a level of resilience. Our findings indicated that 27 and 23% of our cohort were experiencing abnormal symptoms of anxiety and depression, respectively. Comparative cross-sectional HADS data, collected between July to September 2020 among individuals with cerebellar ataxia in Cuba, demonstrated a similar incidence of anxiety (21%) and depression (23%) (45). These rates of anxiety (17%) and depression (20%) are not too dissimilar to those reported prior to the COVID-19 pandemic for 253 individuals with multiple sclerosis (58). While this is encouraging, studies in patients with spinocerebellar and cerebellar ataxia have implied greater levels of anxiety and depression relative to controls during the COVID-19 pandemic (45, 59). Therefore, cultivating healthy coping strategies and resilience during periods of uncertainty in individuals with neurological conditions are essential to improve psychological well-being.

Associations Between Leisure-Time Physical Activity and Psychological Well-Being

It has been argued that the aforementioned changes in HRQoL are driven by social isolation, considerable lifestyle alterations and financial and occupational health concerns triggered by the pandemic (55). One notable lifestyle alteration and potential coping strategy that we have shown to be detrimentally impacted in our cohort due to COVID-19 restrictions is PA. Indeed, multiple studies have identified associations between PA and mental health during the COVID-19 pandemic (13, 14, 60). Structural equation modeling in a mixed sample (multiple sclerosis, n = 497 and controls, $n = 348$) of Italian adults during the COVID-19 lockdown revealed exercise is a valuable tool in managing depressive symptoms (9). We demonstrate evidence that LTPA is associated with symptoms of depression, fatigue and subjective vitality in individuals with a neurologically-related mobility disability. These findings extend the associations of PA beyond mental health pathologies (i.e., depression) to other holistic psychological well-being outcomes (subjective vitality and fatigue) that are often ignored. Subjective vitality is a measure of eudaimonic well-being and is a positive psychological state that has implications for optimal functioning (25). Fatigue is commonly reported by individuals with neurological conditions and it has a substantial detrimental impact on HRQoL (61). Interestingly, homogeneous subgroups were defined with better HRQoL outcomes corresponding to achieving a relatively small LTPA energy expenditure (depression >2.25 MET h/d, fatigue: >3.66 MET h/d, vitality: >3.26 MET h/d). Individuals with physical disabilities should be encouraged to perform these corresponding volumes of LTPA to support HRQoL during the pandemic. However, the causative impact of these LTPA recommendations on HRQoL in this population remains to be longitudinally tested.

TABLE 4 | Recommendations for promoting physical activity in individuals with a neurologically-related mobility disability during the COVID-19 pandemic.

1. Consider synchronous online sessions, where the practitioner can provide real-time feedback and adapt the exercise to meet the individuals needs
2. Enlist help from somebody within the support bubble who is physically present, helping ensure an element of safety
3. The provision of cheap and inclusive exercise equipment if possible (e.g., TheraBands®)
4. Develop a vibrant online community for support and accountability amongst peers
5. Work in multidisciplinary teams to address the interplay with mental health considerations

Implications for Practice and Further Research

In the face of continued COVID-19 restrictions, or future crises, policy makers should consider the provision of services for adults with a physical disability to address exacerbated health inequalities and minimize the barriers to perform PA. Given the importance of PA for both physical and mental health, it has been argued that public health initiatives for clinical populations should incorporate the creation and implementation of interventions to promote safe PA should COVID-19 infection rates rise, prompting further lockdowns (62). To ensure enhanced feasibility and adherence, such interventions should be informed through the lived experiences of the target population. Accordingly, the contextual information gleaned from the free text questions has facilitated the recommendations described in **Table 4** to best facilitate PA in individuals with neurological conditions during a global pandemic. Inclusive online exercise resources for practitioners and individuals with neurological conditions can be found at the end of **Appendix C**. Practitioners working with this population need to be prepared to adapt (e.g., provide home-based online exercise classes) to ensure the imposed COVID-19 restrictions do not have a persisting detrimental effect on HRQoL in individuals with neurological conditions. Longitudinal follow-up studies are warranted to understand the longer-term consequences of COVID-19 and associated containment strategies on PA behaviors and HRQoL in clinically vulnerable individuals with a neurologically-related mobility disability.

