Neurological Manifestations of SARS-CoV-2 Infection: Protocol for a Sub-analysis of the COVID-19 Critical Care Consortium Observational Study

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Introduction: Neurological manifestations and complications in coronavirus disease-2019 (COVID-19) patients are frequent. Prior studies suggested a possible association between neurological complications and fatal outcome, as well as the existence of potential modifiable risk factors associated to their occurrence. Therefore,
INTRODUCTION

Coronavirus disease 2019 (COVID-19) presents with a wide spectrum of symptoms, from mild to severe, up to sequential organ failure and multiple-organ dysfunction (1). Reports of neurological manifestations associated with COVID-19 are increasing in the literature (2, 3). COVID-19 neurological signs can involve either the central nervous system (CNS), peripheral nervous system (PNS), or musculoskeletal system. Fatigue, myalgia, impaired sense of smell and taste, and headache are common neurological manifestations of COVID-19 (4, 5), whereas dizziness, confusion, delirium, agitation, stroke, hypoxic ischemic injury, seizures, encephalitis and coma among others have been reported neurological complications of hospitalized patients (4, 5). In some cases, neurological manifestations have been reported even without a primary respiratory involvement (4, 5). Several explanations have been proposed for the cause of neurological symptoms of COVID-19, but the underlying pathophysiology is not well defined. Putative mechanisms include viral neurotropism, a hyperinflammatory and hypercoagulable state, or pathological brain–lung crosstalk (6). Endothelial dysregulation (7–9) and pro-thrombotic state (10–12) have been widely suspected to be the possible main contributors of the increased risk of neurologic events. Indeed, COVID-19 patients are at high risk of hypoxia, hypotension, and microvascular abnormalities (13–15) which can promote neuroinflammation and excitotoxicity and increased permeability of the blood brain barrier (16). The risk is even more increased by the use of extracorporeal membrane oxygenation (ECMO) support that is a salvage option in COVID-19 critically ill patients with refractory hypoxemia (17). Prior studies suggested a possible association between neurological complications and mortality (18), but more information is required to delineate this association with respect to regional variation, as well as the risk factors associated to the occurrence of neurological complications (19). The aim of this study is to estimate the incidence of neurological complications in critically ill COVID-19 patients. Associations between neurological complications, patient-level variables and outcomes will also be assessed.

METHODS AND ANALYSIS

Study Design

This is a pre-planned sub-analysis of a large international multicenter observational study of patients in participating intensive care units (ICUs) with COVID-19 of the COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCARD). The collaborative consists of investigators from the Asia-Pacific extracorporeal life support organization (APELSO) in collaboration with centers within the SPRINT-SARI and International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Network. In Australia, this study is also supported by collaboration with the “National registry on the treatment and outcomes of patients requiring ECMO” (EXCEL Registry). A panel of 13 experts

Abbreviations: APELSO, Asia-Pacific extracorporeal life support organization; BMI, body mass index; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ECMOCARD, ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease; eCRF, electronic case report form; ICU, intensive care unit; IRB, institutional review board; ISARIC, International Severe Acute Respiratory and emerging Infection Consortium; MRI, magnetic resonance images; mRS, modified Rankin scale; NSE, neuron specific enolase; PNS, peripheral nervous system.

The aim to describe neurological complications in critically ill COVID-19 patients and to assess the associated risk factors, and outcomes. Adult patients with confirmed COVID-19, admitted to Intensive Care Unit (ICU) will be considered for this analysis. Data collected in the COVID-19 Critical Care Consortium study includes patients’ pre-admission characteristics, comorbidities, severity status, and type and severity of neurological complications. In-hospital mortality and neurological outcome were collected at discharge from ICU, and at 28-days.

Ethics and Dissemination: The COVID-19 Critical Care Consortium main study and its amendments have been approved by the Regional Ethics Committee of participating sites. No further approval is required for this secondary analysis.

Trial Registration Number: ACTRN12620000421932.

Keywords: COVID-19, neurological complications, disability, stroke, neurological outcome
in neurocritical care was created in 2020 together with the main protocol of the COVID-19 Critical Care Consortium by the Steering committee of the consortium. The planed this subanalysis and the electronic case report form (eCRF) in February 2020 and followed it up through monthly meeting. The study will be conducted in compliance with the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) (20) (Supplementary Item 1). Trial registration number: ACTRN12620000421932.

Objectives
The primary objective is to identify and describe the type and incidence of neurological complications in COVID-19 patients before and after admission to ICU, for all ICU patients selected patient subgroups (sex, age, country, treatment, COVID-19 wave).

