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Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Hospitalized Patients During the First Year of the COVID-19 Pandemic

Anna M. Cervantes-Arslanian, MD[1–3]
Chakradhar Venkata, MD[4]
Pria Anand, MD[1]
Joseph D. Burns, MD[5–7]
Charlene J. Ong, MD[1,2]
Allison M. LeMahieu, MS[8]
Phillip J. Schulte, PhD[8]
Tarun D. Singh, MD[9]
Alejandro A. Rabinstein, MD[9]
Neha Deo, BS[10]
Vikas Bansal, MBBS, MPH[11]
Karen Boman, BS[12]
Juan Pablo Domecq Garces, MD[11]
Donna Lee Armaignac, PhD, APRN[13]
Amy B. Christie, MD[14]
Roman R. Melamed, MD[15]
Yasir Tarabichi, MD, MSCR[16,17]
Sreekanth R. Cheruku, MD, MPH[18]
Ashish K. Khanna, MD, FCCP, FCCM, FASA[19,20]
Joshua L. Denson, MD, MS[21]
Valerie M. Banner-Goodspeed, MPH[22]
Harry L. Anderson III, MD, FACS, FICS, FCCM, FCCP, FAIM[23]
Ognjen Gajic , MD, MS[11]
Vishakha K. Kumar, MD, MBA[12]
Allan Walkey, MD[24]
Rahul Kashyap, MD, MBA[25]
on behalf of the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group

OBJECTIVES: To describe the prevalence, associated risk factors, and outcomes of serious neurologic manifestations (encephalopathy, stroke, seizure, and meningitis/encephalitis) among patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DESIGN: Prospective observational study.

SETTING: One hundred seventy-nine hospitals in 24 countries within the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry.

PATIENTS: Hospitalized adults with laboratory-confirmed SARS-CoV-2 infection.

INTERVENTIONS: None.

RESULTS: Of 16,225 patients enrolled in the registry with hospital discharge status available, 2,092 (12.9%) developed serious neurologic manifestations including 1,656 (10.2%) with encephalopathy at admission, 331 (2.0%) with stroke, 243 (1.5%) with seizure, and 73 (0.5%) with meningitis/encephalitis at admission or during hospitalization. Patients with serious neurologic manifestations of COVID-19 were older with median (interquartile range) age 72 years (61.0–81.0 yr) versus 61 years (48.0–72.0 yr) and had higher prevalence of chronic medical conditions, including vascular risk factors. Adjusting for age, sex, and time since the onset of the pandemic, serious neurologic manifestations were associated with more severe disease (odds ratio [OR], 1.49; $p < 0.001$) as defined by the World Health Organization ordinal disease severity scale for COVID-19 infection. Patients with neurologic manifestations were more likely to be admitted to the ICU (OR, 1.45; $p < 0.001$) and require critical care interventions (extracorporeal membrane oxygenation: OR, 1.78; $p = 0.009$ and renal replacement therapy: OR, 1.99; $p < 0.001$). Hospital, ICU, and 28-day mortality for patients with neurologic manifestations was higher (OR, 1.51, 1.37, and 1.58; $p < 0.001$), and patients had fewer ICU-free, hospital-free, and ventilator-free days (estimated difference in days, −0.84, −1.34, and −0.84; $p < 0.001$).

CONCLUSIONS: Encephalopathy at admission is common in hospitalized patients with SARS-CoV-2 infection and is associated with worse outcomes. While serious neurologic manifestations including stroke, seizure, and meningitis/encephalitis were less common, all were associated with increased ICU support utilization, more severe disease, and worse outcomes.

KEY WORDS: COVID-19; encephalitis; meningitis; seizure; severe acute respiratory syndrome coronavirus 2; stroke

Overwhelming evidence shows that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes dysfunction of multiple organ systems, including the nervous system. Neurologic symptoms are frequently reported even in patients with mild acute illness and

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for some, these neurologic symptoms may persist as part of long-haul COVID. More serious neurologic manifestations in hospitalized patients, including stroke have been reported in case series, single health system studies, and administrative database studies (1–3), with limited data from multicenter prospective studies (4, 5). We report serious neurologic manifestations of SARS-CoV-2 infection from the Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry (6) and describe prehospital risk factors and associated outcomes.

