

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

Author

Ahmad, Syed Ameen, Mayasi, Yunis, Kelly, Thu-Lan, White, Nicole, Suen, Jacky, Battaglini, Denise, Li Bassi, Gianluigi, Fraser, John F, Premraj, Lavien, Arora, Rakesh C, Bastos, Diego, Whitman, Glenn, Griffee, Matthew, Fanning, Jonathon P, Robba, Chiara, et al.

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1 **Neurological Complications and Outcomes in Critically Ill Patients with COVID-19:**
 2 **Results from International Neurological Study Group from the COVID-19 Critical Care**
 3 **Consortium**

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

9
 10 **Institutions/Affiliations:**

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

32 *S.A.A. and Y.M. contributed equally as co-first authors.

33 **C.R. and S.M.C. contributed equally as co-senior authors.

34 ***COVID-19 Critical Care Consortium Investigators are listed in Appendix.

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45 **Correspondence**

46 Sung-Min Cho, DO, MHS

47 600 N. Wolfe Street

48 Baltimore, MD, 21287

49 Tel: 410-955-8471

50 Email: **csungmi1@jhmi.edu**

51

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54 **Abbreviations:**

55	
56	APACHE II: Acute Physiology and Chronic Health Evaluation II
57	
58	ARDS: Acute respiratory distress syndrome
59	
60	BMI: Body mass index
61	
62	CCCC: COVID-19 Critical Care Consortium
63	
64	CI: Confidence interval
65	
66	CNS: Central nervous system
67	
68	COVID-19: Coronavirus Disease 2019
69	
70	CT: Computed tomography
71	
72	DALYs: Disability-adjusted life-years
73	
74	Dec: December
75	
76	ECMO: Extracorporeal membrane oxygenation
77	
78	eCRF: electronic case report form
79	
80	HIC: High income country
81	
82	HTN: Hypertension
83	
84	ICH: Intracranial hemorrhage
85	
86	ICU: Intensive care unit
87	
88	IQR: Interquartile range
89	
90	IRR: Incidence rate ratio
91	
92	Jan: January
93	
94	Jul: July
95	
96	Jun: June
97	
98	LMIC: Low-middle income country
99	
100	MRI: Magnetic resonance imaging
101	
102	mRS: Modified Rankin Scale
103	
104	MV: Mechanical ventilation

105
106 NSE: Neuron-specific enolase
107
108 PNS: Peripheral nervous system
109
110 S100B: Calcium-binding protein B
111
112 SARS-CoV-2: Severe Acute Respiratory Distress Syndrome Coronavirus-2
113
114 SOFA: Sequential Organ Failure Assessment

115 STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

116

117 **Abstract (200)**

118 **Background:** In this COVID-19 Critical Care Consortium (CCCC) sub-study, we qualified
119 neurological complications associated with SARS-CoV2 infection.

120 **Methods:** The CCCC is an international, multicenter study. Eligible patients were COVID-19
121 patients admitted to intensive care units (ICU) across 23 centers between 1/7/2020 to 6/23/2022.
122 Incidence of neurological complications was estimated as number of events per hospital days and
123 per admission using Poisson regression. Associations between neurological complications and
124 risk factors were assessed using multivariable Poisson regression.

125 **Results:** 713 patients were included. Median age=56 years (interquartile range (IQR)=45-65).
126 Neurological complications reported in 61/480 patients (12.7%) with the majority being ischemic
127 stroke (2.9%), intracranial hemorrhage (ICH) (2.8%), and seizures (2.6%). Multivariable analysis
128 for neurological complications per admitted days showed comorbid neurological conditions
129 (incidence rate ratio (IRR)=6.35, 2.57-15.7) were an independent risk factor for ischemic stroke.
130 Extracorporeal membrane oxygenation (IRR=5.32, 1.52-18.6), low-middle income countries
131 (LMIC) vs high income countries (HIC) (IRR=4.70, 1.62-13.7), and age >55 (IRR=3.66, 1.23-10.9)
132 were independent risk factors for ICH. Co-morbid neurological conditions (IRR=3.43, 1.11-10.6),
133 LMIC vs HIC (IRR=8.69, 2.15-35.2), July-December 2020 vs January-June 2020 (IRR=0.17, 0.04-
134 0.69) and age >55 (IRR=4.05, 1.15-14.3) were independent risk factors for seizure.

135 **Conclusions:** Decision-making should incorporate salient risk factors to inform management of
136 SARS-CoV2 infection and avoid neurological complications.

