Neurological manifestations of COVID-19 in adults and children

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Abbreviations: ARDS =acute respiratory distress syndrome ; COVID-19 =Coronavirus Disease 2019; CNS =Central Nervous System; GCS =Glasgow Coma Scale; ICU =Intensive Care Unit; ISARIC =International Severe Acute Respiratory and emerging Infection Consortium ; SARS-CoV-2 =Severe Acute Respiratory Distress Syndrome Coronavirus-2

ABSTRACT

Different neurological manifestations of COVID-19 in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicenter observational study using the International Severe Acute Respiratory and emerging Infection Consortium cohort across 1507 sites worldwide from January/30th/2020 to May/25th/2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models.

Overall, 161,239 patients (158,267 adults; 2,972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%), and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%), and central nervous system (CNS) infection (0.2%). Each occurred more frequently in ICU than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU vs. non-ICU (7.1% vs. 2.3%, $P<.001$).

Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease, and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure, and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age.

In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Introduction

Since the beginning of the COVID-19 pandemic in 2020, the medical community has had concerns about its neurological effects. COVID-19 is associated with a range of neurological manifestations such as altered consciousness, fatigue, seizures, and altered sense of smell and taste. In addition, in-hospital neurological complications such as stroke, central nervous system (CNS) infection, and seizures have been reported in both adults and children with acute COVID-19.[1-3] Evidence regarding the neurological effects of COVID-19 has evolved over time but was initially based on the early report from Wuhan, China, that 36% of patients had neurological manifestations.[4] That report was followed by multicenter cohort studies,[5-8]comprehensive reviews and meta-analyses,[2,3,9,10] and emerging evidence on CNS involvement of the virus.[11-13] Despite many reports during the pandemic, limited data exist on the prevalence of different neurological manifestations and complications in adults and children with COVID-19. Therefore, a robust, large-scale epidemiological study is needed on the prevalence, risk factors, and outcomes in adults and children with COVID-19. We sought to characterize neurological manifestations of COVID-19 among hospitalized adults and children in a large, international registry, with the aim of determining the prevalence of neurological diagnoses, risk factors, and associations with outcomes; differences between adults and children; and trends over time.

Here, we present data on the prevalence of neurological manifestations and complications from an international cohort of hospitalized COVID-19 patients registered in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 database. This repository collects data from 1507 sites across 61 countries. The primary aim was to describe different neurological manifestations present on admission and in-hospital neurological complications in children and adults. The secondary aims included risk factors, outcomes, and trends over time for in-hospital neurological complications.

Materials and methods

Study design

We conducted a retrospective analysis of a multicentre, international observational dataset to ascertain the prevalence and characteristics of neurological manifestations at hospital admission, and the occurrence of neurological complications during hospitalization. Data were collected according to the ISARIC-WHO Clinical Characterisation Protocol, a prospective study of hospitalised patients that aims to characterise emerging infections.[14] Study sites aimed to enroll

as many hospitalised individuals with COVID-19 as possible, according to locally available resources. Individuals laboratory confirmed SARS-CoV2 infection, and hospitalised (or admitted to ICU according to site implementation), were enrolled. A small number of sites recruited only patients admitted to ICU (**Supplementary Table 1**). Where resource constraints limited recruitment, sites were advised to utilise recruitment strategies to minimise bias.

Of these individuals, 261,161 were evaluated, as of 25 May 2021, for neurological manifestations and in-hospital neurological complications by clinical teams at study sites. The study was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements. Informed consent was taken in most settings, according to locally approved procedures, or waivers where granted. De-identified data were submitted to the ISARIC database by direct entry to Research Electronic Data Capture (REDCap, version 8.11.11, Vanderbilt University, Nashville, TN) hosted by the University of Oxford or by secure file transfer when locally managed data collection systems were used. All data submitted to the ISARIC data platform were harmonized to the CDISC SDTM standard (Study Data Tabulation Model; version 1.7, Clinical Data Interchange Standards Consortium, Austin, TX). Available data included demographics, comorbidities, signs and symptoms, clinical assessments, laboratory data, medications, procedures, and outcomes. Glasgow Coma Score was collected as part of the neurological baseline variable at admission. The study protocol and case report forms (CRFs) are available online (ISARIC CCP and ISARIC CRF, respectively).

Cohorts

The study cohort for analysis included all patients of any age enrolled in the ISARIC/WHO global database with laboratory confirmed COVID-19 infection who were hospitalized between January 30, 2020, and May 25, 2021. Children were defined as those less than 18 years of age. Completed analyses reported outcomes for all patients, in addition to stratification by critical care, defined as admission to intensive care unit (ICU) at any time during hospitalization. We excluded patients who were missing information on hospital admission and discharge dates, ICU admission, or neurological manifestations/complications (**Figure 1**). Availability of data on neurological variables is summarized in **Supplemental Table 1.** Cohort characteristics by geographic region and income classification are summarised in **Supplemental Table** 2. A detailed description of characteristics for all patients included in this dataset is available online

(https://www.medrxiv.org/content/10.1101/2020.07.17.20155218v13).

Selected characteristics documented at hospital admission and during hospitalization were summarized for all patients and grouped by whether or not patients were admitted to the ICU. In addition to ICU admission, we assessed the severity of critical illness and outcomes when invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) was needed for support.

Definitions

Neurological manifestations of COVID-19 at admission that were reported in CRFs included altered consciousness, fatigue, anosmia, dysgeusia, myalgia, and seizure at admission. CRF-reported in-hospital neurological complications were CNS infection (meningitis/encephalitis), new seizures during hospitalization, and stroke.

Outcomes

The primary outcome was the description of neurological manifestations present on admission and in-hospital neurological complications in children and adults. The secondary outcome was in-hospital mortality, accounting for associations with known risk factors, trends over time, and in-hospital neurological complications.

Statistical analysis

All continuous variables are summarized as medians with interquartile ranges (IQRs). Categorical variables are reported as frequencies with percentages. Summaries of data completeness per variable are in **Supplemental Table 3**.

We analyzed neurological manifestations reported at hospital admission and neurological complications during hospitalization using all available data collected as prespecified fields in study CRFs (**Table 1**). For analyses of neurological manifestations and neurological complications, we considered unadjusted prevalence estimates for predefined patient subgroups and adjusted estimates as a function of patient age and time of hospitalization (month/year) using generalized linear models (GLMs). All GLMs assumed a binary response (yes/no) and fixed effects for age, sex, month/year of hospitalization, and contributing study site as a potential confounder (**Figure 1**). Age and month/year of hospitalization were treated as continuous variables and modeled via polynomial terms up to an order of 3 with model selection performed using Akaike's Information Criterion. Model estimates were summarized as marginal effects, and uncertainty was reported by 95% confidence intervals (CIs).

Unadjusted odds ratios (ORs) with 95% CIs were calculated for neurological complications when we compared ICU to non-ICU cohorts in **Table 2**. Adjusted ORs (aORs) from multivariable analyses accounted for prespecified variables and determined the association between covariates and neurological complications.

