Original Research Article

Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium

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Syed Ameen Ahmad, BS[1,*], Yunis Mayasi, MD[1,*], Thu-Lan Kelly, PhD[2], Nicole White, PhD[2], Jacky Suen, PhD[3,4], Denise Battaglini, MD, PhD[5,6], Gianluigi Li Bassi, MD, PhD[3,4,7,8], John F. Fraser, MD, PhD[3,4,7,9], Lavien Premraj, BMsc[3,10], Rakesh C. Arora, MD[11,12], Diego Bastos, MD[13], Glenn Whitman, MD[1], Matthew Griffee[14], Jonathon P. Fanning, MD, PhD[3,4,9], Chiara Robba, MD, PhD[5,15,], Sung-Min Cho, DO, MHS[1,**], and the COVID-19 Critical Care Consortium*****

Abstract

Background: In this COVID-19 Critical Care Consortium (CCCC) sub-study, we qualified neurological complications associated with SARS-CoV2 infection. **Methods:** The CCCC is an international, multicenter study. Eligible patients were COVID-19 patients admitted to intensive care units (ICU) across 23 centers between 1/7/2020 to 6/23/2022. Incidence of neurological complications was estimated as number of events per hospital days and per admission using Poisson regression. Associations between neurological complications and risk factors were assessed using multivariable Poisson regression. **Results:** 713 patients were included. Median age = 56 years (interquartile range (IQR) = 45-65). Neurological complications reported in 61/480 patients (12.7%) with the majority being ischemic stroke (2.9%), intracranial hemorrhage (ICH) (2.8%), and seizures (2.6%). Multivariable analysis for neurological complications per admitted days showed comorbid neurological conditions (incidence rate ratio (IRR) = 6.35, 2.57-15.7) were an independent risk factor for ischemic stroke. Extracorporeal membrane oxygenation (IRR = 5.32, 1.52-18.6), low-middle income countries (LMIC) vs high income countries (HIC) (IRR = 4.70, 1.62-13.7), and age >55 (IRR = 3.66, 1.23-10.9) were independent risk factors for ICH. Co-morbid neurological conditions (IRR = 3.43, 1.11-10.6), LMIC vs HIC (IRR = 8.69, 2.15-35.2), July-December 2020 vs January-June 2020 (IRR = 0.17, 0.04-0.69)

[1]Department of Neurosciences Critical Care, Departments of Neurology, Neurosurgery, Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]School of Public Health & Social Work, Queensland University of Technology, Brisbane, QLD, Australia
[3]Critical Care Research Group, The Prince Charles Hospital, Brisbane, QLD, Australia
[4]Faculty of Medicine University of Queensland, Brisbane, QLD, Australia
[5]Anesthesia and Intensive Care, IRCCS Policlinico San Martino, Genoa, Italy
[6]Department of Medicine, University of Barcelona, Barcelona, Spain
[7]Queensland University of Technology, Brisbane, QLD, Australia
[8]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
[9]Critical Care Medicine, UnitingCare Health, Brisbane, QLD, Australia
[10]Griffith University School of Medicine, Gold Coast, QLD, Australia
[11]Harrington Heart and Vascular Institute, University Hospitals, Cleveland, OH, USA
[12]Division of Cardiac Surgery, Department of Surgery, Case Western Reserve University, Cleveland, OH, USA
[13]Hospital Sao Camilo de Esteio, Esteio, Brazil
[14]Department of Anesthesiology and Perioperative Medicine, University of Utah, Salt Lake City, UT, USA
[15]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy

*S.A.A. and Y.M. contributed equally as co-first authors. **C.R. and S.M.C. contributed equally as co-senior authors. ***COVID-19 Critical Care Consortium Investigators are listed in Appendix.

Corresponding Author:
Sung-Min Cho, DO, MHS, Department of Neurosciences Critical Care, Departments of Neurology, Neurosurgery, Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, 600 N. Wolfe Street Baltimore, MD 21287, USA.
Email: csungmi1@jhmi.edu

and age >55 (IRR = 4.05, 1.15-14.3) were independent risk factors for seizure. **Conclusions:** Decision-making should incorporate salient risk factors to inform management of SARS-CoV2 infection and avoid neurological complications.

Keywords
COVID-19, neurological complications, disability, stroke, neurological outcome, income countries

Background

Respiratory manifestation is the most typical presentation of coronavirus disease-2019 (COVID-19), although the involvement of other organs and systems is common.[1] Neurological complications represent important non-pulmonary effects of COVID-19.[2,3] Recent observational studies reported myalgia, dysgeusia, and taste dysfunction as frequent complications, followed by altered mental status, headache, encephalopathy, alteration of consciousness, ischemic stroke, dizziness, vision impairment, intracerebral hemorrhage, seizure, encephalitis, and Guillain Barre Syndrome.[4] However, the mechanisms underlying the neurological involvement of COVID-19 have not been well elucidated.[5-11] Possible contributors to the development of neurologic complications include disruption and inflammation of the blood-brain barrier,[8,12] endothelial dysregulation,[6,7,9] and formation of pro-thrombotic states.[9-11]