137

138 **Background**

139 Respiratory manifestation is the most typical presentation of coronavirus disease-2019 (COVID-
140 19), although the involvement of other organs and systems is common ¹. Neurological
141 complications represent important non-pulmonary effects of COVID-19 ^{2,3}. Recent observational
142 studies reported myalgia, dysgeusia, and taste dysfunction as frequent complications, followed
143 by altered mental status, headache, encephalopathy, alteration of consciousness, ischemic
144 stroke, dizziness, vision impairment, intracerebral hemorrhage, seizure, encephalitis, and Guillain
145 Barre Syndrome ⁴. However, the mechanisms underlying the neurological involvement of COVID-
146 19 have not been well elucidated ⁵⁻¹¹. Possible contributors to the development of neurologic
147 complications include disruption and inflammation of the blood-brain barrier ^{8,12}, endothelial
148 dysregulation ^{6,7,9}, and formation of pro-thrombotic states ⁹⁻¹¹.

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

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

164 **Methods**

165 **Study design**

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

176 **Objectives**

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

181 **Inclusion and exclusion criteria**

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

187 **Data collection**

188 Data were entered and stored into the central online electronic case report form (eCRF) database
189 managed by Oxford University in an anonymized form between October 3rd, 2020 to January 16th,

190 2023. The data used for this sub-study and main eCRF (*Supplementary Material Item 3-4*) of the
191 COVID-19-CCC study and neuro sub-study are provided in the published protocols ^{19,20}.
192 Pandemic era 1 was defined as January 2020 – June 2020, pandemic era 2 was July 2020 –
193 December 2020, pandemic era 3 was January 2021 – June 2022. Country income was classified
194 using the World Bank definitions from July 2021 ²². In this sub-study, HIC included Austria,
195 Canada, Germany, Italy, Kuwait, Netherlands, United Arab Emirates and the United States of
196 America, while LMIC included Brazil, Indonesia and Libya. The modified Rankin Score (mRS)
197 score is a 6-point neurological disability scale, and an mRS score of < 3 was defined as having a
198 favorable outcome.

199 **Statistical analysis**

200 Descriptive statistics were presented as medians with interquartile ranges (IQR) and frequencies
201 with percentages for continuous and categorical variables, respectively. The incidence of
202 neurological complications was estimated as the number of events per 1,000 admitted days and
203 per 100 ICU admissions using Poisson regression, clustered by center for correlated binary
204 outcomes ²³. Incidence rates were described as both per admitted days and per admission as
205 suggested by the original protocol in order to reveal any meaningful differences in how these two
206 metrics may impact outcomes ^{19,20}. Associations between neurological complications with
207 incidence rates $\geq 1\%$ and clinical risk factors were examined using univariable Poisson regression,
208 and the results were used to inform covariate selection for multivariable analysis. Risk factors
209 considered for selection were age, sex, neurological co-morbidities, LMIC vs HIC, pandemic era,
210 MV and ECMO. Neurological conditions included diseases associated with primary and
211 progressive loss of neuronal structures or function (including cerebral palsy, multiple sclerosis,
212 motor neuron disease, muscular dystrophy, myasthenia gravis, Parkinson's disease, cerebellar
213 degeneration, Alzheimer's Disease, dementias, Huntington's disease), stroke (ischemic stroke,
214 intracranial hemorrhage (including intracerebral hemorrhage, subarachnoid hemorrhage, and
215 subdural hematoma, excluding epidural hematoma)), transient ischemic attack and severe

216 learning difficulty. Use of immunosuppressants immediately prior to hospital admission was not
217 collected for any of the patients in the sub-study. They were included as covariates in multivariable
218 models if incidence rates from univariate analysis of the neurological complications were $\geq 1\%$ for
219 each category of the risk factor. Model results were presented as incidence rate ratios (IRR) with
220 95% confidence intervals [CI]. Complete case analysis only was performed due to the low
221 incidence rates of the non-stroke complications with missing data. Missing data is reflected for
222 each metric collected by the individual sample size (n) of that characteristic.

223 The effect of neurological complications on patient outcomes was assessed using Poisson
224 regression clustered by center for mortality and negative binomial regression for length of hospital
225 stay. Baseline covariates included in the multivariable analysis were age, sex, neurological co-
226 morbidities, LMIC vs HIC and pandemic era. The interaction between country income status and
227 neurological complications was tested and included in the models if the interaction p-value was
228 less than 0.1. Model results were presented as incidence rate ratios (IRR) for mortality and rate
229 ratios (RR) for length stay, with 95% confidence intervals [CI].