Secondary analysis and missing data

We examined associations between neurological complications and in-hospital mortality and used unadjusted analyses to investigate the cumulative incidence of death and discharge up to 100 days from hospitalization. In multivariable analysis, we used logistic regression models to examine associations with the odds of in-hospital mortality based on recorded final disposition. For multivariable analyses, missing data on independent variables were assumed missing at random, and values were imputed by Multiple Imputing using Chained Equations (MICE). To account for differences in data collection across CRFs, MICE was applied independently to each study cohort. Completeness of data included in multivariable analyses of variables is reported in **Supplemental Table 3.** Unadjusted cumulative incidence functions were computed for patients with reported stroke, in-hospital seizures and CNS infection. Functions were further computed for a matched subset of controls, defined as patients who did not experience any neurological complications during hospitalisation. Controls were matched based on study cohort, month/year of hospitalisation, geographical subregion, sex and age (5-year age bands); up to 10 matched controls per patient with a reported neurological complication.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Our primary study cohort included 161 239 patients (158 267 adults and 2972 children) with acute COVID-19 infection, of which 35 993 (22.3%) patients were admitted to an ICU and 125 246 (77.7%) were hospitalized in non-ICU beds (**Figure 1 and Supplemental Figure 1**). Among the ICU cohort, 15 961 (44.3%) were admitted to the ICU on the same day as initial COVID-19 hospitalisation. Demographic characteristics and comorbidities of the COVID-19 cohort are summarized in **Table 1**. Overall, 56.7% were male, and median age was 69 years (IQR=54–81). The median time from symptom onset to hospitalization was 5 days (IQR=1–8).

After hospitalization, 65.6% of patients were discharged alive and 24.1% died; the remaining patients were transferred to other facilities for further treatment (7.1%) or had recovered from COVID-19 but remained hospitalized (3.2%). Among the ICU cohort (n=35 993), more than half of all patients (52.3%) were admitted to the ICU on the first day of admission (**Supplemental Table 4**). ICU patients were younger than non-ICU patients (61 vs. 73 years) and had a higher frequency of obesity (21.4% vs. 11.4%; **Table 1**). Additional characteristics of the ICU cohort, including the use of invasive mechanical ventilation and ECMO, are presented in the **Supplemental Table 4**.

Neurological manifestation at presentation

Adults vs. children

Fatigue was the most commonly reported neurological manifestation of acute COVID-19 at admission (adults: 37.4%; children: 20.4%). All neurological manifestations were more frequent in adults than in children, except for seizures (adults: 1.1%; children: 5.2%). One in 20 children presented with a seizure, a frequency approximately 5 times greater than that in adults (**Table 2**). Notably, altered consciousness was substantially more common in adults (20.9%) than in children (6.8%), and prevalence increased with age (**Table 2, Supplemental Figure 2)**.

ICU vs. non-ICU

Altered consciousness, fatigue, and myalgia were more prevalent in children admitted to the ICU than in children admitted to a non-ICU floor (P<.001), whereas anosmia, dysgeusia, and seizure were similarly present in both cohorts. Surprisingly, adults with COVID-19 infection requiring ICU admission were less likely to present with altered consciousness than those on non-ICU floors (10.8% vs. 24.0%; OR=0.39; 95% CI=0.37–0.40, P<.001) and less likely to have seizure (0.8% vs. 1.2%; OR=0.67; 95% CI=0.58–0.76, P<.001) as their initial neurological presentation (**Table 2**).

In-hospital neurological complications

Adults vs. children

In-hospital neurological complications (CNS infection, seizure, and stroke) were rare in both adults and children. In the overall cohort, 0.22% (95% CI=0.20%–0.24%) had CNS infection, 1.0% (95% CI=0.98%–1.10%) experienced seizures, and 1.5% (95% CI=1.4%–1.5%) suffered acute stroke during the index hospitalization with COVID-19. Again, seizure was more frequent in children (3.0%) than in adults (1.0%; **Table 2**); reported in-hospital seizures decreased with

increasing age (**Figure 2**) The frequency of stroke increased with increasing age. In contrast, CNS infection and seizure proportions steadily decreased with increasing age (**Figure 2**).

ICU vs. non-ICU

In children, ICU patients (n=443) were more likely than non-ICU patients (n=2529) to have in-hospital neurological complications, whereas the frequency of neurological complications was not as distinct in ICU and non-ICU adult cohorts (**Table 2**). Notably, ICU patients who received ECMO had a higher prevalence of stroke (ECMO: 7.2%; non-ECMO: 1.6%; OR=4.68; 95% CI=3.48–6.28, *P*<.001) and seizure (ECMO: 2.8%; non-ECMO: 1.4%; OR=2.02; 95% CI=1.30–3.14, *P*<.001; **Supplemental Table 5**) than those who did not receive ECMO.

Risk factors for in-hospital neurological complications

Chronic neurological disorder was associated with all neurological complications (CNS infection, seizures, and stroke; **Figure 2**). Specifically, underlying hypertension (aOR=1.38; 95% CI=1.25–1.52) and chronic neurological disease (aOR=1.34; 95% CI= 1.21–1.48) increased the odds of acute stroke (**Supplemental Table 6**). Among initial neurological manifestations, only altered consciousness and seizure at presentation were consistently associated with in-hospital neurological complications (**Figure 2**). In other words, patients with acute COVID-19 infection who developed neurological complications more frequently presented with altered consciousness and seizure at admission. As expected, seizure at initial presentation had a strong effect on recurrent seizures (aOR=69.42; 95% CI=60.67–79.43; **Supplemental Table 6**). Altered consciousness at hospital admission was strongly associated with CNS infection (aOR=5.31; 95% CI=4.01–7.04) and moderately associated with seizures (aOR=1.77; 95% CI=1.55–2.03) and stroke (aOR=1.95; 95% CI=1.77–2.15; **Supplemental Table 6**).

Neurological complications were reported more often among patients who received invasive mechanical ventilation during hospitalisation, versus patients who did not. The adjusted odds of stroke (aOR=3.77; 95% CI=2.74–5.19) indicated higher incidence of stroke reported among ECMO patients, as reflected in unadjusted estimates (**Supplementary Table 5**). The reported incidence of all complications decreased over time, most notably for stroke which decreased from 3.5% at the start of the initial COVID-19 outbreak (95% CI=2.63–4.55) to 0.25% by the end of the study timeframe (95% CI=0.13–0.46) (**Figure 2**). Steady declines in seizure and CNS infection were also observed, however, absolute changes were small in line with low baseline incidence (Seizure: 0.64% to 0.44%; CNS infection: 0.63% to 0.004%).