Furthermore, it is known that COVID-19 patients undergoing mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO) can be at higher risk of neurological complications and death.[13,14] In one study, patients requiring ECMO support experienced a high prevalence (5.9%) of ischemic stroke, intracranial hemorrhage (ICH), and hypoxic ischemic brain injury with an associated extremely high mortality (92%).[14] The factors which can increase the risk of neurological complications, as well as the association between neurological complications and outcomes in critically ill COVID-19 patients across different countries, are still unclear, especially for low-middle income countries (LMIC) vs high income countries (HIC).[15-18]

The aim of this preplanned sub-study of the COVID-19 Critical Care Consortium (CCCC) international prospective observational study[19] was to assess the incidence and outcomes of neurological complications in critically ill patients with COVID-19. A secondary aim was to compare these parameters with stratification of patients by income (LMIC vs HIC). Additionally, we hypothesized that the incidence rate of neurological complications may differ based on the type of incidence analysis (per admitted days vs per admission) for the parameters of interest, including income status.

Methods

Study Design

This sub-study was planned at the beginning of the pandemic in 2020 by the Steering committee of the CCCC. A protocol of this sub-study has been previously published.[19,20] The main study has been published and was conducted in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[21] (Supplemental Material Item 1). Trial registration number: ACTRN12620000421932. This sub-study incorporated 23 sites in 11 countries from January 7th, 2020 to June 23rd, 2022 onwards. Sites wishing to participate in the main study were required to provide an Institutional Review Board approval certificate. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by local IRBs for each institution. Due to the retrospective nature of this study, informed consent was waived.

Objectives

The primary objective was to identify and describe the type and incidence of neurological complications in critically ill COVID-19 patients. The secondary objectives were: to describe the impact of neurological complications on outcomes including ICU-mortality, and duration of ICU and hospital stay; to identify factors related to the occurrence of neurological complications.

Inclusion and Exclusion Criteria

According to the CCCC study protocol, all patients (≥18 years) admitted to ICU with COVID-19 were included in this study. For this sub-study, data on neurological complications during ICU stay were required. Definitions of neurological complications can be found in Supplemental Material Item 2. Patients treated with MV or ECMO for other causes than COVID-19 were excluded.

Data Collection

Data were entered and stored into the central online electronic case report form (eCRF) database managed by Oxford University in an anonymized form between October 3rd, 2020 to January 16th, 2023. The data used for this sub-study and main eCRF (Supplemental Material Item 3-4) of the COVID-19-CCC study and neuro sub-study are provided in the published protocols.[19,20] Pandemic era 1 was defined as January 2020 –– June 2020, pandemic era 2 was July 2020 - December 2020, pandemic era 3 was January 2021 – June 2022. Country income was classified using the World Bank definitions from July 2021.[22] In this sub-study, HIC included Austria, Canada, Germany, Italy, Kuwait, Netherlands, United Arab Emirates and the United States of America, while LMIC included Brazil, Indonesia and Libya. The

modified Rankin Score (mRS) score is a 6-point neurological disability scale, and an mRS score of <3 was defined as having a favorable outcome.

Statistical Analysis

Descriptive statistics were presented as medians with interquartile ranges (IQR) and frequencies with percentages for continuous and categorical variables, respectively. The incidence of neurological complications was estimated as the number of events per 1000 admitted days and per 100 ICU admissions using Poisson regression, clustered by center for correlated binary outcomes.[23] Incidence rates were described as both per admitted days and per admission as suggested by the original protocol in order to reveal any meaningful differences in how these 2 metrics may impact outcomes.[19,20] Associations between neurological complications with incidence rates ≥1% and clinical risk factors were examined using univariable Poisson regression, and the results were used to inform covariate selection for multivariable analysis. Risk factors considered for selection were age, sex, neurological co-morbidities, LMIC vs HIC, pandemic era, MV and ECMO. Neurological conditions included diseases associated with primary and progressive loss of neuronal structures or function (including cerebral palsy, multiple sclerosis, motor neuron disease, muscular dystrophy, myasthenia gravis, Parkinson's disease, cerebellar degeneration, Alzheimer's Disease, dementias, Huntington's disease), stroke (ischemic stroke, intracranial hemorrhage (including intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematoma, excluding epidural hematoma)), transient ischemic attack and severe learning difficulty. Use of immunosuppressants immediately prior to hospital admission was not collected for any of the patients in the substudy. They were included as covariates in multivariable models if incidence rates from univariate analysis of the neurological complications were ≥1% for each category of the risk factor. Model results were presented as incidence rate ratios (IRR) with 95% confidence intervals [CI]. Complete case analysis only was performed due to the low incidence rates of the non-stroke complications with missing data. Missing data is reflected for each metric collected by the individual sample size (n) of that characteristic.

The effect of neurological complications on patient outcomes was assessed using Poisson regression clustered by center for mortality and negative binomial regression for length of hospital stay. Baseline covariates included in the multivariable analysis were age, sex, neurological co-morbidities, LMIC vs HIC and pandemic era. The interaction between country income status and neurological complications was tested and included in the models if the interaction *P*-value was less than .1. Model results were presented as incidence rate ratios (IRR) for mortality and rate ratios (RR) for length stay, with 95% confidence intervals [CI].