230 **Results**

231 **Demographic characteristics of the population**

232 After excluding 61 patients who were not admitted to an ICU and 49 with invalid admission dates,
233 713 patients were included from 11 countries and 23 centers; 15 centers were from HIC and 8
234 from LMIC. Demographic and baseline characteristics of our cohort of COVID-19 patients at ICU
235 admission are presented in **Table 1**. For the whole cohort, the median (IQR) age of the cohort
236 was 56 (46-65) years and 272 (38.1%) were female. 410 (57.5%) patients were from a HIC, while
237 303 (42.5%) were from a LMIC. The most common comorbidities were hypertension (HTN)
238 (n=368, 53.4%) and chronic cardiac disease (n=245, 36.2%). 447 patients (62.7%) had invasive
239 MV and 137 (19.2%) required ECMO support.

240

241

242 **Neurological complications**

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

252 The most common central nervous system (CNS) complications were ischemic stroke (21/713,
253 2.9%), ICH (20/713, 2.8%), seizures (12/468, 2.6%), hypoxic ischemic brain injury (9/474, 1.9%),
254 followed by meningitis (2/470, 0.4%). Peripheral nervous system (PNS) complications were
255 uncommon and were mostly categorized as myopathies (10/468, 2.1%). Among the 61 patients
256 with new reported neurological complications, these were diagnosed mainly via computed
257 tomography (CT) scan (n=36, 65.5%) and magnetic resonance imaging (MRI) (n=7, 12.7%).
258 Calcium-binding protein B (S100B) and neuron-specific enolase (NSE) were assessed only in
259 2/61 (3.3%) patients.

260 The unadjusted (crude) incidence rates per 1000 days (95% CI) were 30.5 (20.0-46.6) for
261 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)
262 for seizure, 13.3 (5.94-29.8) for other CNS conditions (such as brain death/atrophy, hallucination,
263 uremic encephalopathy, ventriculomegaly), 22.2 (12.2-40.4) for myopathy, 2.38 (0.33-16.9) for
264 hypogeusia, 2.24 (0.32-15.8) for other PNS conditions, and 19.7 (10.3-37.7) for hypoxic ischemic
265 brain injury (**Table 2**). Incidence rates per 100 admissions are also reported in **Table 2**.

266

267

268 **Risk Factors**

269 In a multivariable analysis of neurological complications per admitted days adjusting for sex, age,
270 pandemic era, country income status, presence of comorbid neurological conditions, and
271 presence of MV or ECMO, comorbid neurological conditions (IRR=6.35, 2.57-15.7) was an
272 independent risk factor for ischemic stroke (**Table 3**). ECMO (IRR=5.32, 1.52-18.6), LMIC vs HIC
273 (IRR=4.70, 1.62-13.7), and age > 55 (IRR=3.66, 1.23-10.9) were independent risk factors for ICH.
274 Co-morbid neurological conditions (IRR=3.43, 1.11-10.6), LMIC vs HIC (IRR=8.69, 2.15-35.2),
275 pandemic era 2 vs 1 (IRR=0.17, 0.04-0.69) and age > 55 (IRR=4.05, 1.15-14.3) were independent
276 risk factors for seizure. Sex, pandemic era 3 vs 1, and MV were not statistically significant risk
277 factors for any complication. Other CNS conditions, myopathy, and hypoxic ischemic brain injury
278 did not have statistically significant independent risk factors (*Supplementary Material Item 6*).
279 Risk factors for neurological complications per admission were similar, although LMIC vs HIC was
280 no longer a statistically significant risk factor for ICH and seizure, or age >55 for seizure (**Table**
281 **3**).

282 **Effect of neurological complications on clinical outcomes**

283 **Supplementary Material Figure 1** depicts final disposition according to the presence of reported
284 neurological complications. For the entire cohort, the median duration of ICU stay was 14 (IQR=7-
285 25) days and hospital stay was 15 (IQR=8-26) days (*Supplementary Material Item 7*). Omitting
286 those with missing neurological data, patients who developed a neurological complication spent
287 a median of 18 (IQR=8-41) days in the ICU and 18 (IQR=11-44) days in the hospital compared to
288 the median 12 (IQR=6-22) and 14 (IQR=7-25) days, respectively, in patients who did not develop
289 a neurological complication. Overall, 315/713 (44.2%) patients died, and of those patients,
290 152/411 (36.9%) were not missing neurological data. Of the patients who developed neurological
291 complications, 49.2% (n=30) died, 31.1% (n=19) were discharged alive, 3.3% (n=2) were still
292 hospitalized at the time of enrollment in this sub-study, 14.8% (n=9) were transferred to another
293 facility, and one patient had missing discharge information. In comparison, of the patients who did

294 not develop a neurological complication, 34.9% (n=122) died, 37.7% (n=132) were discharged
295 alive, 15.7% (n=55) were still hospitalized, 10.0% (n=35) were transferred to another facility, and
296 6 patients had unknown outcomes. Of those who had mRS recorded, 3/44 (6.8%) patients who
297 developed neurological complications had a favorable outcome at discharge from the hospital in
298 comparison to 19/156 (12.2%) of the patients who did not develop a neurological condition.