Mortality

Overall, mortality was significantly higher in adults than in children (24.5% vs. 2.2%, OR=14.3, 95% CI=11.3–18.4, *P*<.001). This contrast held true in both ICU (adults vs. children: 32.5% vs. 7.4%, OR=5.99, 95% CI=4.27-8.71, *P*<.001) and non-ICU settings (adults vs. children: 22.2% vs. 1.3%, OR=21.6, 95% CI=15.6-31.0, *P*<.001). Death was more frequent for patients admitted to the ICU than for those not admitted to the ICU (32.2% vs. 21.8%, OR=1.71, 95% CI=1.67-1.76, *P*<.001; **Table 1**). The likelihood of death rose steadily with increasing age, especially after 25 years of age, in both ICU and non-ICU patients, though mortality at any age was lower in non-ICU patients (**Supplemental Figure 3**). As the COVID-19 pandemic progressed from 2020 to 2021, mortality in the non-ICU cohort decreased significantly but changed little for ICU patients (**Supplemental Figure 2**).

Among ICU patients with neurological complications, the cumulative probability of death increased over the first 30 days of ICU admission (**Supplemental Table 7, Figure 3, and Supplemental Figure 4**). In non-ICU patients with stroke, the cumulative probabilities of death and discharge were similar regardless of admission duration (**Figure 3**).

Discussion

In this study to characterize neurological manifestations of COVID-19 among hospitalized adults and children in the ISARIC registry, we found that nonspecific symptoms of fatigue and altered consciousness were the most common at admission. Altered consciousness was 3.5 times less common in children than in adults, whereas seizure (as an initial manifestation) was 5 times more frequent in children. Altered consciousness and seizure at admission were strong risk factors for in-hospital neurological complications after adjusting for covariates (**Figure 2**). Although there is limited data in cerebrospinal fluid or imaging data to establish the causality or direction association, an important clinical implication of this analysis is that the possibility of CNS infection should be considered for patients presenting with seizures or altered consciousness at the time of hospital admission for COVID-19. Neurological manifestations on presentation, such as anosmia, ageusia, fatigue, and myalgia, were more common in adults admitted to the ICU than in those admitted to a non-ICU floor. However, caution is needed when interpreting these results, as these nonspecific neurological symptoms are reported in up to 80% of surveyed patients with COVID-19.[7,8]

In-hospital neurological complications were infrequent in our cohort, with 1.5% for strokes, 1.0% for seizures, and 0.2% for CNS infections. These rates are in keeping with prior data on adults with COVID-19.[7,8] Authors of the Global Consortium Study of Neurologic Dysfunction in COVID-19, which used detailed definitions of neurological complications for hospitalized patients, reported a 3% incidence of strokes, 1% incidence of seizures, and <1% incidence of CNS infection.[7,8] In the International Multicentre Coronavirus Disease 2019 Critical Care Consortium Study, acute stroke was reported in 2.2% of patients, with hemorrhagic stroke being the dominant type in ICU patients. That study also noted that this risk was 10 times higher in the subset of patients receiving ECMO.[7,8]

Overall mortality was lower in our study cohort at 24.1%, likely because the proportion of patients who required ICU care was relatively lower (22.3%) compared to a systematic review and meta-analysis of 24,983 patients demonstrating 32% ICU admission and 39% in-hospital mortality.[15] Although neurological complications were not common in our study, they have been noted to be the most strongly associated with reduced ability for self-care and worse functional outcome on hospital discharge.[16] In our study, such complications were also associated with in-hospital mortality in our multivariable model estimates (**Supplemental Table 7**). Therefore, given the high prevalence of COVID-19, neurological complications will be a substantial global public health and social care burden in the near future.

Our study showed that the cumulative probability of in-hospital mortality increased most acutely in the first 30 days for ICU patients who had in-hospital neurological complications and was most pronounced for those with stroke. However, it continued increasing up to 100 days after hospital admission, emphasizing the importance of vigilant neurological evaluation for patients with long hospitalizations (**Figure 3**) as large vessel occlusion in acute ischemic stroke is common (>20%)[17] and early detection with standardized neuromonitoring may improve the neurological outcome in ICU patients.[18] Also, it's important to note that the rate of change in the cumulative probability curves decreased over time, indicating the risk and hazard of neurological complications are high early in the disease course. In a previous study that used a 31-day follow-up, the increased frequency of ischemic stroke was 10 times higher than normal in the 14 days after a COVID-19 diagnosis, and the risk remained up to 6 times higher than normal at 31 days.[14,19] The risk of acute myocardial infarction was also assessed to be 5 times higher in the 14 days after a COVID-19 diagnosis. The authors postulated that the underlying mechanisms may

include cytokine-mediated plaque destabilization and hypercoagulability.[14,19] This is likely in line with the fact that early variants were associated with more severe illness requiring hospitalization and ICU admission.[20]

Notably, our study showed a dramatic decline in stroke frequency whereas seizure frequency remained steady over time (**Figure 2**). Several possible explanations might account for the decrease in stroke frequency during the pandemic. Treatment of COVID-19 changed rapidly after the initial clinical experience, such as with widespread use of high-intensity thromboprophylaxis and avoidance of mechanical ventilation (with the concomitant need for more sedation), for example. Global trends in these management approaches may have reduced the impact of COVID-19–related coagulopathy or reduced hypotension and shock associated with aggressive use of mechanical ventilation. Another possibility is that early variants of SARS-CoV-2 had greater inflammatory and coagulopathy effects. Other explanations are that resources for neuroimaging became reduced as the pandemic progressed, with parallel reductions in surveillance for stroke, or that the initial population of patients enrolled in the registry had a greater baseline risk of stroke, before public health messages about high-risk, vulnerable groups taking extra precautions against contracting COVID-19 became widespread. More research is needed to better understand the factors related to this strong trend.

Evidence regarding the neurological effects of COVID-19 in children is more limited than that for adults. Our study included 2365 patients younger than 18 years and noted a different profile and frequency of neurological manifestations in this cohort. Except for seizures, all neurological manifestations and complications were less frequent in children than in adults. Interestingly, we showed a linear decrease in the prevalence of seizures as age increased. This finding is likely consistent with pediatric seizures where febrile seizure or CNS infection related seizures are more common in younger age.[21] A similar pattern was observed for CNS infection, which decreased with age, whereas the prevalence of stroke increased sharply with increasing age (**Figure 2**). A prevalence study in the UK pediatric and adolescent population (<18 years) identified neurological and psychological complications in 52 cases of 1334 children linked to COVID-19.[6] The authors reported a 0.4% incidence of CNS infection and 0.07% incidence of transient ischemic attack.