Results

Demographic Characteristics of the Population

After excluding 61 patients who were not admitted to an ICU and 49 with invalid admission dates, 713 patients were included from 11 countries and 23 centers; 15 centers were from HIC and 8 from LMIC. Demographic and baseline characteristics of our cohort of COVID-19 patients at ICU admission are presented in Table 1. For the whole cohort, the median (IQR) age of the cohort was 56 (46-65) years and 272 (38.1%) were female. 410 (57.5%) patients were from a HIC, while 303 (42.5%) were from a LMIC. The most common comorbidities were hypertension (HTN) (n = 368, 53.4%) and chronic cardiac disease (n = 245, 36.2%). 447 patients (62.7%) had invasive MV and 137 (19.2%) required ECMO support.

Neurological Complications

Neurological complication data are presented in Table 2. New neurological complications were recorded for 61/411 (14.8%) patients after excluding 302 patients with incomplete neurological data. Data were considered incomplete for a patient if all the individual conditions were either all missing, or a combination of absent and missing. Patient demographics for the cohort with complete neurological data are shown in Table 1. There was a higher proportion in LMIC and in the later pandemic era in patients with complete data than the whole cohort. Demographics of patients with complete neurological data by country income status are compared in Supplemental Material Item 5. Patients in HIC had higher rates of mechanical ventilation (91.9% vs 30.9%) and ECMO support (55.7% vs 4.6%) than LMIC.

The most common central nervous system (CNS) complications were ischemic stroke (21/713, 2.9%), ICH (20/713, 2.8%), seizures (12/468, 2.6%), hypoxic ischemic brain injury (9/474, 1.9%), followed by meningitis (2/470, 0.4%). Peripheral nervous system (PNS) complications were uncommon and were mostly categorized as myopathies (10/468, 2.1%). Among the 61 patients with new reported neurological complications, these were diagnosed mainly via computed tomography (CT) scan (n = 36, 65.5%) and magnetic resonance imaging (MRI) (n = 7, 12.7%). Calcium-binding protein B (S100 B) and neuron-specific enolase (NSE) were assessed only in 2/61 (3.3%) patients.

The unadjusted (crude) incidence rates per 1000 days (95% CI) were 30.5 (20.0-46.6) for ischemic stroke, 27.6 (17.7-43.1) for ICH, 4.42 (1.10-17.7, n = 453) for meningitis, 26.6 (15.2-46.7) for seizure, 13.3 (5.94-29.8) for other CNS conditions (such as brain death/atrophy, hallucination, uremic encephalopathy, ventriculomegaly), 22.2 (12.2-40.4) for myopathy, 2.38 (0.33-16.9) for hypogeusia, 2.24 (0.32-15.8) for other PNS conditions, and 19.7 (10.3-37.7) for hypoxic ischemic brain injury (Table 2). Incidence rates per 100 admissions are also reported in Table 2.

Table 1. Demographic and Clinical Characteristics.

Characteristic (# of Available Data)	Patients with Complete Neurological Data (N = 411)	All Patients (N = 713)
Demographics		
Age, median (IQR)	55 (45-65) (n = 411)	56 (45-65) (n = 713)
Age >55, n (%)	201 (48.9) (n = 411)	372 (52.2) (n = 713)
Male sex, n (%)	264 (64.2) (n = 411)	441 (61.9) (n = 713)
BMI, median (IQR) (kg/m^2)	27 (23-31) (n = 313)	28 (25-31) (n = 589)
Pandemic era	(n = 411)	(n = 713)
1: Jan-Jun 2020, n (%)	81 (19.7%)	203 (28.5)
2: Jul-Dec 2020, n (%)	163 (39.7%)	281 (39.4)
3: Jan 2021-Jun 2022, n (%)	167 (40.6%)	229 (32.1)
LMIC, n (%)	262 (63.7) (n = 411)	303 (42.5) (n = 713)
Past medical history		
Hypertension, n (%)	207 (53.1) (n = 390)	368 (53.4) (n = 689)
Chronic cardiac disease, n (%)	187 (48.7) (n = 384)	245 (36.2) (n = 677)
Diabetes, n (%)	133 (35.2) (n = 378)	224 (35.9) (n = 624)
Obesity, n (%)	121 (30.8) (n = 393)	184 (26.7) (n = 688)
Chronic kidney disease, n (%)	67 (17.6) (n = 381)	91 (13.5) (n = 673)
Neurological condition, n (%)	30 (7.3) (n = 411)	43 (6.0) (n = 713)
Smoking, n (%)	65 (28.5) (n = 228)	120 (32.3) (n = 372)
In-hospital data		
Mechanical ventilation, n (%)	218 (53.0) (n = 411)	447 (62.7) (n = 713)
ECMO support, n (%)	95 (23.1) (n = 411)	137 (19.2) (n = 713)
APACHE II score, median (IQR)	15 (10-21) (n = 115)	15 (11-20) (n = 168)
SOFA score, median (IQR)	6 (4-9) (n = 114)	6 (4-8) (n = 165)

Abbreviations: 1. APACHE II Score, acute physiology and chronic health evaluation II score; 2. BMI, body mass index; 3. Dec, december; 4. ECMO, extracorporeal membrane oxygenation; 5. IQR, interquartile range; 6. Jan, january; 7. Jul, july; 8. Jun, june; 9. LMIC, low-middle income country; 10. SOFA Score, sequential organ failure assessment score.
Legend: Demographic and clinical characteristics of patients at hospital admission and treatment during hospital stay. Descriptive statistics are median (interquartile range) or n (%).