Strengths and Limitations

These findings should be considered relative to the study's methodological strengths and limitations. Most importantly, causality cannot be inferred based on our results owing to the cross-sectional nature of the study. Due to the rapidly evolving government restrictions, the survey was not piloted among individuals with a neurological condition prior to its release. Despite this, we utilized population validated PROMs (see **Appendix C**). Strengths of this study include

the use of a data-driven statistical approach (URP-CTREE), multidisciplinary research team and the high response rate (96.5–99.0%) to the optional free-text questions, affording greater individual insights into participants experiences during this time. The pandemic-related nocebo effect (63) may be exacerbated in individuals with neurological conditions, who were considered "at-risk" relative to the general population. The negative expectations of these individuals, possibly fueled by alarming media reports, could have amplified the discomfort and anxiety reported during the COVID-19 pandemic, above and beyond what was actually experienced. There are inherent limitations with using self-report measures to quantify PA, such as potential recall bias (64). However, using the PASIPD is advantageous as it allows the comparison of PA across a heterogenous cohort with varying degrees of mobility impairment (i.e., questions are framed for wheelchair users and ambulatory individuals). While the absolute accuracy of the assigned MET multipliers used in this instrument have not been supported (21), they at least serve as logical constants to rank order the intensity of PA. Furthermore, the PASIPD demonstrates a degree of test-retest reliability and criterion validity that is comparable to self-report PA questionnaires commonly used in the general population (65). Akin to other open e-survey research, the validity of participants self-assessment of eligibility could be deemed a limitation. Cognitive impairment, which may have impacted self-report responses, was not included as an eligibility criterion. Other notable limitations include the heterogeneity of neurological conditions in the cohort, the relatively small number of participants in each diagnostic group and possible self-selection bias, which may influence the representativeness of our cohort. Respondents were predominantly white females, which also limits the generalizability to the wider population of individuals living with a neurological condition. COVID-19 has been shown to have a disproportionate impact on ethnic minority groups (66), indicating that further research is required to address this gap.

Conclusion

Our findings indicate that LTPA was associated with depressive symptoms, fatigue, and subjective vitality in individuals with a neurologically-related mobility disability during the COVID-19 pandemic. Understanding ways to better support individuals with a physical disability to maintain health promoting behaviors during a period of uncertainty, such as a global pandemic, war or natural disaster is of utmost importance. Further research is required to inform wider public health recommendations targeting the specific and unique needs of adults with a physical disability as COVID-19 restrictions are eased.

CODE AVAILABILITY

The code to run the analysis as well as create the figures and tables can be found on our Github repository (https://github.com/jutzca/COVID-19_Excercise_Neurological_Conditions).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical approval was obtained from the University of Birmingham Science, Technology, Engineering and Mathematics ethics committee (ERN_20-0689). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Material preparation and data collection was performed by TN. Statistical analyses were performed by CJ (quantitative data), NH, and JV (qualitative data). The first draft of the manuscript was written by TN, CJ, NH, and JV. All authors contributed to the study conception and design, commented on previous versions of the manuscript, and have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.699884/full#supplementary-material

Supplementary Figure 1 | Pattern of missing data. Pink squares indicate missing values and blue squares denote complete data.

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Tele-Neurorehabilitation During the COVID-19 Pandemic: Implications for Practice in Low- and Middle-Income Countries