METHODS

Ethics and Standardization

The study was approved by Institutional Review Boards (IRBs) at participating centers, with the Mayo Clinic serving as the primary IRB (Number 20-002610). The study was conducted under a waiver of consent. The study is registered at ClinicalTrials.gov (identifier NCT04323787).

Data Collection

The VIRUS: COVID-19 Registry contains de-identified, HIPAA compliant data characterizing patients hospitalized with SARS-CoV-2 infection. Study sites entered the data through Research Electronic Data Capture, a secure web-based software and workflow methodology for electronic collection and management of research data (7, 8).

Study Population and Protocol

This is an international prospective, cross-sectional, observational study of hospitalized patients (age 18 yr and older) with SARS-CoV-2 infection (6) between March 25, 2020, and March 9, 2021. Patients who tested positive for SARS-CoV-2 via polymerase chain reaction within 21 days of hospitalization were included. Patients without outcome data or hospital discharge/mortality status were excluded. The manifestations of interest (encephalopathy, seizure, stroke, meningitis/encephalitis) were defined in the Critical Care Data Dictionary provided to the study sites. Patients with encephalopathy at admission were identified from the registry database. Encephalopathy during hospitalization was not captured due to concern for multiple confounders often present in hospitalized patients and concerns for potential inconsistent acquisition of this data point. Seizure, stroke, and meningitis/encephalitis were assessed as admission diagnoses or hospital complications. Patient demographics, comorbidities, medication use, critical care interventions, hospital complications, and clinical outcomes were extracted from the registry database. The prevalence of neurologic manifestations was determined in aggregate as well as for each condition.

Variables

Overall demographics, prehospitalization medical conditions, and outcomes of the study population were stratified by whether patients had one of the neurologic manifestations of interest. We used an ordinal scale proposed by the World Health Organization (WHO) to measure the disease severity due to COVID-19 (9). The outcome recorded corresponds with the highest severity level recorded during a patient's index hospitalization. Other outcomes included ICU admission, mortality (hospital, ICU, and 28 d), and hospital-free, ICU-free, and ventilator-free days.

Statistical Analysis

Patient demographics were summarized using median (25th–75th) for continuous variables and frequency counts and percentages for categorical variables. These characteristics were presented separately for patients with and without neurologic manifestations. We evaluated the frequency of neurologic manifestations and the association of outcomes with neurologic manifestations.

We used unadjusted logistic regression models to assess the association between neurologic manifestations and patient characteristics. To account for clustering of patients within hospitals, we used models fitted with generalized estimating equations (GEEs) and an exchangeable working correlation. We used similar unadjusted logistic regression models with GEE to test the association between stroke and patient characteristics of interest. Unadjusted and multivariable adjusted logistic regression models with GEE assessed the association between neurologic manifestations and binary outcomes of interest. Similarly, we assessed the association between neurologic manifestations and continuous outcomes using unadjusted and multivariable adjusted linear regression models

with GEE. Adjustment variables included age, sex, and admission date in quarter year since March 2020.

There was minimal missing data for key variables (**Supplemental Table 1**, http://links.lww.com/CCX/A977). We used multiple imputation to handle missing data for variables assuming data are missing at random. Fifty imputed datasets were created, analyses run on each, and results pooled across imputations to account for uncertainty in missingness. Two-tailed *p* values of 0.05 or less were considered statistically significant. Data management and statistical analysis were performed in SAS Studio 3.8 (SAS Institute, Cary, NC).

RESULTS

Prevalence of Neurologic Manifestations

The VIRUS registry enrolled 65,850 hospitalized patients (age > 18 yr) from March 25, 2020, to March 9, 2021. At time of data analysis, 16,225 patients had information regarding 28-day outcomes or hospital discharge mortality and were included (**Fig. 1**). Serious neurologic manifestations were noted in 2,092 patients (12.9%), with 1,840 (11.3%) diagnosed at admission. This was largely driven by the finding of encephalopathy in 1,656 patients (10.2%) at admission. Four hundred fourteen patients (2.6%) developed stroke, seizure, or meningitis/encephalitis at admission or during hospitalization. Among the serious neurologic manifestations, stroke was reported in 331 patients (2.0%), seizures occurred in 243 patients (1.5%), and meningitis/encephalitis occurred in 73 patients (0.4%).