Risk Factors

In a multivariable analysis of neurological complications per admitted days adjusting for sex, age, pandemic era, country income status, presence of comorbid neurological conditions, and presence of MV or ECMO, comorbid neurological conditions (IRR = 6.35, 2.57-15.7) was an independent risk factor for ischemic stroke (Table 3). ECMO (IRR = 5.32, 1.52-18.6), LMIC vs HIC (IRR = 4.70, 1.62-13.7), and age >55 (IRR = 3.66, 1.23-10.9) were independent risk factors for ICH. Co-morbid neurological conditions (IRR = 3.43, 1.11-10.6), LMIC vs HIC (IRR = 8.69, 2.15-35.2), pandemic era 2 vs 1 (IRR = 0.17, 0.04-0.69) and age >55 (IRR = 4.05, 1.15-14.3) were independent risk factors for seizure. Sex, pandemic era 3 vs 1, and MV were not statistically significant risk factors for any complication. Other CNS conditions, myopathy, and hypoxic ischemic brain injury did not have statistically significant independent risk factors (Supplemental Material Item 6). Risk factors for neurological complications per admission were similar, although LMIC vs HIC was no longer a statistically significant risk factor for ICH and seizure, or age >55 for seizure (Table 3).

Effect of Neurological Complications on Clinical Outcomes

Supplemental Material Figure 1 depicts final disposition according to the presence of reported neurological complications. For the entire cohort, the median duration of ICU stay was 14 (IQR = 7-25) days and hospital stay was 15 (IQR = 8-26) days (Supplemental Material Item 7). Omitting those with missing neurological data, patients who developed a neurological complication spent a median of 18 (IQR = 8-41) days in the ICU and 18 (IQR = 11-44) days in the hospital compared to the median 12 (IQR = 6-22) and 14 (IQR = 7-25) days, respectively, in patients who did not develop a neurological complication. Overall, 315/713 (44.2%) patients died, and of those patients, 152/411 (36.9%) were not missing neurological data. Of the patients who developed neurological complications, 49.2% (n = 30) died, 31.1% (n = 19) were discharged alive, 3.3% (n = 2) were still hospitalized at the time of enrollment in this sub-study, 14.8% (n = 9) were transferred to another facility, and one patient had missing discharge information. In comparison, of the patients who did not develop a neurological complication, 34.9% (n = 122) died, 37.7% (n = 132) were discharged alive, 15.7% (n = 55)

Table 2. Incidence Rates for New Reported Neurological Complications.

Complication (N)	n (%)	Incidence Rate (95% CI) per 1000 Days	Incidence Rate (95% CI) per 100 Admissions
Any neurological complication (n = 480)	61 (12.7)	130 (102-165)	12.7 (10.1-16.1)
Ischemic stroke (n = 713)	21 (2.9)	30.5 (20.0-46.6)	2.95 (1.93-4.49)
Intracranial hemorrhage (n = 713)	20 (2.8)	27.6 (17.7-43.1)	2.81 (1.82-4.32)
Meningitis (n = 470)	2 (.4)	4.42 (1.10-17.7)	0.43 (0.11-1.70)
Transverse myelitis (n = 464)	0 (0)	—	—
Seizure (n = 468)	12 (2.6)	26.6 (15.2-46.7)	2.56 (1.47-4.48)
Other central nervous system complications (n = 468)	6 (1.3)	13.3 (5.9-29.8)	1.28 (.58-2.84)
Alzheimer's	1 (.2)		
Brain atrophy	1 (.2)		
Brain death	1 (.2)		
Hallucination	1 (.2)		
Uremic encephalopathy	1 (.2)		
Ventriculomegaly	1 (.2)		
Myopathy (n = 468)	10 (2.1)	22.2 (12.2-40.4)	2.14 (1.16-3.94)
Hypogeusia or hyposmia (n = 438)	1 (.2)	2.38 (.33-16.9)	0.23 (.03-1.62)
Hypoxic ischemic brain injury (n = 474)	9 (1.9)	19.7 (10.3-37.7)	1.90 (.99-3.63)
Any neurological complication (n = 411)	61 (14.8)	152 (120-192)	14.8 (11.8-18.7)
Number of neurological complications (n = 411)			
1	43 (10.5)		
2	15 (3.6)	—	—
3	3 (.7)		

Abbreviations: 1. CI, confidence interval.
Legend: Reported new neurological complications after hospital admission and crude incidence rates per 1000 hospital days and 100 admissions. Patients with missing complication data have been excluded.

were still hospitalized, 10.0% (n = 35) were transferred to another facility, and 6 patients had unknown outcomes. Of those who had mRS recorded, 3/44 (6.8%) patients who developed neurological complications had a favorable outcome at discharge from the hospital in comparison to 19/156 (12.2%) of the patients who did not develop a neurological condition.