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The importance of neurorehabilitation services for people with disabilities is getting well-recognized in low- and middle-income countries (LMICs) recently. However, accessibility to the same has remained the most significant challenge, in these contexts. This is especially because of the non-availability of trained specialists and the availability of neurorehabilitation centers only in urban cities owned predominantly by private healthcare organizations. In the current COVID-19 pandemic, the members of the Task Force for research at the Indian Federation of Neurorehabilitation (IFNR) reviewed the context for tele-neurorehabilitation (TNR) and have provided the contemporary implications for practicing TNR during COVID-19 for people with neurological disabilities (PWNDs) in LMICs. Neurorehabilitation is a science that is driven by rigorous research-based evidence. The current pandemic implies the need for systematically developed TNR interventions that is evaluated for its feasibility and acceptability and that is informed by available evidence from LMICs. Given the lack of organized systems in place for the provision of neurorehabilitation services in general, there needs to be sufficient budgetary allocations and a sector-wide approach to developing policies and systems for the provision of TNR services for PWNDs. The pandemic situation provides an opportunity to

optimize the technological innovations in health and scale up these innovations to meet the growing burden of neurological disability in LMICs. Thus, this immense opportunity must be tapped to build capacity for safe and effective TNR services provision for PWNDs in these settings.

Keywords: neurorehabilitation, tele-rehabilitation system, neurological disability, COVID-19, pandemic (COVID-19), low- and middle-income countries

INTRODUCTION

Neurological disorders are the leading causes of disability globally (1). During the past three decades, there is an absolute increase in people with neurological disability (PWND) by ∼77.3% (2). A substantial proportion of this neurological disability burden are borne by low- and middle-income countries (LMICs) (3). Although there are several advances in the prevention and management of neurological disorders globally, factors such as demographic (increasing aging population) and epidemiological transitions (increasing non-communicable diseases) are consistently adding up to this burden (4).

The recent COVID-19 pandemic has tremendously halted most of the efforts toward combating the growing burden of neurological disorders, especially in LMICs (5). People with neurological disability (PWND) are unable to access neurorehabilitation services (5). Although access to such services was not available even during the pre-pandemic times, it is even harder to access during the COVID-19 pandemic (6). The shortage of specialists involved in neurorehabilitation, such as physiatrists, neurologists, rehabilitation nurses, physiotherapists, neuropsychologists, occupational therapists (OTs), speech and language pathologists, prosthetists and orthotists, and nutritionists, in LMICs has become even more acute in these settings (7). The neurorehabilitation specialists also experience an ambiguous situation during the pandemic due to the lack of specific guidelines to provide neurorehabilitation services for PWND (8).

Telerehabilitation has been perceived as a key innovation and an effective strategy to combat the existing pandemic situation and reduce the global burden of disability (9). Telecommunication technology has been a powerful tool to enhance the provision of health, education, and development services during the COVID-19 pandemic worldwide (10). It is also envisaged to be a game-changer in addressing the global burden of disability (9, 10). Even during the pre-pandemic times, these telecommunication technologies were substantially optimized to provide uninterrupted neurological rehabilitation services and care for PWNDs. They are popularly known as tele-neurorehabilitation (TNR) services (11). TNR is gaining considerable momentum globally in recent times (12). Though TNR services are well-organized and guided by good quality evidence in high-income countries (HICs), these services are yet to be systematically developed and tested for feasibility, acceptability, and effectiveness in LMICs (11, 13). In the current COVID-19 pandemic, the members of the Task Force for research at the Indian Federation of Neurorehabilitation (IFNR) reviewed the context for TNR and have provided the contemporary implications for practicing TNR during COVID-19 for PWNDs in LMICs. This critical reflection from the task force would potentially help to arrive at a policy or consensus for the provision of TNR services for PWNDs in LMICs.

The Practice of TNR in LMICs

With the largest number of internet users in Latin America, Brazil has introduced, accelerated emergency regulations for provision of tele-rehabilitation, and remotely delivered interventions to promote access to rehabilitation (14). A review of home-based tele-rehabilitation services in Southeast Asian countries found that the completion rates of interventions accessed by people with disabilities have been ∼80% in China and South Korea (15). A recent survey from the sub-continent (India) had showed close to 80% of the rehabilitation facilities with basic tele-rehabilitation infrastructure (16). However, tele-health and rehabilitation services are not available and are poorly utilized by the government primary care systems in many countries in the region of Sub-Saharan Africa (17).