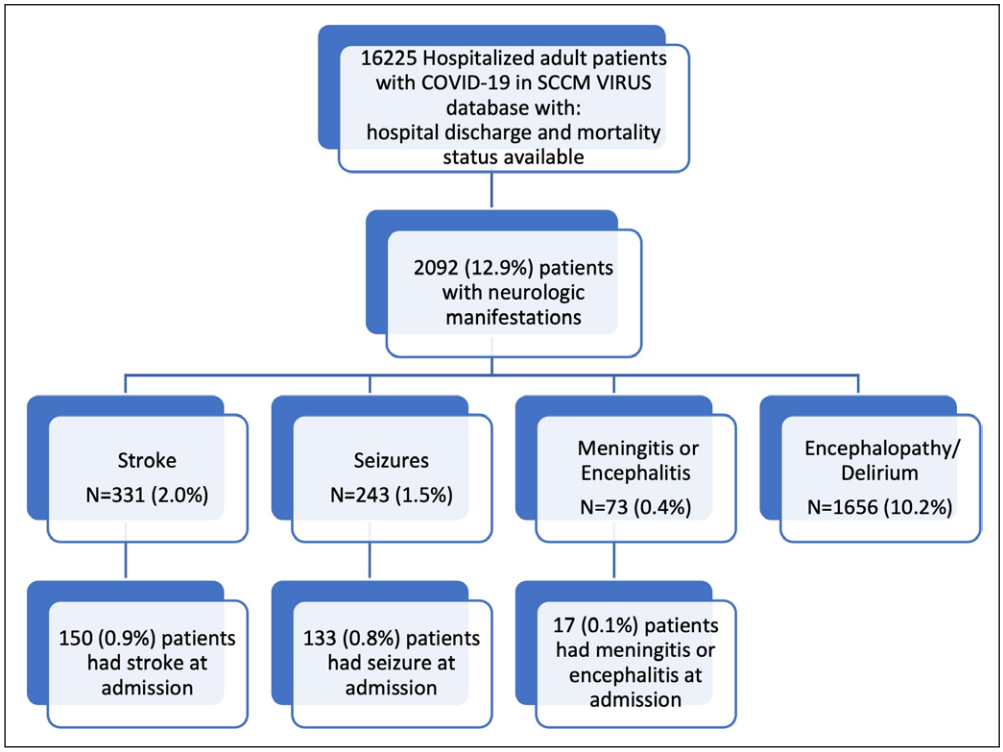

Figure 1. Flowchart of patients included in the study and the prevalence of neurologic manifestations. The total number of patients with neurologic manifestations is less than the sum of the four manifestations, as some patients had more than one manifestation. SCCM = Society of Critical Care Medicine, VIRUS = Viral Infection and Respiratory Illness Universal Study.

Characteristics of Patients Who Developed Neurologic Manifestations

Older patients were more likely to develop neurologic manifestations (median age, 72.0 yr; interquartile range [IQR], 61.0–81.0 yr compared with median age, 61.0 yr; IQR, 48.0–72 yr in those without; $p < 0.001$). Neurologic manifestations occurred equally in men and women. When compared with White patients, Black patients had higher odds of developing neurologic manifestations (odds ratio [OR], 1.26; 1.09–1.46; $p = 0.002$) and South Asian patients had lower odds for developing neurologic manifestations (OR, 0.33; 0.18–0.61; $p < 0.001$) (**Supplemental Table 2**, http://links.lww.com/CCX/A977). Patients with neurologic manifestations were more likely to have medical comorbidities (**Table 1**). The ORs for these associations are shown in **Table 2**. Most notably, a history of stroke or neurologic disorder increased the odds of developing a neurologic manifestation 3.62 times (3.22–4.08; $p < 0.001$) and specifically dementia conferred the highest risk (4.74; 3.97–5.65; $p < 0.001$) of all factors identified.