For patients with a new neurological condition, 7/9 (77.8%) of those with a hypoxic ischemic brain injury experienced an in-hospital death, followed by 15/20 (75%) ICH patients, 7/12 (58.3%) seizure patients, 1/2 (50%) meningitis patients, and 10/21 (47.6%) ischemic stroke patients. Excluding other PNS conditions, the longest median hospital length of stay (in days) was for myopathy (45, IQR = 38-56), followed by seizure (23, IQR = 12-38), meningitis (20, IQR = 19-21), and ischemic stroke (18, IQR = 11-38) (Supplemental Material Item 8).

Crude mortality rates per admitted days were higher in patients who developed neurological complications than those who did not in LMIC [66.7% vs 31.1%; 705 (95% CI 468, 1062) vs 317 (95% CI 252, 399) per 1000 admitted days], but not HIC [38.9% vs 45.3%; 135 (95% CI 75, 245) vs 207 (95% CI 157, 275) per 1000 admitted days] (Table 4).

There was a significant interaction between neurological complications and country income status in regression models for mortality, but not hospital length of stay. Length of stay was significantly longer in those with neurological complications in unadjusted analysis (RR = 1.51, 95% CI 1.15, 1.99), but not after adjustment for risk factors (RR = 1.22 (95% CI 0.97, 1.55)) (Supplemental Material Item 9). Figure 1 is a forest plot of adjusted rate ratios for hospital length of stay and incidence rate ratios for mortality. Mortality incidence was higher after neurological complications in LMIC [per admitted days: IRR = 1.83 (95% CI 1.35, 2.47); per admission: IRR = 2.02 (95% CI 1.67, 2.44)] but there was no difference in HIC [per admitted days: IRR = 0.61 (95% CI 0.32, 1.18); per admission: IRR = 0.81 (95% CI 0.51, 1.28)]. Hospital length of stay was significantly shorter in LMIC than HIC (RR = 0.41 (95% CI 0.34, 0.49)). Age over 55 was associated with a lower length of stay (RR = 0.84 (95% CI 0.72, 0.98)) and higher mortality [per admitted days: IRR = 1.90 (95% CI 1.36, 2.67); per admission: IRR = 1.63 (95% CI 1.25, 2.12)].

Discussion

This neurological sub-study of the CCCC Study was designed with the aim to obtain an overview of neurological complications in a large international multicenter cohort of critically ill COVID-19 patients, including recruitment from

Table 3. Multivariable Analysis of Incidence Rate Ratios of Risk Factors for Neurological Complications.

Outcome	Variable	Incidence Rate Ratio (95% CI), (days)	Incidence Rate Ratio (95% CI), (Admissions)
Ischaemic stroke		n = 688	n = 713
	Male vs female	1.20 (.51, 2.86)	1.20 (.49, 2.92)
	Age >55	1.29 (.50, 3.36)	1.25 (.51, 3.10)
	Jul-Dec 2020 vs Jan-Jun 2020	.51 (.20, 1.32)	.59 (.25, 1.40)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	.28 (.06, 1.37)	.25 (.05, 1.15)
	LMIC vs HIC	2.87 (.97, 8.48)	1.80 (.70, 4.63)
	Co-morbid neurological condition	6.35 (2.57, 15.7)	7.15 (3.04, 16.9)
	Mechanical ventilation	1.72 (.43, 6.87)	1.56 (.50, 4.84)
	ECMO	1.12 (.28, 4.46)	1.96 (.48, 7.97)
ICH		n = 688	n = 713
	Male vs female	.66 (.27, 1.61)	.65 (.27, 1.57)
	Age >55	3.66 (1.23, 1.9)	3.45 (1.24, 9.59)
	Jul-Dec 2020 vs Jan-Jun 2020	.37 (.12, 1.17)	.46 (.15, 1.40)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	.63 (.19, 2.16)	.79 (.22, 2.89)
	LMIC vs HIC	4.70 (1.62, 13.7)	1.82 (.67, 4.93)
	Co-morbid neurological condition	2.15 (.48, 9.68)	2.00 (.49, 8.13)
	Mechanical ventilation	3.30 (.58, 18.9)	3.25 (.64, 16.6)
	ECMO	5.32 (1.52, 18.6)	6.62 (1.74, 25.2)
Seizure		n = 451	n = 468
	Male vs female	.39 (.14, 1.10)	.37 (.13, 1.09)
	Age >55	4.05 (1.15, 14.3)	3.44 (.96, 12.4)
	Jul-Dec 2020 vs Jan-Jun 2020	.17 (.04, .69)	.18 (.05, .70)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	.45 (.14, 1.49)	.34 (.09, 1.27)
	LMIC vs HIC	8.69 (2.15, 35.2)	4.10 (.97, 17.3)
	Co-morbid neurological condition	3.43 (1.11, 1.6)	4.02 (1.11, 14.6)
	Mechanical ventilation	2.85 (.97, 8.40)	2.41 (.70, 8.30)
	ECMO	3.22 (.75, 13.9)	4.66 (.97, 22.5)
Any neurological complication		n = 396	n = 411
	Male vs female	.67 (.43, 1.05)	.74 (.48, 1.14)
	Age >55	1.65 (.96, 2.83)	1.59 (.98, 2.59)
	Jul-Dec 2020 vs Jan-Jun 2020	.47 (.25, .88)	.49 (.27, .90)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	1.00 (.58, 1.72)	.82 (.49, 1.38)
	LMIC vs HIC	1.35 (.69, 2.62)	.66 (.37, 1.19)
	Co-morbid neurological condition	3.53 (2.05, 6.09)	3.27 (1.90, 5.63)
	Mechanical ventilation	2.08 (1.03, 4.21)	1.99 (1.02, 3.90)
	ECMO	.92 (.47, 1.80)	1.38 (.73, 2.61)