The practice of tele-health and rehabilitation had been an emerging science in improving access to healthcare and rehabilitation globally, even before the COVID-19 pandemic (18). The current pandemic has enabled its growth manifold by default worldwide. Tele-health and rehabilitation have become inevitable to meet the demands of those who need continued support globally (19). There have been a wide range of interventions and rationale for TNR. However, the experiences and evidence for organized provision of TNR services are very limited in LMICs.

Most types of TNR services in LMICs are used for two primary purposes: 1. clinical assessment and 2. therapeutic rehabilitation (20). The practice of neurorehabilitation has become more rewarding with the introduction/facilitation of TNR practice during COVID times. Guidelines for remote prescribing in several LMICs have also created access to medicines and strengthen primary care during the pandemic (21). A substantial amount of patient referrals are currently handled remotely through TNR (22). Tele-consultations are seen as equally effective and efficient as the face-to-face interaction with the added advantage of avoiding unnecessary exposure to infections (23). PWNDs are assessed and treated in their actual living environment, which is highly encouraging for the patients. It also reduces the service cost, and it cuts down the cost of traveling to access rehabilitation (23, 24). Therapeutic progress is currently being well-documented because of the auto-digitization features of telecommunication technology (23, 24). Overall, access to rehabilitation has improved with the introduction of TNR

services. PWNDs who cannot travel due to their disability and the lockdown restrictions can still access rehabilitation and care without any access barriers and opportunity cost. Both providers of neurorehabilitation and the consumers are continuing to adapt to deliver and access services through TNR, respectively, in the current pandemic situation.

Implications for Practice of TNR in LMICs During the COVID-19 Pandemic

Basal Implications

Overall, there are several implications to evaluate PWNDs and provide specialized, comprehensive multidisciplinary neurorehabilitation through TNR services in LMICs (8, 25). A key aspect to remember is that there must not be any compromise on the objectivity of the assessment or evaluation and therapeutic approaches for the management of the needs of PWNDs. Neurorehabilitation is a science that is driven by rigorous research-based evidence. Therefore, assessing and providing neurorehabilitation services, whether provided in-person or using telerehabilitation, must not have any compromise on its objectivity and evidence for evaluation and treatment. The current pandemic implies the need for systematically developed TNR interventions that is evaluated for its feasibility and acceptability and that is informed by available evidence from LMICs.

It is essential to understand the implications of TNR as this would enable identification of effective strategies for comprehensive assessment and treatment that can meet the needs of PWNDs. Though a potential opportunity, TNR cannot entirely replace the actual ways of delivering neurological rehabilitation (26). Neurologists can consult patients, provide treatment, and prescribe medications and referrals as appropriate. Optimizing TNR services for consultations had been proven feasible in HICs before and during the pandemic times (10, 18). However, available resources such as adequate internet bandwidth, devices with required configurations, and information management systems for implementing TNR services need to be in place. For instance, close to 1/3 of the Brazilian population lack access to internet (27). Although the providers have access to basic tele-rehabilitation infrastructure like in India, the consumers need to have internet access to avail such services (16).

Physiatrist Perspectives

From a physiatrist's perspective, continuity of treatment and care is something that TNR services could seamlessly support. PWNDs need continued care, and that can be enhanced through multidisciplinary neurorehabilitation team consultations led by the physiatrist virtually (28). Many South-Asian countries including India had come up with national guidelines on this (28, 29). Singapore's guidelines were considered comparatively comprehensive (29). Assessment of basic vital parameters, neurological status, pain, sleep, energy, spasticity, bladder and bowel, and mobility status; functionality of tracheostomy, feeding tube, and urinary catheters; patient and caregiver education; appropriate instructions for providing basic support; and interventions to prevent secondary complications are feasible with trained manpower keeping in mind the nature and course of the disease. However, to operationalize this, PWNDs and their caregivers must be thoroughly educated about these aspects of TNR. The literacy and understanding about tele-rehabilitation and use of tele-communication technologies for rehabilitation has been poor among those PWNDs even before the pandemic in many LMICs especially in Sub-Saharan Africa (29, 30). Considering these aspects will be crucial to enhance TNR services and enable service providers to achieve neurorehabilitation goals in a realistic way within their environment.