299 For patients with a new neurological condition, 7/9 (77.8%) of those with a hypoxic
300 ischemic brain injury experienced an in-hospital death, followed by 15/20 (75%) ICH patients,
301 7/12 (58.3%) seizure patients, 1/2 (50%) meningitis patients, and 10/21 (47.6%) ischemic stroke
302 patients. Excluding other PNS conditions, the longest median hospital length of stay (in days) was
303 for myopathy (45, IQR=38-56), followed by seizure (23, IQR=12-38), meningitis (20, IQR=19-21),
304 and ischemic stroke (18, IQR=11-38) (*Supplementary Material Item 8*).

305 Crude mortality rates per admitted days were higher in patients who developed
306 neurological complications than those who did not in LMIC [66.7% vs 31.1%; 705 (95% CI 468,
307 1062) vs 317 (95% CI 252, 399) per 1,000 admitted days], but not HIC [38.9% vs 45.3%; 135
308 (95% CI 75, 245) vs 207 (95% CI 157, 275) per 1,000 admitted days] (**Table 4**).

309 There was a significant interaction between neurological complications and country
310 income status in regression models for mortality, but not hospital length of stay. Length of stay
311 was significantly longer in those with neurological complications in unadjusted analysis (RR =
312 1.51, 95% CI 1.15, 1.99), but not after adjustment for risk factors (RR = 1.22 (95% CI 0.97, 1.55))
313 (*Supplementary Material Item 9*). **Figure 1** is a forest plot of adjusted rate ratios for hospital length
314 of stay and incidence rate ratios for mortality. Mortality incidence was higher after neurological
315 complications in LMIC [per admitted days: IRR = 1.83 (95% CI 1.35, 2.47); per admission: IRR =
316 2.02 (95% CI 1.67, 2.44)] but there was no difference in HIC [per admitted days: IRR = 0.61 (95%
317 CI 0.32, 1.18); per admission: IRR = 0.81 (95% CI 0.51, 1.28)]. Hospital length of stay was
318 significantly shorter in LMIC than HIC (RR = 0.41 (95% CI 0.34, 0.49)). Age over 55 was
319 associated with a lower length of stay (RR = 0.84 (95% CI 0.72, 0.98)) and higher mortality [per

320 admitted days: IRR = 1.90 (95% CI 1.36, 2.67); per admission: IRR = 1.63 (95% CI 1.25, 2.12)].

321

322 **Discussion**

323 This neurological sub-study of the CCCC Study was designed with the aim to obtain an overview
324 of neurological complications in a large international multicenter cohort of critically ill COVID-19
325 patients, including recruitment from LMICs as well as HICs. COVID-19 may manifest critical
326 involvement of multiple organ systems in severe disease stage, and neurological complications
327 represent a potentially devastating complication of coronavirus disease ¹. In this analysis, a >12%
328 prevalence of new neurological complications was observed which included ischemic stroke
329 (2.9%), ICH (2.8%), and seizure (2.6%). Myopathy was the most common complication involving
330 the peripheral nervous system.

331 SARS-CoV2 infection has been shown to have a higher rate of ischemic stroke when
332 compared to other viral infections (influenza A/B), even when adjusting for ICU admission ²⁴.
333 Several recent reports discuss the possible pathophysiology of the innate immune response to
334 SARS-CoV2 infection leading to thromboembolic and in-situ microthromboses. The activation of
335 the inflammasome, as well as disruption of the angiotensin-renin system, can lead to activation
336 of the complement system—resulting in endothelial damage and microthromboses ^{25–27}. Studies
337 have demonstrated that viral infections can lead to seizures, either through direct neural injury, or
338 by decreasing the seizure threshold in a predisposed host ²⁸. Therefore, local neuroinvasion can
339 lead to seizures as well as long-term epilepsy ²⁹. It has been demonstrated that severe or fatal
340 influenza infection can cause seizures, but at a rate of 2.1 percent, slightly lower than this cohort
341 of SARS-CoV2 infection related seizures ³⁰. In our study, the need for ECMO was observed to be
342 an independent risk factor for ICH. This data is in accordance with a recent meta-analysis that
343 revealed COVID-19 patients on ECMO support who developed neurological complications had
344 worse outcomes and higher mortality ³¹. However, it is possible that ECMO cannulation itself can
345 lead to worse neurological injury ¹³.