Abbreviations: 1. CI, confidence interval; 2. Dec, december; 3. ECMO, extracorporeal membrane oxygenation; 4. HIC, high income country; 5. ICH, intracranial hemorrhage; 6. Jan, january; 7. Jul, july; 8. Jun, june; 9. LMIC, low-middle income country.
Legend: Multivariable analysis of incidence rate ratios of risk factors for neurological complications per admitted days and admission for major neurological complications. Patients with missing data have been excluded.

LMICs as well as HICs. COVID-19 may manifest critical involvement of multiple organ systems in severe disease stage, and neurological complications represent a potentially devastating complication of coronavirus disease.[1] In this analysis, a >12% prevalence of new neurological complications was observed which included ischemic stroke (2.9%), ICH (2.8%), and seizure (2.6%). Myopathy was the most common complication involving the peripheral nervous system.

SARS-CoV2 infection has been shown to have a higher rate of ischemic stroke when compared to other viral infections (influenza A/B), even when adjusting for ICU admission.[24] Several recent reports discuss the possible pathophysiology of the innate immune response to SARS-CoV2 infection leading to thromboembolic and in-situ microthromboses. The activation of the inflammasome, as well as disruption of the angiotensin-renin system, can lead to activation of the complement system—resulting in endothelial damage and microthromboses.[25-27] Studies have demonstrated that viral infections can lead to seizures, either through direct neural injury, or by decreasing the seizure threshold in a predisposed host.[28] Therefore, local

Table 4. Length of Stay and Crude In-Hospital Mortality Incidence Rates by Neurological Complication and Income Region for the Cohort With Complete Neurological Data.

	Length of Stay (Days), Median (IQR)		Mortality Rate, n/N (%)		Crude Mortality Rate per 1000 Admitted Days (95% CI)	
	Any Neurological Complication		Any Neurological Complication		Any Neurological Complication	
Income Region	No (N = 336)	Yes (N = 60)	No (N = 344)	Yes (N = 60)	No (N = 331)	Yes (N = 59)
LMIC	11 (6-18)	12 (9-17)	74/238 (31.1)	16/24 (66.7)	317 (252, 399)	705 (468, 1062)
HIC	24 (15-41)	36 (18-52)	48/106 (45.3)	14/36 (38.9)	207 (157, 275)	135 (75, 245)

Abbreviations: 1. IQR, interquartile range; 2. CI, confidence interval; 3. LMIC, low-middle income country; 4. HIC, high income country.
Legend: Length of stay and crude in-hospital mortality incidence rates by neurological complication and income region for the cohort with complete neurological data. Patients with missing data have been excluded.