Secondary objectives include: To evaluate the effect of neurological complications on outcomes after COVID-19, i.e., mortality, duration of ICU and hospital stay, neurological outcome (modified Rankin scale, mRS) at discharge, incidence of delirium and cognitive outcome at discharge. To identify factors related to the occurrence of neurological complications (including neurological injury due to the antiviral therapy).

Specific Sub-analysis
Secondary sub-analyses will also include the investigation of (1) magnetic resonance images (MRI) or computed tomography (CT) features; (2) serum biomarkers [neuronal injury markers (S100B, neuron specific enolase, NSE), endothelial dysfunction markers, inflammatory markers].

Inclusion and Exclusion Criteria
The COVID-19 Critical Care Consortium included all COVID-19 patients (≥18 years) admitted to ICU for receiving critical care with confirmed or suspected COVID-19 respiratory disease. For this specific sub-analysis, further inclusion criteria will be available data on neurological complications/manifestations. Patients treated with mechanical ventilation or ECMO for other causes than COVID-19 will be excluded.

Study Procedures and Setting
The protocol of the main study has been previously published (21). Participants in the COVID-19 Critical Care Consortium Observational Study are recruited at multiple sites in over 52 countries from 1st January 2020 onwards.

Data Collection
Data collection started from the commencement of COVID-19 pandemic and is planned to continue until completion of COVID-19 pandemic, as judged by the World Health Organization. According to the COVID-19 Critical Care Consortium Observational Study protocol (21) and neurological sub-study protocol, the following data will be collected: general patient characteristics, age, gender, body mass index (BMI), country, previous chronic comorbidities, scores of severity; premorbid scores [modified Rankin scale (0–6 points), Figure 1; new neurological complications, laboratory findings, imaging, and management of neurological complications (Supplementary Item 2); patient outcome (mortality at discharge, at 28-days, withdrawal of life-saving therapy and reason; mRS at ICU discharge, mRS at 28 days after discharge). Main eCRF of the COVID-19 critical care consortium study and neuro sub-study are provided in the Supplementary Items 3, 4.

Data Management
Data are stored in the central online eCRF database managed by the Oxford University in anonymized form, in order to preserve confidentiality of information in medical records. The Username and password will be assigned by the Oxford University during the registration process for individual Research Coordinators or Site Investigators. All electronic data transfer between study site and database will be username and password protected. The Participant List of the Neurology sub-study is maintained locally and is not to be transferred to any other location. Confidentiality of the participant will be maintained unless disclosure is required by law.

Data entry and management will be coordinated by ISARIC and ECMOCARD steering committee, including programming and data management support. ANZIC-RC and ISARIC will act as custodian of the data. The University of Queensland (Australia) will receive data from the data custodians via data sharing agreements. The management committee of the trial will take responsibility for the content and integrity of any data.

Definition of Neurological Complications
Definition of neurological complications (23–32) is listed in Table 1.

Statistical Analysis Plan
Planned analyses will comprise of descriptive summaries and regression-based methods for estimating associations between patient-level variables, neurological complications, and outcomes. Descriptive statistics for summarizing the study cohort will be presented as medians with interquartile ranges and frequencies with percentages for continuous and categorical variables, respectively. As an observational study, missing data are expected; a data completeness summary will accompany descriptive summaries for all variables considered. The incidence of neurological complications will be calculated as the number of events per 1,000 ICU days and as the number of events divided by the total number of ICU admissions. Incidence will be estimated per complication using logistic and Poisson regression; Poisson models will include patient days as an offset to account for varying ICU exposure. Baseline models will be adjusted for patient-level variables (e.g., sex, age, country) and calendar time to account for the timing of different COVID-19 waves. Additional covariates will be informed by univariate analysis and penalized regression techniques to address the secondary objective related to incidence.

Analysis of associations between neurological complications and clinical outcomes will be examined using generalized linear mixed models for binary outcomes and parametric survival models for time-to-event outcomes. Evidence of potential associations, including patient demographics and clinical signs assessed during ICU admission, will initially be assessed using
FIGURE 1 | Modified Rankin Scale (mRS). The Modified Rankin Score (mRS) is a 6-point disability scale with possible scores ranging from 0 to 6 (from 0 = no symptoms to 6 = dead). A score of 0–3 indicate mild to moderate disability and a score of 4–5 indicate severe disability. From Wade (22).