Demographics and past medical history profiles differed among neurologic manifestations (**Supplemental Table 3**, http://links.lww.com/CCX/A977). There was no difference in the odds of developing neurologic manifestations related to

TABLE 1.
Demographics and Past Medical History of Patients With and Without Neurologic Manifestations (*n* = 16,225)

Characteristic	Neurologic Manifestations (*n* = 2,092)	No Neurologic Manifestations (*n* = 14,133)	*p*
Age, median (Q1–Q3), *n* = 16,225	72.0 (61.0–81.0)	61.0 (48.0–72.0)	< 0.001
Gender, *n* = 16,213, *n* (%)			0.029
Female	948 (45)	6,045 (43)	
Male	1,143 (55)	8,077 (57)	
Body mass index, median (Q1–Q3), *n* = 12,239	27.5 (23.7–32.9)	29.4 (25.4–34.9)	< 0.001
Race, *n* = 16,202, *n* (%)			< 0.001
Black or African American	689 (33)	3,197 (23)	
Mixed race	32 (2)	498 (4)	
Other	176 (8)	1,575 (11)	
South Asian	26 (1)	1,377 (10)	
Unknown	30 (1)	214 (2)	
West Asian	29 (1)	243 (2)	
White	1,110 (53)	7,006 (50)	< 0.001
Past medical history, *n* = 16,225, *n* (%)			
Hypertension	1,406 (67)	7,593 (54)	< 0.001
Diabetes	887 (42)	4,960 (35)	< 0.001
Coronary artery disease	616 (29)	2,795 (20)	< 0.001
Cardiac arrhythmia	345 (16)	1,205 (9)	< 0.001
Stroke or other neurologic disorders	611 (29)	1,273 (9)	< 0.001
Valvular heart disease	85 (4)	306 (2)	< 0.001
Congestive heart failure	349 (17)	1,319 (9)	< 0.001
Dyslipidemia/hyperlipidemia	513 (25)	2,787 (20)	< 0.001
Chronic kidney disease	466 (22)	1,850 (13)	< 0.001
Chronic dialysis	88 (4)	347 (2)	< 0.001
Liver disease	77 (4)	451 (3)	0.240
Obesity	357 (17)	2,911 (21)	< 0.001
Chronic pulmonary disease (not asthma)	310 (15)	1,742 (12)	0.001
Asthma	153 (7)	1,402 (10)	< 0.001
Hypothyroidism	244 (12)	1,163 (8)	< 0.001
Dementia	444 (21)	659 (5)	< 0.001
Solid tumor without metastasis	194 (9)	844 (6)	< 0.001
Hematologic malignancy	81 (4)	538 (4)	0.880
Metastatic cancer	50 (2)	243 (2)	0.032
HIV/AIDS or other immunosuppression	30 (1)	153 (1)	0.160
History of solid organ or bone marrow transplant	24 (1)	218 (2)	0.160
Substance use disorder	118 (6)	400 (3)	< 0.001
Prehospital medication use, *n* = 16,225, *n* (%)			
Aspirin	609 (29)	2,658 (19)	< 0.001
Statin	841 (40)	3,998 (28)	< 0.001
Anticoagulant	293 (14)	1,290 (9)	< 0.001

TABLE 2.
Odds Ratios for Neurologic Manifestations

Univariate Logistic Regression Models		
Risk Factor	**OR (95% CI)**	***p***
Age[a]	1.21 (1.18–1.24)	< 0.001
Sex	1.04 (0.94–1.15)	0.436
Time since pandemic		0.357
4–6 mo	1.21 (0.92–1.60)	0.178
7–9 mo	1.07 (0.77–1.49)	0.679
10–12 mo	1.00 (0.68–1.48)	0.980
Hypertension	1.51 (1.34–1.70)	< 0.001
Cardiac arrhythmia	1.78 (1.55–2.04)	< 0.001
Diabetes	1.29 (1.16–1.43)	< 0.001
Coronary artery disease	1.47 (1.30–1.66)	< 0.001
Stroke or other neurologic disorder	3.62 (3.22–4.08)	< 0.001
Dementia	4.74 (3.97–5.65)	< 0.001
Chronic kidney disease	1.66 (1.43–1.92)	< 0.001
Dialysis	1.46 (1.12–1.91)	0.005
Chronic liver disease	1.08 (0.81–1.44)	0.588
Substance use	1.77 (1.41–2.22)	< 0.001
Smoking history		0.117
Current smoker	1.36 (1.08–1.70)	0.009
Former smoker	1.01 (0.86–1.19)	0.890
Unknown	1.36 (0.93–1.99)	0.117
Prehospital aspirin	1.59 (1.41–1.78)	< 0.001
Prehospital statins	1.46 (1.30–1.64)	< 0.001
Prehospital anti-coagulants	1.43 (1.24–1.65)	< 0.001

OR = odds ratio.