Neuropsychological Perspectives

In this pandemic context, the neuropsychologist is expected to conduct neuropsychological evaluations and provide psychotherapy and cognitive rehabilitation for PWNDs through TNR (31, 32). However, it urges the understanding of its key implications. For instance, in Israel, the neuropsychological assessment services were postponed due to the pandemic with many people requiring such services put on a long waiting list. To combat this, the Israel government had developed remote solutions to meet the increasing demand for such services (33). Though these guidelines keep getting developed in many LMICs, some caveats need to be considered especially when it comes to administering standardized neuropsychological tests. There are significant differences between conducting a standardized neuropsychological evaluation in an ideal environment as compared to a virtual environment. Interpretation of the evaluations might differ and may not be the same while this is carried out virtually (33). Also, the neurorehabilitation team may have to rely substantially on the caregivers and patients to engage in the sessions proactively.

Physiotherapy Perspectives

Given the high demand for physiotherapy services in LMICs, neuro-physiotherapists are accustomed to evaluate the range of motion, strength, muscle tone, and endurance of PWNDs through eye-balling sometimes. They are also competent to conduct a thorough neurological examination, including cranial nerve testing through performance-based assessments. Therefore, it is feasible to assess neurological disability remotely through TNR services (34, 35). However, the provision of actual therapy or intervention using specialized techniques must be carried out with utmost safety considerations. During the provision of TNR physiotherapy services, patients and caregivers may not comprehend the instructions as they do this in-person, leading to serious untoward incidences. Hence, many HICs like Australia and the UK recommend developing highly competent inter-professional rehabilitation services as well as a frameworks or guidelines to enhance the provision of physiotherapy services remotely using technology (36).

Speech–Language Pathology Perspectives

Speech–language pathologists (SLPs) are one of the key neurorehabilitation professionals who are not easily available and accessible in LMICs (37). It was estimated that there were only 2,500 SLPs in India, which is an acute shortage of such key neurorehabilitation professionals delivering care (38). However, it is commonly perceived that provision of assessment and

rehabilitation for patients with neurological and neurosurgical disorders presenting with safe swallowing, speech, language, and cognitive-communication dysfunctions are some of the key aspects to include during tele-practice by SLPs across all age group in LMICs (39). Use of hybrid methods could also be a potential strategy in the management of neurodevelopmental and acquired communication disorders, dysarthria, oropharyngeal dysphagia, and cognitive-communication disorders experienced by patients reporting in outpatient as well as in-patient settings (40). There are examples from certain countries like the Indian Speech and Hearing Association that had published the tele-practice guidelines and specific resource material for speech–language pathology and audiology services in India (41). However, it is well-known that even during the pre-pandemic times, it was estimated that only 10%-12% of SLPs tend to use tele-practice as a strategy for providing SLP services in India (38). A similar survey recently in Croatia had also estimated that only 3% of those SLPs surveyed had completed a formal training related to tele-practice in SLP services. Several consumers in the survey expressed the lack of equipment and trust on the effectiveness of tele-practice as the reasons for non-utilization of such services (42). Hence, organizing TNR services provided for swallowing and cognitive communication requires careful planning and efficient strategies for implementation.

Occupational Therapy Perspectives

For OTs, it is critical to give utmost importance to performance than hospital-based rehabilitation, thus making TNR feasible for neuro-OTs (43). OTs are meant to assess and therapeutically manage the actual occupational performance of PWNDs like participation in activities of daily living (ADL), work, and leisure in their home/social environment (44). This strategy could help provide need-based, scientific, and therapeutically rigorous OT services using TNR framework in real-life contexts. Given that many occupational therapy assessments are based on function, it is also possible to incorporate real-life functional assessments for PWNDs. It would also provide immense opportunities for OTs to standardize these assessments for neurorehabilitation in the future in such contexts. Similar to the context of the SLPs, OTs are also scarce globally and especially in LMICs. The most frequently cited domains where OTs are scarce are directly related to conditions that predispose neurological disabilities. Therefore, it is of utmost importance that professional resources and expertise like OTs and SLPs must be protected and developed to address the needs of PWNDs through TNR during the COVID-19 pandemic.