346 Multiple observational studies have been conducted to evaluate acute respiratory distress
347 syndrome (ARDS) incidence and outcomes. One such study, The Large Observational Study to
348 Understand the Global Impact of Severe Acute Respiratory Failure- LUNG SAFE trial, a
349 multinational trial that included 29,144 patients—of which around 10% developed ARDS^{32,33}. In
350 that cohort, 23% of ARDS patients required mechanical ventilator support, and it was shown that
351 median length of hospital stay was 17 days, and that of ICU stay was 10 days. Mortality ranged
352 from 35% to 40%, with higher mortality rates in more severe cases.^{32,33} In our cohort, all patients
353 were admitted to a critical care unit, more than 50% of whom required respiratory support (MV
354 and/or ECMO). Additionally, patients who developed neurological complications had a median
355 length ICU stay of 18 days in comparison to 12 days for those who did not develop a neurological
356 complication. Furthermore, our study showed that patients who developed a neurological
357 complication had a mortality of 49.2% in comparison to the 34.9% with no reported neurological
358 complication. Mortality rates depended on the type of neurological complication, with 77.8% of
359 hypoxic ischemic brain injury patients dying in hospital compared with 10% with myopathy. Taken
360 together, this cohort data is in accordance with previous observational studies reflecting ARDS
361 incidence and outcomes with the added benefit of seeing how the development of neurological
362 complications impacts these factors. Additionally, it is known that patients on ECMO support
363 experience significant long-term neuropsychiatric and neurocognitive outcomes³⁴. Therefore,
364 further investigation of the mechanisms and risk of memory and cognitive disorders in critically-ill
365 patients (and not only in patients on ECMO) is required.

366 Epidemiological studies support the idea that LMIC accrue a bulk of the burden of non-
367 communicable neurological deaths and disability-adjusted life-years (DALYs)³⁵. This is in
368 accordance with this cohort, which demonstrated the increased incidence of complications per
369 admitted days such as seizures and ICH. Additionally, there was a significant interaction between
370 income region and neurological complications, with mortality being higher in those with
371 neurological complications in LMIC, but not in HIC. LMIC have been observed to experience

372 higher SARS-CoV2 case-infection rates compared to HIC, whilst also having limitations of health
373 infrastructure such as decreased number of intensive care beds, hospital beds, as well as
374 availability of ventilators ³⁶. These factors might be an underlying substrate for more advanced
375 and thus severe stage of infection, which is exacerbated by the fact that these countries have
376 higher rates of non-communicable disease comorbidities that include HTN and diabetes ^{36,37}.
377 Taken together, more severe infections and higher prevalence of comorbid conditions associated
378 with higher rates of stroke in LMIC may be the substrate for the higher observed rates of
379 neurological complications. This is supported by the fact that stroke risk in the full CCC registry is
380 greater in LMIC vs. HIC ³⁸. In this study, however, higher complication rates in LMIC were
381 associated with the number of admitted days and not per admission. This suggests that other
382 factors, such as shorter length of stay, may explain the differences that we observed. More
383 research, support, and resources are necessary to understand the reasons for these differences
384 in order to diminish the disproportionate burden that LMIC countries face in response to severe
385 SARS-CoV2 infection and associated neurological complications.

386 It has also been demonstrated that patients admitted to the emergency department with
387 previous comorbid neurological conditions were more likely to have a more severe form of SARS-
388 CoV2 infection ³⁹. Additionally, hospitalized patients with COVID-19 were more likely to develop
389 neurological conditions, such as encephalopathy, if they were older and had a previous comorbid
390 neurological condition ⁴⁰. Thus, the development of neurological complications related to SARS-
391 CoV2 infection might be facilitated by an already compromised blood brain barrier, neuronal
392 dysfunction, or preexisting cerebral atrophy—though more studies are needed to identify
393 causality. These factors are exacerbated by the fact that during the pandemic, the accessibility
394 and availability of CT scan for diagnosis was scarce ⁴¹. Therefore, patients with neurological
395 comorbidities may benefit from enhanced surveillance of new neurological complications. In
396 particular, low-cost neurodiagnostic tools in resource limited settings are essential for patients
397 from LMICs.