[a]ORs are displayed per 5 yr old.

The reference group for sex is Male. The reference group for race is White. The reference group for time since pandemic is 1–3 mo. The reference group for smoking history is none.

the time since the pandemic began. The ORs for risk factors for stroke are shown in **Supplemental Table 4** (http://links.lww.com/CCX/A977).

ICU Support Interventions

Adjusting for age, sex, and time since the pandemic began, patients with neurologic manifestations had higher odds of receiving extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT), and were less likely to undergo prone position ventilation (**Table 3**). Patients with stroke had 3.20 odds (1.94–5.28; $p < 0.001$) of requiring ECMO and 3.23 odds (1.83–5.71; $p < 0.001$) of requiring RRT, whereas there was no difference seen in proning. Patients with seizure had 2.78 higher odds (1.28–6.04; $p = 0.010$) of requiring ECMO. Patients with encephalopathy at admission had higher odds of requiring RRT (1.78; 1.20–2.65; $p = 0.004$) but were less likely to undergo proning (OR, 0.66; 0.52–0.83; $p < 0.001$ for proning on ventilator and OR, 0.47; 0.32–0.68; $p < 0.001$ for self-proning). ORs for ICU intervention by subtype are found in **Supplemental Table 5** (http://links.lww.com/CCX/A977).

TABLE 3.
ICU Support Utilization and Clinical Outcomes

ICU Support Interventions for Patients With Neurologic Manifestations (Covariate Adjusted Model)				
	Unadjusted		Adjusted	
ICU Intervention	OR (95% CI)	*p*	OR (95% CI)	*p*
Neurologic manifestations				
Extracorporeal membrane oxygenation	1.27 (0.82–1.95)	0.281	1.78 (1.16–2.74)	0.009
Renal replacement therapy	2.08 (1.63–2.65)	< 0.001	1.99 (1.50–2.65)	< 0.001
Proning on ventilation	0.78 (0.62–0.98)	0.031	0.78 (0.62–0.98)	0.035
Self-proning (not on ventilation)	0.47 (0.35–0.63)	< 0.001	0.49 (0.37–0.66)	< 0.001
Adjustment variables were age, sex, and time since the pandemic began				
Clinical Outcomes of Patients With Neurologic Manifestations (Proportional Odds Model)				
	Unadjusted		Adjusted	
Outcome	Estimate[a] (95% CI)	*p*	Estimate[a] (95% CI)	p
Neurologic manifestations				
Admitted to ICU	1.51 (1.32–1.74)	< 0.001	1.45 (1.27–1.65)	< 0.001
Hospital mortality	2.06 (1.84–2.30)	< 0.001	1.51 (1.37–1.68)	< 0.001
ICU mortality	1.75 (1.55–1.97)	< 0.001	1.37 (1.24–1.52)	< 0.001
28-d mortality	2.18 (1.95–2.43)	< 0.001	1.58 (1.43–1.76)	< 0.001
Hospital-free days	−1.73 (−2.45 to −1.01)	< 0.001	−1.34 (−1.99 to −0.69)	< 0.001
ICU-free days	−0.89 (−1.37 to −0.40)	< 0.001	−0.84 (−1.29 to −0.39)	< 0.001
Ventilation-free days	−0.92 (−1.36 to −0.48)	< 0.001	−0.84 (−1.27 to −0.42)	< 0.001

OR = odds ratio.

[a]Estimates are ORs for ICU admission, hospital mortality, ICU mortality, and 28-d mortality. Estimate for hospital-free days is the estimated difference in days alive and out of hospital in the 28 d from admission; patients who die have zero hospital-free days. Estimate for ICU-free days is the estimated difference in days alive and out of the ICU in the 28 d from admission; patients who die in the ICU have zero ICU-free days. Estimate for ventilation-free days is the estimated difference in days off of ventilation in the 28 d from admission.