Challenges and Recommendations for the Implementation of TNR Services in LMICs

Though there are several feasible aspects for implementing TNRs for PWNDs, it is also necessary to understand the barriers that need to be considered with caution. Not everything could be feasible, especially considering how rehabilitation services are organized for PWDs in general in LMICs. Therefore, it is highly pertinent to tease out the barriers for TNR services provided to PWNDs in LMICs.

Table 1 depicts the non-feasible aspects of TNR, especially in LMICs. The first and foremost aspect that may not be feasible while implementing TNR in LMICs is the comprehensive and intrinsically detailed neurological evaluation and treatment. This is especially because some of the evaluation and treatment require safe hands-on as well as moving and handling patients, and one cannot do this in TNR. Similarly, neurologists and physiatrists cannot prescribe certain drugs through TNR (45). There are also certain criteria for patient exclusion unless the TNR service is exclusively developed for the requirements. People with severe cognitive-perceptual, emotional, and behavioral issues, young children, and frail elderly patients with silent aspiration, visual, speech, and hearing impairment can most often be excluded from a comprehensive TNR service that may not be available to all in the LMIC context. PWNDs and their caregiver cooperation, privacy, and non-distractible environment are also some key aspects that could prove challenging and non-feasible while providing TNR services.

From the perspective of the TNR service providers, it is imperative that one needs prior training and sufficient experience in using TNR to deliver neurorehabilitation. This particular aspect is taken for granted since most providers assume that using a smartphone or computer can qualify them to deliver TNR services during the pandemic. It is also important that the neurorehabilitation providers do not lose objectivity of the evaluation and treatment while delivering TNR interventions

TABLE 1 | Non-feasible aspects of tele-neurorehabilitation.

Non-feasible aspects of tele-neurorehabilitation
Assessment and treatment
• Comprehensive as well as specific **n**eurological evaluations (**c**ranial **n**erve **e**xamination (V, VI, VII), **c**erebellar symptoms, **h**igher **c**ortical **s**enses, **r**etinal examinations, **v**isual **n**eglect examinations, **g**rading of **m**uscle tone and strength, **d**ynamic **b**alance, **p**assive **r**ange of **m**otion, TCDs, **f**unctional **s**wallow **a**ssessment)
• Young children and frail older adults with speech and hearing impairment
• **People** with severe cognitive, emotional, or **behavioral** issues
• Specific **specialized** therapy techniques that require the therapist to move and handle patients such as neurodevelopmental therapies
• Safe swallowing therapy as well as a safe, comprehensive cognitive-communication therapy
• Prescription of **s**chedule X drugs
• Adherence to professional, **l**egal, and ethical standards
• Prior TNR training and/or experience
• Patient cooperation
• Non-distractible environment
• Private space
• The objectivity of the assessment and treatment

TABLE 2 | Barriers to implementation of TNR services in LMICs.

Barriers to implementation of TNR services		
Scientific	**Technical**	**Administrative**
Competencies	Resources	Feasibility
Ethics	Skills	Acceptability
Quality	Infrastructure	Governance
Evidence	Innovations	TNR literacy

since there is a high possibility for this to happen in the LMIC contexts. Despite the non-existence of any regulatory framework, the neurorehabilitation provider must maintain their highest legal, professional, and ethical standards to deliver safe and effective rehabilitation.

There are three kinds of clear-cut challenges to the implementation of TNR services for PWNDs in LMICs. They are the scientific, technological, and administrative aspects of implementing TNR. **Table 2** provides more details of these aspects. From a scientific perspective, delivering TNR services requires specific competencies, and those competencies are not necessarily taught or achieved by neurorehabilitation professionals exclusively in the pre-pandemic times (46). However, competencies for delivering TNR services play a crucial role in making appropriate professional judgments and decisions for the patients. Lack of specific training and education to achieve such competencies within the curriculum of these professionals is a huge challenge (47). Similarly, striking a balance between patient autonomy and non-maleficence in decision making is very difficult when there is no evidence for such decisions in LMICs. TNR services are just emerging to bridge the gaps in access in LMICs and may not hold the same evidence for treatment delivered in person.