398 A unique aspect of the CCCC Study is the prospective and international nature of the
399 study—since it allows for an analysis from a diverse patient population spanning many countries
400 (including LMIC), hospital networks, and patient demographics. Additionally, we collected details
401 that allowed for an in-depth examination of the many factors contributing to COVID-19 outcomes
402 and the development of complications. However, this study has some limitations that are
403 important to highlight. For one, the lack of a matched control cohort (critical care hospitalization
404 not caused by SARS-CoV2 infection) makes it difficult to contextualize reported incidence values
405 for neurological complications specifically due to COVID-19. Since this was a sub-study of the
406 CCCC, the number of participating centers and total number of patients was lower than previously
407 published reports due to lack of funding. For one, two large centers (HIC Kuwait and LMIC
408 Indonesia) comprise more than 1/3rd of the patients in the sub-study. The practices of these two
409 large centers, such as the threshold by which patients are discharged/transferred, may influence
410 the overall results. Additionally, it is likely that treatment practices varied widely between centers
411 and between countries—most notably when comparing HICs to LMICs. These differences are not
412 accounted for in our cohort and might bias results. Finally, there may have been under-reporting
413 of neurological complications, particularly early in the pandemic, and some centers had missing
414 data—including those for neurological complications. This may affect data generalizability and
415 interpretation.

416 **Conclusions**

417 We have sought to assess the incidence of neurological complications in critically ill patients with
418 COVID-19 and to report the outcomes of neurologic complications in this patient population. An
419 understanding of the neurological complications that arise, and the factors which may predispose
420 a patient to them, can be used to inform medical decision making in critical care contexts. Of
421 particular focus, this study demonstrates that patients from LMIC had higher neurological
422 complication rates per admitted days and shorter hospital stay in comparison to HIC, and that

423 patients with neurological complications in LMIC were at higher risk of death. Future studies
424 should continue to analyze the neurological complications that may arise for all patients with
425 severe SARS-CoV2 infection, paying attention to the disproportionate burden patients from LMIC
426 face.

427 **Details Page:**

- 428 1) This manuscript complies with all instructions to authors.
- 429 2) The authorship requirements have been met and the final manuscript was approved by all
430 authors.
- 431 3) The manuscript has not been published elsewhere and is not under consideration by
432 another journal.
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- 558

559 **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, <i>n</i> (%)	201 (48.9) (n=411)	372 (52.2) (n=713)
Male sex, <i>n</i> (%)	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, <i>n</i> (%)	81 (19.7%)	203 (28.5)
2: Jul-Dec 2020, <i>n</i> (%)	163 (39.7%)	281 (39.4)
3: Jan 2021-Jun 2022, <i>n</i> (%)	167 (40.6%)	229 (32.1)
LMIC, <i>n</i> (%)	262 (63.7) (n=411)	303 (42.5) (n=713)
Past Medical history		
Hypertension, <i>n</i> (%)	207 (53.1) (n=390)	368 (53.4) (n=689)
Chronic cardiac disease, <i>n</i> (%)	187 (48.7) (n=384)	245 (36.2) (n=677)
Diabetes, <i>n</i> (%)	133 (35.2) (n=378)	224 (35.9) (n=624)
Obesity, <i>n</i> (%)	121 (30.8) (n=393)	184 (26.7) (n=688)
Chronic kidney disease, <i>n</i> (%)	67 (17.6) (n=381)	91 (13.5) (n=673)
Neurological condition, <i>n</i> (%)	30 (7.3) (n=411)	43 (6.0) (n=713)
Smoking, <i>n</i> (%)	65 (28.5) (n=228)	120 (32.3) (n=372)
In-hospital Data		
Mechanical ventilation, <i>n</i> (%)	218 (53.0) (n=411)	447 (62.7) (n=713)

ECMO support, <i>n</i> (%)	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)

560

561 Abbreviations: 1. APACHE II Score, Acute Physiology and Chronic Health Evaluation II Score; 2.

562 BMI, Body mass index; 3. Dec, December; 4. ECMO, Extracorporeal membrane oxygenation; 5.

563 IQR, Interquartile range; 6. Jan, January; 7. Jul, July; 8. Jun, June; 9. LMIC, Low-Middle income

564 country; 10. SOFA Score, Sequential Organ Failure Assessment Score

565

566 Legend: Demographic and clinical characteristics of patients at hospital admission and treatment

567 during hospital stay. Descriptive statistics are median (interquartile range) or *n* (%).

568 **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 (0.4)	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 (0.58-2.84)
Alzheimer's	1 (0.2)		
Brain atrophy	1 (0.2)		
Brain death	1 (0.2)		
Hallucination	1 (0.2)		
Uremic encephalopathy	1 (0.2)		
Ventriculomegaly	1 (0.2)		
Myopathy (n=468)	10 (2.1)	22.2 (12.2-40.4)	2.14 (1.16-3.94)
Hypogeusia or Hyposmia (n=438)	1 (0.2)	2.38 (0.33-16.9)	0.23 (0.03-1.62)
Hypoxic ischemic brain injury (n=474)	9 (1.9)	19.7 (10.3-37.7)	1.90 (0.99-3.63)
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 (0.7)		

569

570 Abbreviations: 1. CI, Confidence interval

571

572 Legend: Reported new neurological complications after hospital admission and crude incidence

573 rates per 1000 hospital days and 100 admissions. Patients with missing complication data have

574 been excluded.