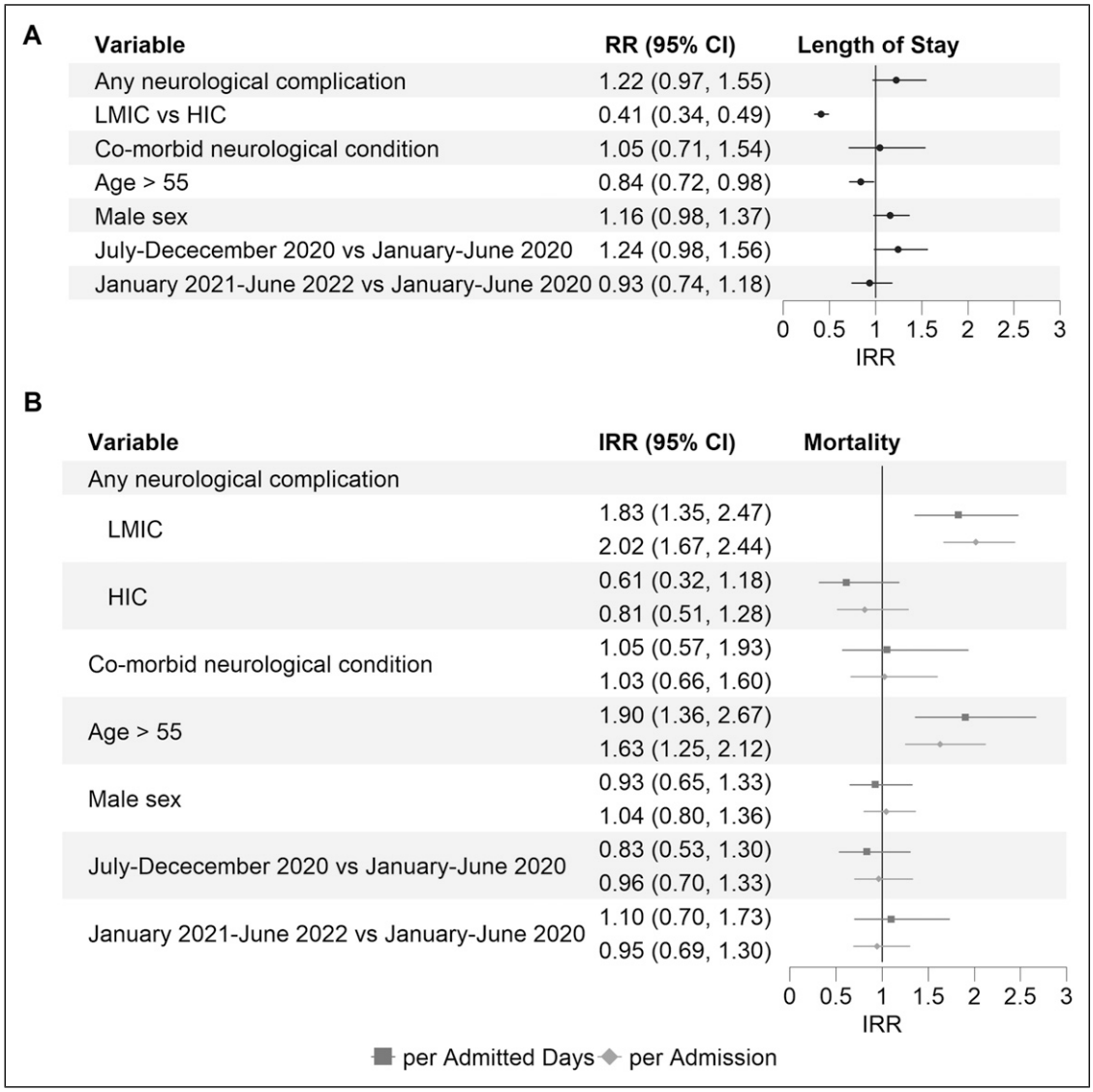

Figure 1. Multivariable adjusted rate ratios (RR) for length of stay and incidence rate ratios (IRR) for mortality. Abbreviations: 1. RR, rate ratio; 2. CI, confidence interval; 3. HIC, high income country; 4. LMIC, low-middle income country; 5. IRR, incidence rate ratio. Legend: multivariable adjusted rate ratios (RR) for length of stay and incidence rate ratios (IRR) for mortality.

neuroinvasion can lead to seizures as well as long-term epilepsy.[29] It has been demonstrated that severe or fatal influenza infection can cause seizures, but at a rate of 2.1 percent, slightly lower than this cohort of SARS-CoV2 infection related seizures.[30] In our study, the need for ECMO was observed to be an independent risk factor for ICH. This data is in accordance with a recent meta-analysis that revealed COVID-19 patients on ECMO support who developed neurological complications had worse outcomes and higher mortality.[14] However, it is possible that ECMO cannulation itself can lead to worse neurological injury.[13]

Multiple observational studies have been conducted to evaluate acute respiratory distress syndrome (ARDS) incidence and outcomes. One such study, The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure- LUNG SAFE trial, a multinational trial that included 29,144 patients—of which around 10% developed ARDS.[31,32] In that cohort, 23% of ARDS patients required mechanical ventilator support, and it was shown that median length of hospital stay was 17 days, and that of ICU stay was 10 days. Mortality ranged from 35% to 40%, with higher mortality rates in more severe cases.[31,32] In our cohort, all patients were admitted to a critical care unit, more than 50% of whom required respiratory support (MV and/or ECMO). Additionally, patients who developed neurological complications had a median length ICU stay of 18 days in comparison to 12 days for those who did not develop a neurological complication. Furthermore, our study showed that patients who developed a neurological complication had a mortality of 49.2% in comparison to the 34.9% with no reported neurological complication. Mortality rates depended on the type of neurological complication, with 77.8% of hypoxic ischemic brain injury patients dying in hospital compared with 10% with myopathy. Taken together, this cohort data is in accordance with previous observational studies reflecting ARDS incidence and outcomes with the added benefit of seeing how the development of neurological complications impacts these factors. Additionally, it is known that patients on ECMO support experience significant long-term neuropsychiatric and neurocognitive outcomes.[33] Therefore, further investigation of the mechanisms and risk of memory and cognitive disorders in critically-ill patients (and not only in patients on ECMO) is required.