Delivering TNR services has become a necessity in the pandemic situation. However, it must not compromise safe, effective, and good quality patient care that the patient may have received otherwise (36). Obtaining consent for the provision of therapeutic interventions through TNR services is not as easy as doing it in person. PWNDs and their primary caregivers must be thoroughly informed about the pros and cons of the decisions or choices available for treatment, enabling them to consent (48, 49). Given that neurorehabilitation professionals are accountable and responsible for their patients, due considerations must be provided to the scientific, professional, and ethical aspects of delivering TNR services for PWNDs.

There are several technological challenges in delivering TNR services. Aspects such as availability of telecommunication technologies such as computers, tablets, and smartphones; technological access features such as connectivity, bandwidth, data storage and management, server capacity, synchronization, and network; skilled workforce to synergistically support the implementation of TNR services; and the infrastructure for hosting and delivering TNR services for PWNDs must be ensured before embarking into service provision through TNR (50). These aspects require tremendous resources in terms of both funding and technology. It also requires skilled telecommunication experts to work with neurorehabilitation experts to innovate TNR interventions that are safe, effective, and of high public health value.

Additionally, from the perspective of the TNR service providers, it is imperative that one needs prior training and sufficient experience in using TNR to deliver neurorehabilitation. This particular aspect is taken for granted since most providers assume that using a smartphone or computer can qualify them to deliver TNR services during the pandemic. It is also important that the neurorehabilitation providers do not lose objectivity of the evaluation and treatment while delivering TNR interventions

since there is a high possibility for this to happen in the LMIC contexts. Despite the non-existence of any regulatory framework, the neurorehabilitation provider must maintain their highest legal, professional, and ethical standards to deliver safe and effective rehabilitation.

Even if the scientific and technological challenges are addressed, administering TNR services is an immense strategic challenge. TNR service itself is an innovative intervention that must be feasible for implementation. In LMICs, much of the health and rehabilitation services is accessed through the private sector; hence, ensuring uniformity in the services and standards similar to the public run services may be challenging (51). Rehabilitation facilities can be small, with only an out-patient facility to a comprehensive in-patient facility. Similarly, the neurorehabilitation team can be a small team with a minimum of neurologists and physiotherapists to a comprehensive team with a physiatrist, OTs, SLPs, orthotist, and neuropsychologist in addition to the neurologist and physiotherapist (8). Therefore, implementation of TNR services within this wide range of service structure is highly challenging. It would certainly require a strong system of governance mechanisms to ensure the quality and safety of TNR services delivered in these facilities. To develop or strengthen the existing governance mechanisms, one must have TNR literacy. Without understanding the principles of neurorehabilitation and the application of telecommunication technology in it, it is not possible to govern TNR services in any context.

The same applies to the primary stakeholder of TNR services. PWNDs and caregivers must have TNR literacy or at least be technology literates to optimize TNR services (7). Without this literacy, patients and caregivers might not find value for their time and resources invested and potentially may not accept TNR services for themselves or their loved ones. It is also a crucial challenge to educate all the stakeholders, primarily the patients and their caregivers, about the benefits of TNR in LMICs.

Recommendations From the IFNR Research Task Force

Given the lack of organized systems in place for the provision of neurorehabilitation services in general, there needs to be sufficient budgetary allocations and a sector-wide approach to the development of policies and systems for the provision of TNR services for PWNDs. These allocations and actions must be from the Department of the Ministry of Health and all other ministries/departments, such as education, technology, telecommunications, and social justice, in a convergent manner (52). By default, the existing pandemic situation provided an opportunity to optimize the technological innovations in health and scale up these innovations to meet the growing burden of neurological disability in LMICs. Thus, this immense opportunity must be tapped to build capacity for safe and effective TNR services provision for PWNDs in these settings.