575 **Table 3. Multivariable analysis of incidence rate ratios of risk factors for neurological**
 576 **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 (0.51, 2.86)	1.20 (0.49, 2.92)
	Age > 55	1.29 (0.50, 3.36)	1.25 (0.51, 3.10)
	Jul-Dec 2020 vs Jan-Jun 2020	0.51 (0.20, 1.32)	0.59 (0.25, 1.40)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	0.28 (0.06, 1.37)	0.25 (0.05, 1.15)
	LMIC vs HIC	2.87 (0.97, 8.48)	1.80 (0.70, 4.63)
	Co-morbid Neurological Condition	6.35 (2.57, 15.7)	7.15 (3.04, 16.9)
	Mechanical Ventilation	1.72 (0.43, 6.87)	1.56 (0.50, 4.84)
	ECMO	1.12 (0.28, 4.46)	1.96 (0.48, 7.97)
ICH		n=688	n=713
	Male vs Female	0.66 (0.27, 1.61)	0.65 (0.27, 1.57)
	Age > 55	3.66 (1.23, 10.9)	3.45 (1.24, 9.59)
	Jul-Dec 2020 vs Jan-Jun 2020	0.37 (0.12, 1.17)	0.46 (0.15, 1.40)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	0.63 (0.19, 2.16)	0.79 (0.22, 2.89)
	LMIC vs HIC	4.70 (1.62, 13.7)	1.82 (0.67, 4.93)
	Co-morbid Neurological Condition	2.15 (0.48, 9.68)	2.00 (0.49, 8.13)
	Mechanical Ventilation	3.30 (0.58, 18.9)	3.25 (0.64, 16.6)

Outcome	Variable	Incidence Rate Ratio (95% CI), (days)	Incidence Rate Ratio (95% CI), (admissions)
	ECMO	5.32 (1.52, 18.6)	6.62 (1.74, 25.2)
Seizure		n=451	n=468
	Male vs Female	0.39 (0.14, 1.10)	0.37 (0.13, 1.09)
	Age > 55	4.05 (1.15, 14.3)	3.44 (0.96, 12.4)
	Jul-Dec 2020 vs Jan-Jun 2020	0.17 (0.04, 0.69)	0.18 (0.05, 0.70)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	0.45 (0.14, 1.49)	0.34 (0.09, 1.27)
	LMIC vs HIC	8.69 (2.15, 35.2)	4.10 (0.97, 17.3)
	Co-morbid Neurological Condition	3.43 (1.11, 10.6)	4.02 (1.11, 14.6)
	Mechanical Ventilation	2.85 (0.97, 8.40)	2.41 (0.70, 8.30)
	ECMO	3.22 (0.75, 13.9)	4.66 (0.97, 22.5)
Any neurological complication		n=396	n=411
	Male vs Female	0.67 (0.43, 1.05)	0.74 (0.48, 1.14)
	Age > 55	1.65 (0.96, 2.83)	1.59 (0.98, 2.59)
	Jul-Dec 2020 vs Jan-Jun 2020	0.47 (0.25, 0.88)	0.49 (0.27, 0.90)
	Jan 2021-Jun 2022 vs Jan-Jun 2020	1.00 (0.58, 1.72)	0.82 (0.49, 1.38)
	LMIC vs HIC	1.35 (0.69, 2.62)	0.66 (0.37, 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	0.92 (0.47, 1.80)	1.38 (0.73, 2.61)

577

578 Abbreviations: 1. CI, Confidence interval; 2. Dec, December; 3. ECMO, Extracorporeal
579 membrane oxygenation; 4. HIC, High income Country; 5. ICH, Intracranial hemorrhage; 6. Jan,
580 January; 7. Jul, July; 8. Jun, June; 9. LMIC, Low-Middle income Country;

581

582 Legend: Multivariable analysis of incidence rate ratios of risk factors for neurological
583 complications per admitted days and admission for major neurological complications. Patients
584 with missing data have been excluded.