Epidemiological studies support the idea that LMIC accrue a bulk of the burden of non-communicable neurological deaths and disability-adjusted life-years (DALYs).[34] This is in accordance with this cohort, which demonstrated the increased incidence of complications per admitted days such as seizures and ICH. Additionally, there was a significant interaction between income region and neurological complications, with mortality being higher in those with neurological complications in LMIC, but not in HIC. LMIC have been observed to experience higher SARS-CoV2 case-infection rates compared to HIC, whilst also having limitations of health infrastructure such as decreased number of intensive care beds, hospital beds, as well as availability of ventilators.[35] These factors might be an underlying substrate for more advanced and thus severe stage of infection, which is exacerbated by the fact that these countries have higher rates of non-communicable disease comorbidities that include HTN and diabetes.[35,36] Taken together, more severe infections and higher prevalence of comorbid conditions associated with higher rates of stroke in LMIC may be the substrate for the higher observed rates of neurological complications. This is supported by the fact that stroke risk in the full CCC registry is greater in LMIC vs HIC.[37] In this study, however, higher complication rates in LMIC were associated with the number of admitted days and not per admission. This suggests that other factors, such as shorter length of stay, may explain the differences that we observed. More research, support, and resources are necessary to understand the reasons for these differences in order to diminish the disproportionate burden that LMIC countries face in response to severe SARS-CoV2 infection and associated neurological complications.

It has also been demonstrated that patients admitted to the emergency department with previous comorbid neurological conditions were more likely to have a more severe form of SARS-CoV2 infection.[38] Additionally, hospitalized patients with COVID-19 were more likely to develop neurological conditions, such as encephalopathy, if they were older and had a previous comorbid neurological condition.[39] Thus, the development of neurological complications related to SARS-CoV2 infection might be facilitated by an already compromised blood brain barrier, neuronal dysfunction, or preexisting cerebral atrophy—though more studies are needed to identify causality. These factors are exacerbated by the fact that during the pandemic, the accessibility and availability of CT scan for diagnosis was scarce.[40] Therefore, patients with neurological comorbidities may benefit from enhanced surveillance of new neurological complications. In particular, low-cost neurodiagnostic tools in resource limited settings are essential for patients from LMICs.

A unique aspect of the CCCC Study is the prospective and international nature of the study—since it allows for an analysis from a diverse patient population spanning many countries (including LMIC), hospital networks, and patient demographics. Additionally, we collected details that allowed for an in-depth examination of the many factors contributing to COVID-19 outcomes and the development of complications. However, this study has some limitations that are important to highlight. For one, the lack of a matched control cohort (critical care hospitalization not caused by SARS-CoV2 infection) makes it difficult to contextualize reported incidence values for neurological complications specifically due to COVID-19. Since this was a sub-study of the CCCC, the number of participating centers and total number of patients was lower than previously published reports due to lack of funding. For one, 2 large centers (HIC Kuwait and LMIC Indonesia) comprise more than 1/3rd of the patients in

the sub-study. The practices of these 2 large centers, such as the threshold by which patients are discharged/transferred, may influence the overall results. Additionally, it is likely that treatment practices varied widely between centers and between countries—most notably when comparing HICs to LMICs. These differences are not accounted for in our cohort and might bias results. Finally, there may have been underreporting of neurological complications, particularly early in the pandemic, and some centers had missing data—including those for neurological complications. This may affect data generalizability and interpretation.

Conclusions

We have sought to assess the incidence of neurological complications in critically ill patients with COVID-19 and to report the outcomes of neurologic complications in this patient population. An understanding of the neurological complications that arise, and the factors which may predispose a patient to them, can be used to inform medical decision making in critical care contexts. Of particular focus, this study demonstrates that patients from LMIC had higher neurological complication rates per admitted days and shorter hospital stay in comparison to HIC, and that patients with neurological complications in LMIC were at higher risk of death. Future studies should continue to analyze the neurological complications that may arise for all patients with severe SARS-CoV2 infection, paying attention to the disproportionate burden patients from LMIC face.

Appendix

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CCCC	COVID-19 Critical Care Consortium
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CT	Computed tomography
DALYs	Disability-adjusted life-years
Dec	December
ECMO	Extracorporeal membrane oxygenation
eCRF	electronic case report form
HIC	High income country
HTN	Hypertension
ICH	Intracranial hemorrhage
ICU	Intensive care unit
IQR	Interquartile range
IRR	Incidence rate ratio
Jan	January
Jul	July
Jun	June
LMIC	Low-middle income country
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MV	Mechanical ventilation
NSE	Neuron-specific enolase
PNS	Peripheral nervous system
S100B	Calcium-binding protein B
SARS-CoV-2	Severe Acute Respiratory Distress Syndrome Coronavirus-2
SOFA	Sequential Organ Failure Assessment
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

Authors' Note

This manuscript complies with all instructions to authors. The authorship requirements have been met and the final manuscript was approved by all authors. The manuscript has not been published elsewhere and is not under consideration by another journal. Reporting checklist STROBE utilized.

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Author Contributions

SAA and YM analyzed and interpreted the data and were major contributors in writing the manuscript. LK ran the statistical analysis, created figures and tables, and was a contributor in writing the manuscript. All authors read and approved the final manuscript.

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Ethical Statement

Ethical Approval

The Covid-19 Critical Care Consortium main study and its amendments have been approved by the Regional Ethics Committee of participating sites. Trial registration number: ACTRN12620000421932.

ORCID iD

Syed Ameen Ahmad https://orcid.org/0000-0002-6179-5252

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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