Adjustment variables were age, sex, and time since pandemic.

Hospital and Clinical Outcomes

Patients who developed neurologic manifestations had greater odds of requiring ICU admission, higher mortality (hospital, ICU, and 28-d), and a lower number of ICU-, hospital-, and ventilator-free days (Table 3 and **Supplemental Table 5,** http://links.lww.com/CCX/A977). Patients with encephalopathy were more likely to be admitted to the ICU and had higher mortality (hospital, ICU, and 28-d). Meningitis/encephalitis was associated with higher odds of ICU admission and fewer hospital-free, ICU-free, and ventilator-free days but did not have higher mortality. Clinical outcomes by manifestation are found in Supplemental Table 5 (http://links.lww.com/CCX/A977).

Disease Severity

The WHO ordinal disease severity in COVID-19 was higher in patients with serious neurologic manifestations (**Fig. 2**). In the proportional odds regression model adjusted for age, sex, and time since the pandemic, we found disease severity was higher for patients who developed neurologic manifestations (OR, 1.49; 1.36–1.63; $p < 0.001$) (**Supplemental Table 6,** http://links.lww.com/CCX/A977). Among these conditions, the highest odds for higher disease severity were seen in patients with meningitis/encephalitis (OR, 2.07; 1.34–3.20; $p < 0.001$). Stroke (OR, 1.91; 1.55–2.35; $p < 0.001$), encephalopathy (OR, 1.36; 1.24–1.52; $p < 0.001$), and seizure