Severe illness requiring ICU admission was closely associated with in-hospital neurological complications. Invasive mechanical ventilation and especially extracorporeal

support were associated with elevated risks of neurological complications (**Supplemental Table 5**). The risk of stroke was 8.3% among those receiving extracorporeal support, substantially higher than the 4.5% frequency reported in the Extracorporeal Life Support Registry among patients receiving veno-venous ECMO for non-COVID-19 acute respiratory distress syndrome (ARDS).[22]

Limitations

The spectrum of neurological manifestations and complications of COVID-19 is broader than the CRF terms included in the patient registry. Patient recruitment strategies varied between sites and were subject to staff and resource limitations, introducing the possibility of recruitment bias in some sites. Challenges exist in defining and capturing neurological manifestations[1] and in establishing causation,[23] especially in complex ICU patients with ARDS and when COVID-19 therapies can have iatrogenic neurological side effects. For analysis of neurological manifestations, we used data available at the time of hospital admission; however, data availability on neurological complications was limited to reports at any time during hospitalization. Having neurological manifestations at admission such as seizure or altered consciousness may have biased clinicians to investigate and find more in-hospital neurological complications. The use of sedative and analgesic drugs within the ICU setting may have influenced the reporting of these variables. Additional information on the timing of neurological complications would have allowed for more detailed analysis on the risk of complications over the course of hospitalization and time-dependent associations with mortality, as well as the timing of invasive ventilation and ECMO relative to the development of complications.[8] Certain variables such as Glasgow Coma Scale and smoking status where there is a large missingness in data should be interpreted carefully. Also, the absence of control patients without COVID-19 in the ISARIC dataset prevented estimation of specificity or positive and negative predictive values. Future studies need to more rigorously apply standardized definitions, report temporal relationships, and exclude alternate etiologies to better differentiate primary COVID-19 neurological sequelae from associated comorbidities and iatrogenic causes. Additionally, it is essential that ongoing research into neurological complications of COVID-19 record vaccination status, the temporal relationship between presentation and neurological complications, and the specific COVID-19 variant affecting the patient. Finally, we did not investigate Guillain-Barré

Syndrome (GBS), as it was not part of the CRF. However, it is of particular relevance given the COVID-19 vaccine hesitancy worldwide. GBS is reported to occur at 145 excess cases per 10 million people after a positive SARS-CoV-2 test, which is greater than the 38 excess cases of GBS per 10 million people receiving ChAdOx1nCoV-19 vaccinations.[24]

Conclusions

We report a low but not insignificant prevalence of neurological complications that can be anticipated in hospitalized patients with COVID-19. This study adds to the body of evidence that adults and children have different neurological manifestations and in-hospital complications after acute COVID-19 infection. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age. The results of this study can assist in healthcare planning given the long-term impact of these complications.

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Antonelli, M. declares unrestricted research grants from GE and Estor/Toray, Board participation from Pfizer and Shionogi. All unrelated to the present work

Bosse, Hans Martin is co-investigator for placebo studies in infants and children in clinical trials by Actelion/Janssen (Johnson&Johnson), outside the submitted work

Cheng, M. declares grants from McGill Interdisciplinary Initiative in Infection and Immunity, grants from Canadian Institutes of Health Research, during the conduct of the study; personal fees from GEn1E Lifesciences (as a member of the scientific advisory board), personal fees from nplex biosciences (as a member of the scientific advisory board), outside the submitted work. He is the co-founder of Kanvas Biosciences and owns equity in the company. In addition, M. Cheng

reports a patent Methods for detecting tissue damage, graft versus host disease, and infections using cell-free DNA profiling pending, and a patent Methods for assessing the severity and progression of SARS-CoV-2 infections using cell-free DNA pending.

Cholley, B. declares personal fees (for lectures and participation to advisory boards) from Edwards, Amomed, Nordic Pharma, and Orion Pharma.

Cruz-Bermúdez, J.L. declares personal fees from Elsevier for advice, outside the submitted work.

Cummings, M. and O'Donnell, M. participated as investigators for clinical trials evaluating the efficacy and safety of remdesivir (sponsored by Gilead Sciences) and convalescent plasma (sponsored by Amazon) in hospitalized patients with COVID-19. Support for this work is paid to Columbia University.

Dalton, H. declares personal fees for medical director of Innovative ECMO Concepts and honorarium from Abiomed/BREETHE Oxi-1 and Instrumentation Labs. Consultant fee, Entegrion Inc., Medtronic and Hemocue.

Dyrhol-Riise, AM, declares grants from Gilead outside this work.

Deplanque, D. declares personal fees from Biocodex, Bristol-Myers Squibb and Pfizer (advisory boards)

Donnelly, C.A. declares research funding from the UK Medical Research Council and the UK National Institute for Health Research.

Douglas, J.J. declares personal fees from lectures from Sunovion and Merck; consulting fees from Pfizer.

Durante-Mangoni, E. declares funding via his Institution from MSD, Pfizer, and personal fees or participation in advisory boards or participation to the speaker's bureau of Roche, Pfizer, MSD, Angelini, Correvio, Nordic Pharma, Bio-Merieux, Abbvie, Sanofi-Aventis, Medtronic, Tyrx and DiaSorin.

Grasselli, G. declares personal fees from Getinge, Biotest, Draeger Medical, Fisher & Paykel, MSD and unrestricted research grant from MSD and Fisher & Paykel, all outside the submitted work.

Gruner, H has nothing to declare with respect to the present work.

Guerguerian AM. Participated as site investigator for the Hospital For Sick Children, Toronto, Canada as a site through SPRINT-SARI Study via the Canadian Critical Care Trials Group

sponsored in part by the Canadian Institutes of of Health Research.

Hammond, TC declares consulting fees from Regeneron, Pfizer and Agenus.

Ho, A. declares grant funding from Medical Research Council UK, Scottish Funding Council - Grand Challenges Research Fund, and the Wellcome Trust, outside this submitted work.

Holter, J. C. reports grants from Research Council of Norway grant no 312780, and from Vivaldi Invest A/S owned by Jon Stephenson von Tetzchner, during the conduct of the study.

Hulot, J.S. reports grants from Bioserenity, Sanofi, Servier and Novo Nordisk.; speaker, advisory board or consultancy fees from Amgen, Astra Zeneca, Bayer, Bioserenity, Boerhinger Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Novo Nordisk, Vifor (all unrelated to the present work)

Kimmoun, A. declares personal fees (payment for lectures) from Baxter, Aguettant, Aspen.

Kumar, D. declares grants and personal fees from Roche, GSK and Merck; and personal fees from Pfizer and Sanofi.

Kutsogiannis, D.J. declares personal fees for a lecture from Tabuk Pharmaceuticals and the Saudi Critical Care Society

Kutsyna, G. declares the study consulting fee for clinical trial ClinicalTrials.gov Identifier: NCT04762628

Laffey, J. reports that he has received fees for consultancy from GlaxoSmithKline and from Baxter Therapeutics for work outside the scope of this work.

Lairez, O. declares grant funding from Pfizer; conference fees from Amicus, GE Healthcare, Novartis, Sanofi-Genzyme, and Takeda-Shire; and consultancy fees from Alnylam, Amicus, Pfizer, Takeda-Shire.

Lee, J. reports grants from European Commission PREPARE grant agreement No 602525, European Commission RECOVER Grant Agreement No 101003589 and European Commission ECRAID-Plan Grant Agreement 965313825715 supporting the conduct, coordination and management of the work.