TABLE 1 | Definition of neurological complications/manifestations.

| Neurological complication                          | Definition                                                                                                                                 |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| **Central nervous system**                        |                                                                                                                                              |
| Ischemic stroke (23)                              | Neurological deficit due to an acute focal injury in the central nervous system caused by vascular involvement such as occlusion and cerebral infarction. |
| Intracranial hemorrhage (23, 24)                  | Bleeding that occurs inside the skull. Hemorrhagic stroke: neurological deficit due to an acute focal injury in the central nervous system caused by vascular involvement with intracerebral or subarachnoid hemorrhage. Subdural hematoma: collection of blood under the dura mater. |
| Encephalitis/meningitis (25)                      | Severe inflammatory disorder of the brain or meninges or parenchyma.                                                                      |
| Transverse myelitis and other spinal cord pathologies (26) | Inflammatory disorder with acute or subacute motor-sensory and autonomic spinal cord dysfunction.                                         |
| Epilepsy, seizures, and generalized convulsive status epilepticus (27, 28) | Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by neurobiological, cognitive, psychological, and social consequences. Seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Generalized convulsive status epilepticus is defined in adults and children older than 5 years as ≥5 min of (1) continuous seizure or (2) two or more discrete seizures between which there is incomplete recovery of consciousness. |
| Delirium (29)                                      | Acute change in consciousness and attention caused by an organic condition.                                                                |
| **Peripheral nervous system**                     |                                                                                                                                              |
| Guillain-Barré Syndrome (30)                      | Inflammatory immune-mediated polyradiculoneuropathy with acute onset that manifests with tingling, progressive weakness, autonomic disfunction and pain. |
| Critical illness myopathy/neuropathy (31)         | Neuromuscular weakness in the intensive care setting.                                                                                      |
| Hypogeusia/hyposmia (32)                          | Quantitative disorders characterized by reduction of taste or smell.                                                                       |
| Others                                            |                                                                                                                                              |
| Hypoxic-ischemic brain injury (33)                | Reduction in blood supply, oxygen supply or utilization that determines a decreased oxygen delivery to the brain and post cardiac arrest hypoxic ischemic brain injury (reduction in blood supply, oxygen supply or utilization that determines a decreased oxygen delivery to the brain due to cardiac arrest). |

univariate analysis. Results of univariate analysis will be used to inform variable selection for multivariable analysis. Multivariable models for all study objectives will be adjusted for known confounders as fixed or random effects, including study center, country, and calendar time. Model results will be presented as odds ratios (binary outcomes), relative risks (count outcomes) or hazard ratios (time-to-event outcomes) with 95% confidence intervals and p-values from hypothesis tests as appropriate.

**Study Status**

The protocol version is 1.2.8 of the COVID-19 Critical Care Consortium Observational Study available at https://www.elso.
Incidence and Types of Neurological Manifestations and Complications of COVID-19

The importance of investigating neurological manifestations in COVID-19, assessing their risk factors, and association with outcome is justified by the increasing identification in the available literature of many studies which reported high morbidity and mortality and poor neurological outcome in COVID-19 patients who manifest neurological complications, with the need for identifying and investigating such alterations in a bigger cohort of COVID-19 critically ill patients. Indeed, regarding each of the identified neurological manifestations of COVID-19, the data are fragmentary and come from different small cohorts. Myalgia, dysgeusia, and taste dysfunction were frequently reported (33% of cases), altered mental status in 32%, headache 29%, encephalopathy 26%, alteration of consciousness 13%, stroke 12%, dizziness 10%, vision impairment 6%, intracerebral hemorrhage, 5%, seizure 4%, encephalitis 2%, and GBS 1% (35). Intracranial hemorrhage was identified in 477 patients with a prevalence of 0.85% and a mortality of 52% suggesting a very poor prognosis despite rare incidence (36). The prevalence of intracranial hemorrhage, ischemic stroke, and hypoxic ischemic brain injury was higher in patients with COVID-19 who underwent ECMO support (5.9%) with a mortality of 92% (17). Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis have been reported in 46 patients with COVID-19 only, of whom 32% died (37).