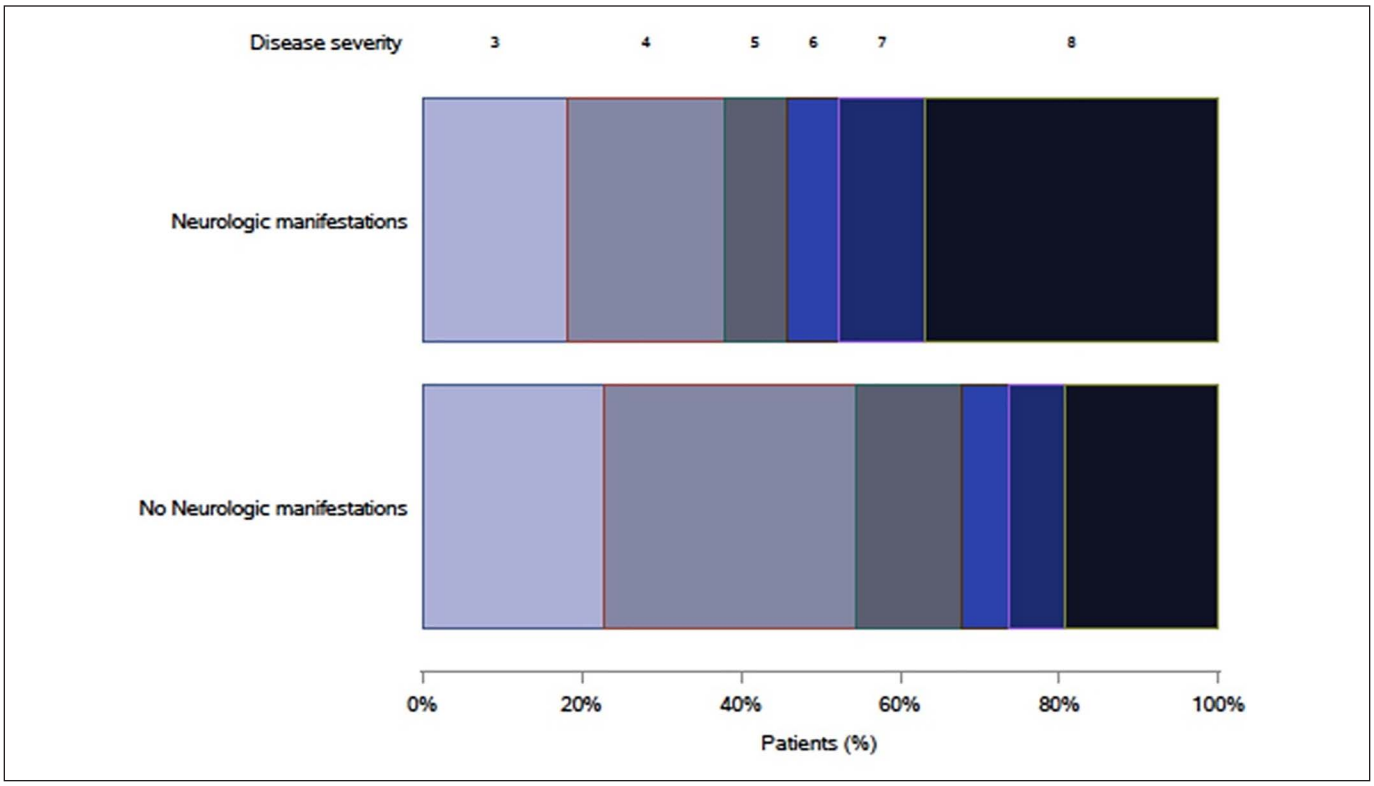

Figure 2. Outcomes between patients with and without neurologic manifestations according to the World Health Organization's ordinal scale for disease severity. Disease severity score of 3 indicates hospitalized with no supplemental oxygen; 4—requiring oxygen by mask or nasal prongs; 5—required noninvasive ventilation or high-flow oxygen support; 6—intubation and mechanical ventilation; 7—ventilation with additional organ support (vasopressors, renal replacement therapy, extracorporeal membrane oxygenation) and a disease severity score of 8 indicates death.

(OR, 1.81; 1.43–2.30; $p < 0.001$) were also associated with greater disease severity.

Sensitivity Analyses

To determine the influence of overall severity of illness, we analyzed a smaller cohort of patients with Sequential Organ Failure Assessment (SOFA) scores available on hospital day 1 ($n = 9{,}544$). When adjusted for age, SOFA score, sex, and time since the pandemic, patients with neurologic manifestations continued to have higher odds of ICU, hospital and 28-day mortality (OR, 1.18, 1.26, and 1.31, respectively; all with $p < 0.005$). In this model, stroke was associated with higher odds of ICU admission, mortality (hospital, ICU, and 28-d), and fewer hospital-, ICU-, and ventilator-free days. Only stroke was independently associated with an increased WHO severity (OR, 1.65; 1.24–2.2; $p < 0.001$) (**Supplemental Table 7**, http://links.lww.com/CCX/A977).

DISCUSSION

We report the prevalence, demographics, prehospital risk factors, and outcomes of patients with serious neurologic manifestations over the first year of the pandemic within a large international multicenter prospective registry of hospitalized patients with SARS-CoV-2 infection. Our findings show that encephalopathy at hospital admission is present in at least one in 10 patients with SARS-CoV-2 infection, while stroke, seizures, and meningitis/encephalitis were much less common at admission or during hospitalization. All serious neurologic manifestations were associated with increased disease severity, greater need for ICU interventions, longer length of stay and ventilator use, and higher mortality. Our findings underscore the importance of neurologic manifestations of SARS-CoV-2 infection.

While encephalopathy in COVID may be attributed to many etiologies, there is evidence to suggest that in

some patients, encephalopathy may be associated with cerebrovascular disease. A large cohort study found that COVID infection of any severity was associated with increased risk of stroke in the 6 months following discharge, but highest among those with encephalopathy during hospitalization, with almost one in 10 of such patients going to have an ischemic stroke (10). In our study, we observed that stroke patients often had encephalopathy at admission irrespective of the timing of stroke (admission vs during hospitalization). Neuropathology of severe cases with encephalopathy suggests widespread cerebrovascular changes, including microhemorrhage, diffuse intravascular microthrombosis, and endotheliitis (11–13). Similarly, brain MR images of patients with encephalopathy frequently demonstrate ischemic strokes even when not clinically apparent (14–16), and may show microhemorrhages with associated leukoencephalopathy (17), and white matter changes consistent with posterior reversible encephalopathy syndrome (18).