There have been several assumptions globally when attempting to understand the implications of TNR services. The primary assumption is that everyone has sufficient

information and knowledge about both TNR and the COVID-19 pandemic. This assumption gives anyone the leverage to start TNR services. However, this could be detrimental if the science and standards for practice are not evidence-based. In the context of LMICs and the pandemic, the neurorehabilitation team can give due importance to the performance of the neurologically disabled rather than to sophisticated clinical procedures to ensure TNR becomes a reality in these settings. This can enable bridging the gaps in evidence with relevant science and rigor. This subsequently eludes the scientific community to the need for innovations that can connect people and professionals through technology in this pandemic and beyond. The future of neurorehabilitation could radically change, if we utilize these learning from the pandemic period to make TNR services accessible, affordable, and available (53, 54).

CONCLUSION

A potential link must be established between the remote TNR services and in-person neurological rehabilitation service provision. This could add value to the health and social care systems that were previously developed for serving the needs of PWND. The link must have due considerations to the needs of the PWNDs. It must also include the needs of the primary caregivers and family who provide continuous support to PWND before, during, and even in the post-pandemic situation. There is a definite implication that this link must strike a balance between access and availability of neurorehabilitation services. This is especially required in LMICs. There is also a need to make accessibility and availability of TNR services consistent across geography, disciplines, and conditions. This is potentially possible by reducing the variation and inconsistencies in terms of the intensity of rehabilitation measured by the dosage, duration, team expertise involved, and goals set and achieved for PWND in LMICs. An amalgamation of the existing system (pre-pandemic) with the innovative TNR systems to support PWND during the pandemic situation could be a feasible solution. This could serve as a potentially possible strategy, even in the future post-pandemic era.

This situation highlights the importance of two key aspects for immediate attention. The first is building the capacity of the patients, caregivers, and families with rigorous evidence-based training using simple protocols and culturally acceptable versions of optimizing TNR services. The training should also be provided to the providers of TNR services especially in terms of safe and effective use of telecommunication technology for neurological rehabilitation. Second, there is a need for immense government support to legitimately develop resources for TNR services such as guidelines and research evidence and address the growing burden of neurological disabilities in LMICs. The IFNR research task force has realized this opportunity to support the PWNDs in need and also the government. It had initiated the development of systematic action plans toward addressing the burden of neurological disabilities. As a first logical step, IFNR aims to develop a national guideline for the provision of TNR in India, and it recommends the same for all LMICs.

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

On behalf of the IFNR Taskforce, all the authors contributed equally toward the development of this manuscript. All authors agree to be accountable for the content of the work.

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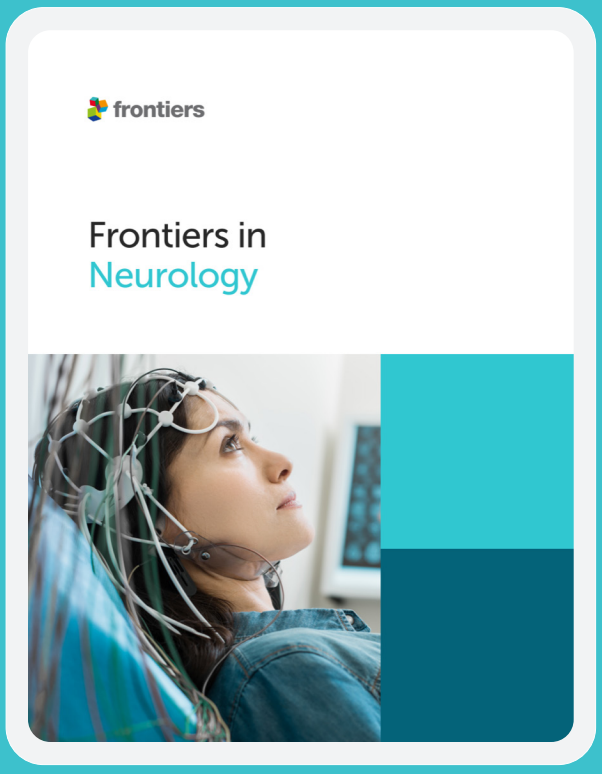
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