Risk Factors for Neurological Manifestations and Complications of COVID-19

Regarding risk factors and association of neurological manifestations with outcome, a systematic review revealed that patients who suffer from a severe COVID-19 have more CNS involvement, neurological symptoms, and association with stroke. More severe patients had higher D-dimer and C-reactive protein levels than non-severe patients and presented multiple organ involvement (38). Myalgia, acute cerebrovascular disease, elevated creatin kinase, and lactate dehydrogenase were associated with more severe disease (3), while delirium on admission is a good predictor of mortality outcome in COVID-19 (39). In a cohort of 1,072 patients, age, headache at presentation, preexisting neurologic disease, invasive mechanical ventilation, and neutrophil/lymphocyte ratio ≥ 9 were independent predictors of new neurologic complications (40). In another study, the CT lung disease severity score was predictive of acute abnormalities on neuroimaging in patients with COVID-19 with neurologic manifestations (41). In a retrospective analysis, previous neurological history did not impact mortality, whereas new neurological manifestations were predictors of death (42). In a large cohort of 3,055 COVID-19 patients, preexisting neurological disorders were associated with higher risk of developing new neurological manifestations (2).
Outcome of COVID-19 Patients With Neurological Manifestations and Complications

Patients affected by COVID-19 with neurological manifestations were noted to have an impaired quality of life in 49% of cases, with a residual disability at 6-months in 52%, impaired cognition in 69%, and persistence of anxiety and depression in 32% (43). Neurological outcome in 135 patients with COVID-19 at 3-months follow-up was impaired (44), and a significant patient number still suffer from neurological sequelae 1 year after SARS-CoV-2 infection (45). A large multicentric study investigating delirium in 4,530 COVID-19 patients revealed that acute brain dysfunction was highly prevalent and prolonged in critically ill patients with COVID-19, with benzodiazepines and lack of family visitation identified to be risk factors for its development (46). After 6 months, in a cohort of 236,379 patients with COVID-19, neurological and psychiatric manifestations had an estimated incidence of 33.62 and 12.84%, respectively (47). Clinical outcome was evaluated in a cohort of 267 patients, concluding that patients with cerebrovascular disease had the worst prognosis (48).

Potential Pitfalls and Unintended Effects of This Study

Taken together, a large number of case reports and case series, despite coming mainly from small cohorts and local studies raise interest around the need for clarification about type and incidence of COVID-19 neurological manifestations, risk factors, and association with outcome on large scale, thus encouraging to better plan for possible management and therapeutics for neurological complications in critically ill COVID-19 patients. A limitation of current available data in the literature is that most of the data come from small cohorts, that could be addressed by using the larger COVID-19 Critical Care Consortium. Our study is unique in a way that we can address both limitations by studying the questions with international cohort with granular neurological variables. According to the design of our study, no unintended effects are expected. However, some limitations should be addressed. Being an observational study, it can be exposed to bias and confounding. Additionally, it cannot be used to demonstrate causality.

CONCLUSIONS

In conclusion the present study will provide new information on a global scale regarding the incidence and type of neurological complications, risk factors, and associated outcomes in COVID-19 with clinical applications.

ETHICS STATEMENT

The study will be conducted in compliance with the current version of the COVID-19 Critical Care Consortium and Neurologic sub-study protocol. Protocol version and subsequent amendment will be submitted and approved by the Local Ethics Committee in compliance to national standards. Sites wishing to participate will be required to provide the COVID-19 Critical Care Consortium Research Coordinator with an Institutional Review Board (IRB) approval certificate. The regulations of the COVID-19 Critical Care Consortium state that this study will not require individual patient consent as an observational study. Data of this study is already recorded as part of routine clinical care, therefore justifying participant enrolment using a waiver of consent. However, for any location that deems individual consent necessary, informed consent will be managed in accordance with the local regulations of each involved IRB. In particular, in patients who meet the inclusion/exclusion criteria, informed consent will be obtained directly from the patient, either before the study or retrospectively in case the patient is unconscious at the time of enrolment. If the patient is unable to provide a consent form upon admission, informed consent will be obtained by his/her next of kin.

AUTHOR CONTRIBUTIONS

DB drafted the manuscript and planned the methodology and the outcomes. S-MC and CR revised the manuscript and supervised the methodology and outcomes. DB, LP, MGr, SH, JE, GW, DBR, RA, LD, EG, MA, VW, AN, SD, GS, BP, DK, EM, AA-E, S-SS, MP, MGi, GF, PP, AP, NW, GL, JS, CR, and S-MC helped in the revision and methodology and approved the final version. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Bill & Melinda Gates Foundation, Grant number INV-034765; The University of Queensland; The Wesley Medical Research; The Prince Charles Hospital Foundation; The Health Research Board of Ireland. GL was a recipient of the BITRECS fellowship; the BITRECS project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement no. 754550 and from the La Caixa Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006. JS was funded by the Advance Queensland fellowship program.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930217/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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