Lee, T.C. declares research salary support from les Fonds de recherche du Québec – Santé.

Lefèvre, B. declares travel/accommodation/meeting expenses from Mylan and Gilead, all outside the submitted work.

Lellouche, F. declares grants from CIHR for COVID-19 studies, is co-founder and administrator of Oxynov.inc, fees from Fisher&Paykel, Vygon and Novus

Lemaignen, A. declares personal fees (payment for lectures) from MSD and Gilead; and

travel/accommodation/meeting expenses from Pfizer.

Leone, M declares personal fees from Gilead, MSD, Aspen, Ambu and Amomed

Lescure, F.X. declares personal fees (payment for lectures) from Gilead, MSD; and travel/accommodation/meeting expenses from Astellas, Eumedica, MSD.

Lim, W.S. declares his institution has received unrestricted investigator-initiated research funding from Pfizer for an unrelated multicentre cohort study in which he is the Chief Investigator, and research funding from the National Institute for Health Research, UK for various clinical trials outside the submitted work.

Liu, K. reports personal fees from MERA and receives a salary from TXP Medical completely outside the submitted work.

Maier, Lars S. has nothing to declare with respect to the present work.

Martin-Blondel G declares support for attending meetings and personal fees from BMS, MSD, Janssen, Sanofi, Pfizer and Gilead for lectures outside the submitted work.

Martin-Loeches I. declared lectures for Gilead, Thermofisher, Pfizer, MSD; advisory board participation for Fresenius Kabi, Advanz Pharma, Gilead, Accelerate, Merck; and consulting fees for Gilead outside of the submitted work.

Mentré F, declares consulting fees from IPSEN, Servier and Da Volterra, and reports research grants to her group from Sanofi, Roche, Servier and Da Voleterra, all outside the submitted work.

Montrucchio, G declares personal fees for lecture from Pfizer, Gilead outside the submitted work.

Murthy, S declares receiving salary support from the Health Research Foundation and Innovative Medicines Canada Chair in Pandemic Preparedness Research.

Nichol, A. declares a grant from the Health Research Board of Ireland to support data collection in Ireland (CTN-2014-012), an unrestricted grant from BAXTER for the TAME trial kidney substudy and consultancy fees paid to his institution from AM-PHARMA.

Nseir S. declares lectures for Gilead, Pfizer, MSD, Biomérieux, Fischer and Paykel, and Bio Rad, outside the submitted work.

Openshaw, P. has served on scientific advisory boards for Janssen/J&J, Oxford Immunotech Ltd, GSK, Nestle and Pfizer (fees to Imperial College). He is Imperial College lead investigator on EMINENT, a consortium funded by the MRC and GSK. He is a member of the RSV Consortium

in Europe (RESCEU) and Inno4Vac, Innovative Medicines Initiatives (IMI) from the European Union.

Peltan, I.D. declares grant support from the National Institutes of Health and, outside the submitted work, grant support from Centers for Disease Control and Prevention, National Institutes of Health, and Jannsen and payments to his institution from Regeneron and Asahi Kasei Pharma.

Pesenti, A. declares personal fees from Maquet, Novalung/Xenios, Baxter, and Boehringer Ingelheim.

Peytavin G., declares consulting fees (for lectures and/or participation in advisory boards) and travel grants from Gilead Sciences, Janssen, Merck, Takeda, Theratechnologies, and ViiV Healthcare.

Poissy, J. declares personal fees from Gilead for lectures, outside the submitting work

Povoa, P. declares personal fees (for lectures and advisory boards) from MSD, Technophage, Sanofi, and Gilead.

Póvoas, D. declares consulting fees (for lectures and/or participation in advisory boards) from Roche and Viiv Healthcare; and travel/accommodation/meeting expenses from Abbvie, Gilead Sciences, Janssen Cilag, Merck Sharp & Dohme and ViiV Healthcare

Rewa, O. declares honoraria from Baxter Healthcare Inc and Leading Biosciences Inc.

Rossanese, A. declares consulting fees (for lectures and/or participation to advisory boards) from Emergent BioSolutions and Sanofi Pasteur, but all outside of the frame of the submitted work.

Săndulescu, O. has been an investigator in COVID-19 clinical trials by Algernon Pharmaceuticals, Atea Pharmaceuticals, Regeneron Pharmaceuticals, Diffusion Pharmaceuticals, and Celltrion, Inc. and Atriva Therapeutics, outside the scope of the submitted work.

Semple, M.G. reports grants from DHSC National Institute of Health Research UK, from the Medical Research Council UK, and from the Health Protection Research Unit in Emerging & Zoonotic Infections, University of Liverpool, supporting the conduct of the study; other interest in Integrum Scientific LLC, Greensboro, NC, USA, outside the submitted work.

Serpa Neto, A. declares personal lecture fees from Drager outside the submitted work.

Serrano-Balazote, P.. declares funding via his Institution from Novartis and Janssen, and personal fees or participation in advisory boards or participation to the speaker's bureau of Roche, all outside of the submitted work.

Shrapnel, S. participated as an investigator for an observational study analysing ICU patients with COVID-19 (for the Critical Care Consortium including ECMOCARD) funded by The Prince Charles Hospital Foundation during the conduct of this study. S. Shrapnel reports in kind support from the Australian Research Council Centre of Excellence for Engineered Quantum Systems (CE170100009).

Streinu-Cercel, Adrian has been an investigator in COVID-19 clinical trials by Algernon Pharmaceuticals, Atea Pharmaceuticals, Regeneron Pharmaceuticals, Diffusion Pharmaceuticals, and Celltrion, Inc., outside the scope of the submitted work.

Streinu-Cercel, Anca has been an investigator in COVID-19 clinical trials by Algernon Pharmaceuticals, Atea Pharmaceuticals, Regeneron Pharmaceuticals, Diffusion Pharmaceuticals, and Celltrion, Inc. and Atriva Therapeutics, outside the scope of the submitted work.

Summers, C. reports that she has received fees for consultancy for Abbvie and Roche relating to COVID-19 therapeutics. She was also the UK Chief Investigator of a GlaxoSmithKline plc sponsored study of a therapy for COVID, and is a member of the UK COVID Therapeutic Advisory Panel (UK-CTAP). Outside the scope of this work, Dr Summers' institution receives research grants from the Wellcome Trust, UKRI/MRC, National Institute for Health Research (NIHR), GlaxoSmithKline and AstraZeneca to support research in her laboratory.

Susanne Dudman reports grants from Research Council of Norway grant no 312780.

Tedder, R. reports grants from MRC/UKRI during the conduct of the study. In addition, R. Tedder has a patent United Kingdom Patent Application No. 2014047.1 "SARS-CoV-2 antibody detection assay" issued.

Terzi, N. reports personal fees from Pfizer, outside the submitted work.

Timsit, J.F. participated in an advisory board for MSD, Pfizer, nabriva, Gilead, Shionoghi, Medimune outside the submitted work. JF Timsit declared lecture fees from MSD, Biomerieux, Pfizer, Shionoghi.