585

586 **Table 4: Length of stay and crude in-hospital mortality incidence rates by neurological**
 587 **complication and income region for the cohort with complete neurological data.**

588

	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)

589

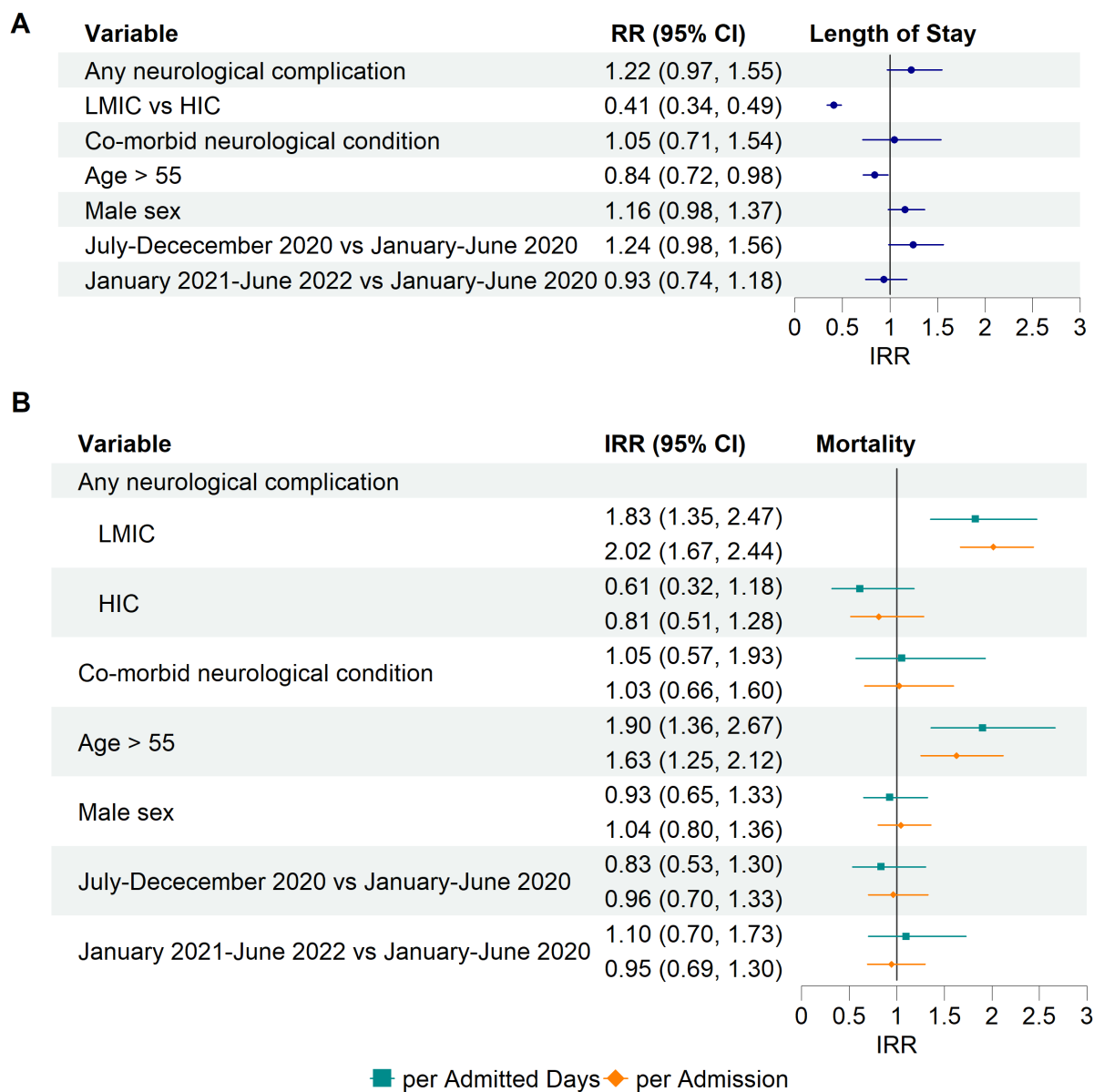
590

591 Abbreviations: 1. IQR, interquartile range; 2. CI, Confidence interval; 3. LMIC, Low-Middle
 592 income Country; 4. HIC, High income Country.

593

594 Legend: Length of stay and crude in-hospital mortality incidence rates by neurological
 595 complication and income region for the cohort with complete neurological data. Patients with
 596 missing data have been excluded.

597 **Figure 1: Multivariable adjusted Rate Ratios (RR) for length of stay and incidence rate**
 598 **ratios (IRR) for mortality.**



599
 600
 601 Abbreviations: 1. RR, Rate Ratio; 2. CI, Confidence interval; 3. HIC, High income Country; 4.

602 LMIC, Low-Middle income Country; 5. IRR, Incidence Rate Ratio.

603

604 Legend: Multivariable adjusted rate ratios (RR) for length of stay and incidence rate ratios (IRR)

605 for mortality.

606

607