Turtle, L. reports grants from MRC/UKRI during the conduct of the study and fees from Eisai for delivering a lecture related to COVID-19 and cancer, paid to the University of Liverpool.

Ullrich, R. reports grant funding to his institution from Apeptico, APEIRON, Biotest, Bayer, CCORE and Philips, as well as personal fees from Biotest. He holds European patent EP15189777.4 "Blood purification device" and equity in CCORE Technology GesmbH, a medical device research and development company.

Visseaux B. declares personal fees from BioMérieux, Qiagen and Gilead and research grants from Qiagen, all outside the submitted work.

West, E. reports grant funding from the Firland Foundation, the US CDC, and the Bill and Melinda Gates Foundation for studies of COVID-19, and grant funding from the US NIH for studies of other respiratory infections.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

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Figure Legends

Figure 1 Origin of study cohorts and breakdown of subgroups (ICU, non-ICU, adult, and children).

Figure 2 Results of multivariable analysis of neurological complications. A, Age trends. B, Trends over time. C, Forest plot for remaining fixed effects, including confounders. Raw values (Figure 2C) are presented in Supplemental Table 5. CNS, central nervous system; UK-CCP, United Kingdom Clinical Characterisation Protocol; COVID-19 CCC, COVID-19 Critical Care Consortium.

Figure 3 Cumulative probability (unadjusted, days) for in-hospital mortality (death) and discharge alive from hospital (discharge) for patients who developed neurological complications. Results are stratified by intensive care unit (ICU) and non-ICU cohorts. CNS, central nervous system.

Table 1 Characteristics Reported at Hospital Admission and Clinical Outcomes of all, ICU, and non-ICU Admitted COVID-19 Patients

	All patients (n=161 239)	ICU cohort (n=35 993)		Non-ICU cohort (n=125 246)	
		Adult (n=35 550)	Children (n=443)	Adult (n=122 717)	Children (n=2529)
Demographics					
Age, median (IQR), y	69 (54–81)	61 (51–71)	6 (1–14)	73 (56–83)	7 (1–14)
Sex, male, n (%)	91 380 (56.7)	23 270 (65.5)	249 (56.2)	66 463 (54.2)	1398 (55.3)
Time from first symptom of COVID-19 to hospitalization, median (IQR), days	5 (1–8)	6 (2–9)	2 (1–6)	4 (1–8)	2 (1–5)
Ethnicity, n (%)					
Black	4937 (3.1)	1789 (5.0)	45 (10.2)	2992 (2.4)	111 (4.4)
Caucasian	101 887 (63.2)	14 681 (41.3)	132 (29.8)	85 959 (70.0)	1115 (44.1)
Southeast Asian	19 724 (12.2)	8684 (24.4)	100 (22.6)	10 219 (8.3)	721 (28.5)
Mixed ethnicity	874 (0.5)	167 (0.5)	11 (2.5)	648 (0.5)	48 (1.9)
Other	5923 (3.7)	1 829 (5.1)	32 (7.2)	3926 (3.2)	136 (5.4)
Comorbidities reported at hospital admission					
Asthma, n (%)	19 386 (12.2)	4134 (11.8)	25 (5.7)	15 082 (12.5)	146 (5.8)
Chronic cardiac disease, n (%)[a]	43 821 (27.7)	6451 (18.4)	47 (10.7)	37 242 (31.0)	81 (3.2)
Chronic kidney disease, n (%)[b]	23 255 (14.7)	2995 (8.5)	11 (2.5)	20 198 (16.8)	52 (2.1)
Chronic neurological disorder, n (%)[c]	17 199 (10.9)	2372 (6.8)	53 (12.0)	4646 (12.2)	128 (5.1)
Chronic pulmonary disease, n (%)[d]	22 624 (14.3)	2 935 (8.4)	14 (3.2)	19 631 (16.3)	44 (1.8)
Dementia[e], n (%)	17 543 (11.6)	596 (1.8)	0 (0)	16 942 (14.6)	5 (0.2)
Diabetes mellitus, n (%)	47 406 (29.8)	11 839 (33.7)	53 (12.1)	35 362 (29.2)	153 (6.1)
GCS at admission, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)
Hypertension, n (%)	61 601 (45.2)	14 456 (46.3)	26 (6.4)	47 058 (45.9)	61 (2.7)
Liver disease, n (%)	5044 (3.1)	1122 (3.2)	7 (1.6)	3901 (3.2)	14 (0.6)
Obesity, n (%)	19 117 (13.7)	6833 (21.6)	18 (4.5)	12 217 (11.7)	49 (2.1)
Smoking, n (%)[f]	38 071 (39.8)	6514 (36.0)	10 (3.6)	31 477 (41.9)	70 (3.2)
Mechanically ventilated, n (%)	19 130 (12.1)	18 614 (53.2)	153 (34.9)	18 767 (52.9)	363 (0.3)
Outcome, n (%)					
Continued hospitalization	5216 (3.2)	3030 (8.5)	28 (6.3)	2138 (1.7)	20 (0.8)
Died	38 847 (24.1)	11 568 (32.5)	33 (7.4)	27 213 (22.2)	33 (1.3)
Discharged	105 770 (65.6)	18 225 (51.3)	337 (76.1)	84 859 (69.2)	2349 (92.9)
Transferred to other facility	11 406 (7.1)	2727 (7.7)	45 (10.2)	8507 (6.9)	127 (5.0)
Time from hospitalization to outcome, median (IQR), days					
Continued hospitalization	28 (6–37)	7 (4–28)	9 (3–28)	37 (29–61)	34 (31–64)
Death	11 (6–20)	12 (7–20)	7 (5–16)	11 (6–20)	9 (4–15)
Discharged	9 (5–17)	13 (8–24)	9 (4–14)	9 (5–16)	4 (2–11)
Transfer to other facility	15 (8–28)	16 (7–34)	5 (3–13)	15 (9–27)	9 (4–12)

GCS, Glasgow coma scale; ICU, intensive care unit; IQR, interquartile range.

See Supplementary Table 2 for a summary of data completeness on baseline characteristics.

[a]Chronic cardiac disease: any of coronary artery disease, heart failure, congenital heart disease, cardiomyopathy, or rheumatic heart disease; not hypertension.

[b]Chronic kidney disease: chronic estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or history of kidney transplantation.

[c]Chronic neurological disorder: any of cerebral palsy, multiple sclerosis, motor neuron disease, muscular dystrophy, myasthenia gravis, Parkinson's disease, stroke, severe learning difficulty.

[d]Chronic pulmonary disease: chronic bronchitis, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, bronchiectasis, interstitial lung disease, pre-existing requirement for long-term oxygen therapy; not asthma.

[e]Clinical diagnosis of dementia

[f]Smokers included current and former smokers.

Table 2 Neurological Manifestations Reported at Hospital Admission and Neurological Complications Reported During Hospitalization of all, ICU, and non-ICU Admitted COVID-19 Patients

	All patients[a] (n=161 239)	ICU cohort[a] (n=35 993)	Non-ICU cohort[a] (n=125 246)	Unadjusted OR[b] (95% CI)	*P* value
Neurological manifestations reported at hospital admission					
Altered consciousness					
Children	161/2365 (6.80)	50/418 (12)	111/1947 (5.70)	2.25 (1.55–3.18)	<0.001
Adults	30 569/146 269 (20.90)	3687/34 052 (10.80)	26 882/112 217 (24.00)	0.39 (0.37–0.40)	<0.001
Anosmia					
Children	48/2135 (2.20)	3/312 (0.96)	45/1823 (2.50)	0.38 (0.09–1.06)	0.110
Adults	6589/110 315 (6.00)	1637/26 022 (6.30)	4952/84 293 (5.90)	1.08 (1.01–1.14)	0.013
Dysgeusia					
Children	39/2068 (1.90)	4/299 (1.30)	35/1769 (2.00)	0.67 (0.20–1.70)	0.445
Adults	8028/108 491 (7.40)	1814/25 387 (7.10)	6214/83 104 (7.50)	0.95 (0.90–1.01)	0.077
Fatigue					
Children	548/2680 (20.40)	122/401 (30.40)	426/2279 (18.70)	1.90 (1.50–2.41)	<0.001
Adults	54 205/145 029 (37.40)	12 380/33 395 (37.10)	41 825/111 634 (37.50)	0.98 (0.96–1.01)	0.191
Myalgia					
Children	191/2526 (7.60)	48/376 (12.80)	143/2150 (6.70)	2.05 (1.44–2.89)	<0.001
Adults	23 638/139 538 (16.90)	6428/32 379 (19.90)	17 210/107 159 (16.10)	1.29 (1.25–1.34)	<0.001
Seizure					
Children	124/2403 (5.20)	28/429 (6.50)	96/1974 (4.90)	1.37 (0.87–2.80)	0.160
Adults	1558/142 554 (1.10)	267/33 685 (0.79)	1291/108 869 (1.20)	0.67 (0.58–0.76)	<0.001
Neurological complications reported during hospitalization					
CNS infection[c]					
Children	10/2962 (0.34)	3/438 (0.68)	7/2524 (0.28)	2.49 (0.65–8.62)	0.147
Adults	342/157 456 (0.22)	162/35 047 (0.46)	180/122 409 (0.15)	3.66 (3.04–4.42)	<0.001
Seizure[d]					
Children	88/2965 (3.0)	31/439 (7.10)	57/2526 (2.30)	4.42 (3.02–6.47)	<0.001
Adults	1558/157 524 (0.99)	468/35 073 (1.30)	1090/122 451 (0.89)	1.68 (1.52–1.84)	<0.001
Stroke[e]					
Children	3/2864 (0.10)	2/405 (0.49)	1/2459 (0.04)	18.63 (2.75–364.82)	0.009
Adults	2273/152 325 (1.50)	591/33 266 (1.80)	1682/119 059 (1.40)	1.39 (1.29–1.51)	<0.001

CNS, central nervous system; ICU, intensive care unit; non-ICU, patients not admitted to the ICU at any point during hospitalization; OR, odds ratio.

[a]Unadjusted OR compares the groups ICU and non-ICU.

[b]Data are presented as n/total n (%). Total n differs for each category because of missing data.

[c]CNS infection includes meningitis or encephalitis.

[d]Seizure regardless of cause (e.g. febrile or due to epilepsy)

[e]Stroke may be a clinical diagnosis, with or without supportive radiological findings

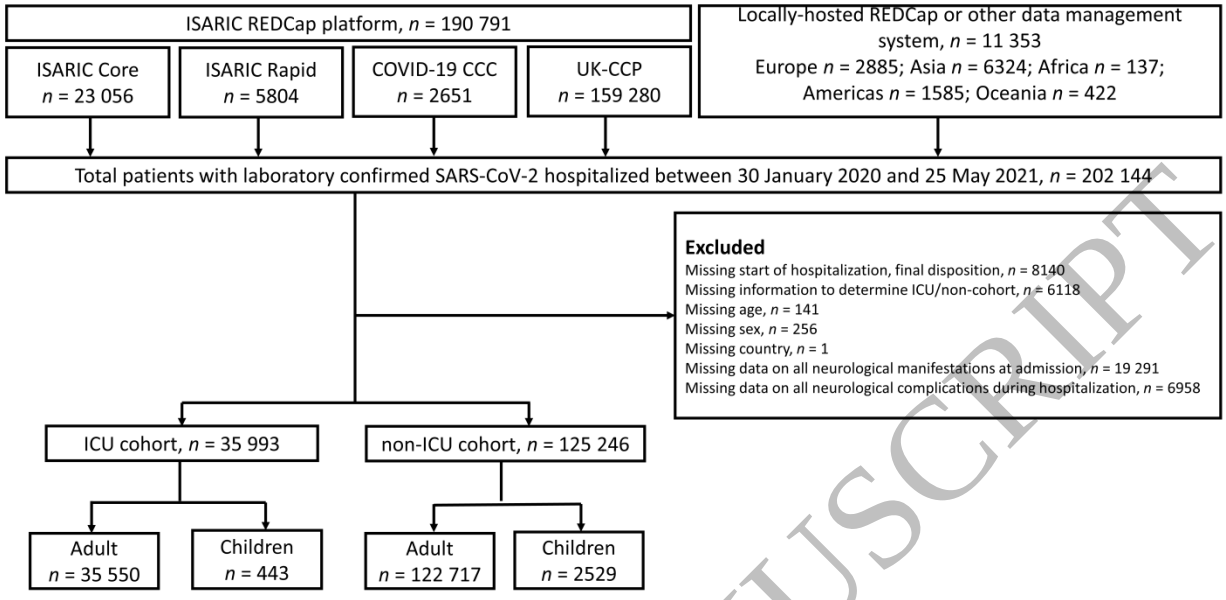

Figure 1
324x165 mm (.36 x DPI)

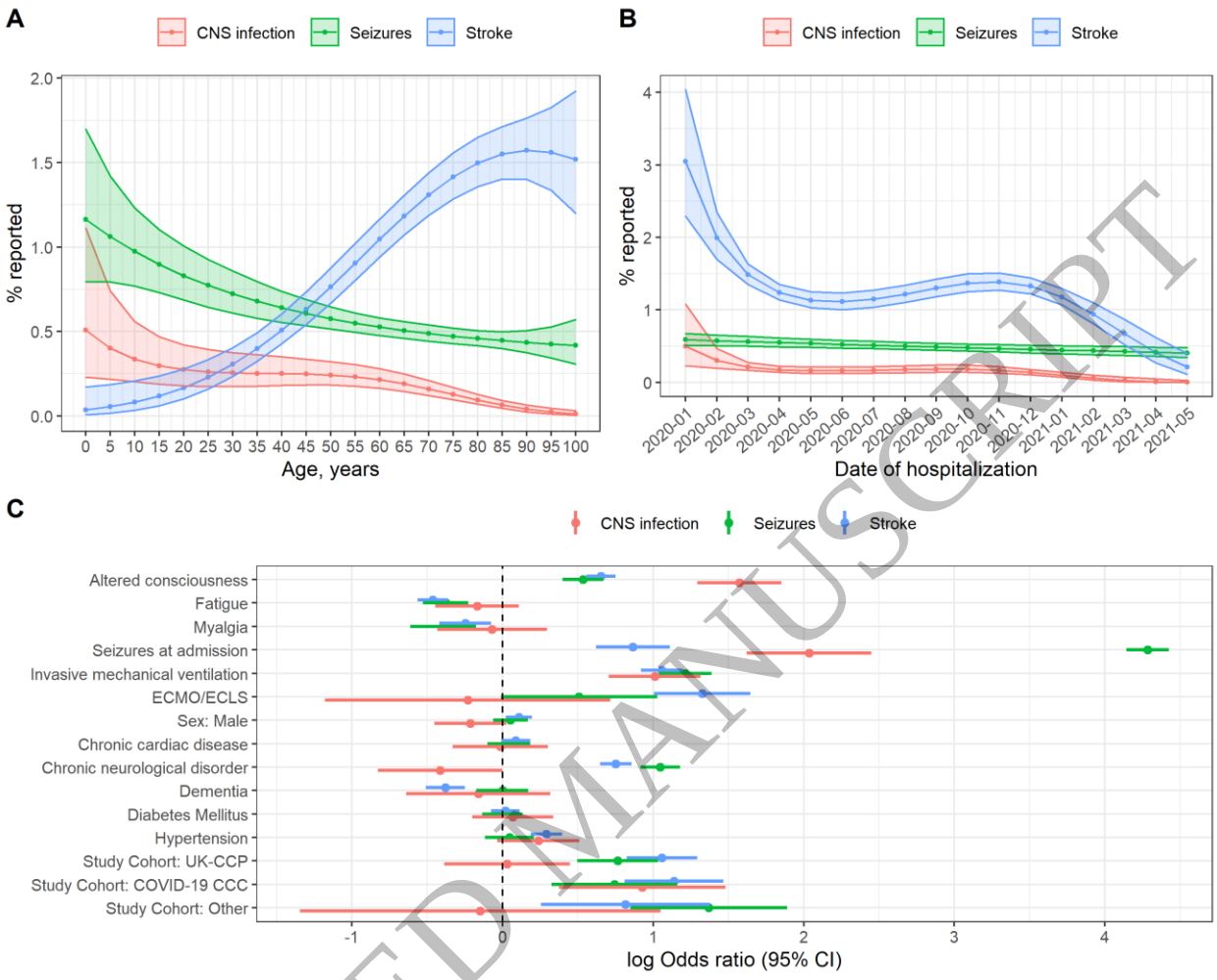

Figure 2
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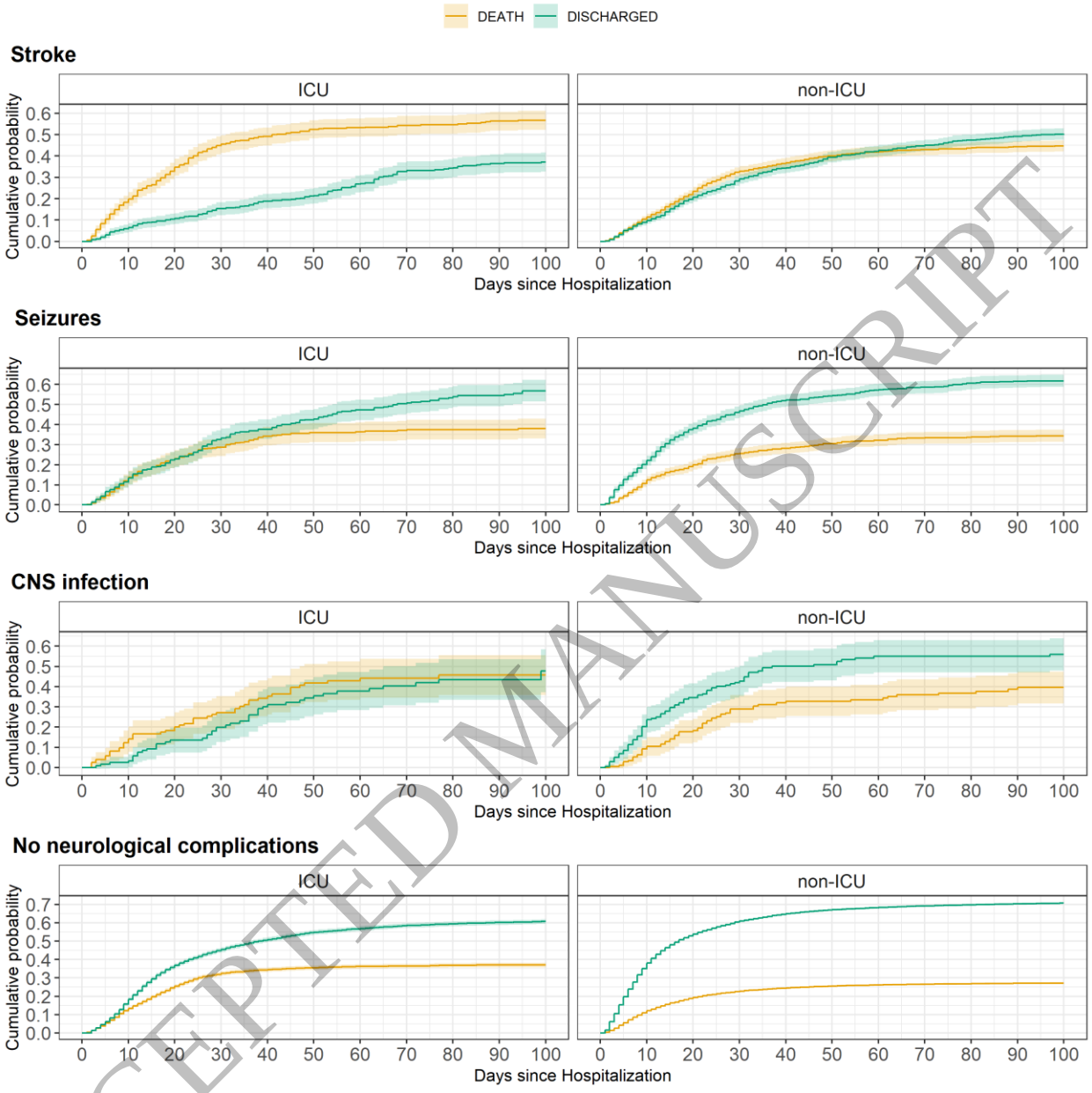

Figure 3
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