Encephalopathy has been uniformly associated with poorer short-term outcomes (2, 19), and this is supported by our findings of increased risk of ICU admission, utilization of RRT, and mortality. Little is known about the prognosis of critically ill COVID survivors with encephalopathy at hospital discharge. Growing literature provides optimism about delayed recovery of consciousness and benefit of intensive rehabilitation (20, 21).

Patients with stroke had increased use of ICU interventions including ECMO and RRT. Without knowledge of timing of stroke relative to these advanced treatments, we cannot determine the direction of the association. The majority of studies (22–25), but not all (26, 27) report stroke occurrence predominantly in critically ill patients. In our study, almost half of patients with stroke associated with SARS-CoV-2 infection were diagnosed upon admission, arguing against the idea that stroke occurs solely later in the course of prolonged critical illness. We found that stroke is associated with increased disease severity independent of hospital day 1 SOFA scores. This mirrors findings in a large meta-analysis including greater than 67,000 patients, where the odds of inhospital mortality in patients with COVID-19 and stroke were greater than those of uninfected stroke patients (28).

In our study, patients with strokes were on average older with the majority having underlying vascular risk factors, with greatest risk in those with a history of prior stroke and/or dementia. This suggests exacerbation of underlying cardiovascular and cerebrovascular disease as a main culprit etiology. However, many series reported younger average age in patients with stroke (27, 29, 30) and a meta-analysis has shown that while strokes on average occurred in older COVID-19 infected patients, patients with COVID-19 infection and stroke were typically younger than uninfected patients with stroke (25). It is notable that 13% of patients with stroke in our cohort had no identifiable vascular risk factors. Other early studies similarly noted an absence of typical risk factors in some patients (30), suggesting that stroke in COVID-19 may also occur due to less common mechanisms such as virally mediated hypercoagulability, cardiac-specific effects, cerebrovascular arteriopathy, or endotheliitis (11, 31–35).

Neurologic manifestations differed by race. Black patients had an increased frequency of stroke, seizure, and encephalopathy when compared with White patients. This mirrors data from single center studies showing increased neurologic manifestations, in particular stroke, among Black and Latinx patients (30, 36, 37). This could be due to disparities in underlying vascular risk factors, severity of illness at presentation, or potential differences in host tropism. Higher mortality for Black patients with COVID-19 associated stroke has been reported despite similar stroke severity at admission (38). Given the association of neurologic manifestations with poorer outcomes, further study is desperately needed to understand why these differences occur and what can be done to intervene.

Our study had several limitations. As a large multicenter general critical care registry, the primary study was not designed to capture important details that would define the neurologic manifestations, such as whether a stroke was ischemic or hemorrhagic, nor variables that would help characterize risk factors and neurologic outcomes. We were unable to determine the prevalence of overall encephalopathy in hospitalized patients with SARS-CoV-2 infection as this could only be captured as an admission symptom. We suspect there was under-reporting of neurologic manifestations among the most critically ill. Reduced ability to obtain diagnostic testing due to resource limitations during the pandemic or unstable clinical conditions may also have led to decreased diagnosis of neurologic

manifestations. Finally, because of our cross-sectional approach, we were unable to determine the sequence of events and define the severity of illness at the time of onset of neurologic manifestations.

Despite these limitations, our multicenter international study enhances the global understanding of the prevalence, risk factors, and outcomes for neurologic manifestations in hospitalized patients with SARS-CoV-2 infection. Strengths of this study include the large volume of patients included and the prospective method of data collection. Our study is unique including patients across the first year of the pandemic, therefore, describing near exclusively infection with the original SARS-CoV-2 strain (39). Furthermore, given the study period, the patients included did not likely have preexisting immunity to SARS-CoV-2 from vaccination or prior infection, which may be of value to future research.

In conclusion, encephalopathy occurs frequently upon hospital admission in patients with SARS-CoV-2 infection, while other serious neurologic manifestations are rare. All serious neurologic manifestations are associated with worse outcomes, including an increased risk of death. Further study is greatly needed to better understand which populations are most at risk for developing neurologic manifestations, the underlying pathophysiology of these manifestations, and how neurologic manifestations can be prevented and treated.

1 *Department of Neurology, Boston University School of Medicine and Boston Medical Center, Boston, MA.*

2 *Department of Neurosurgery, Boston University School of Medicine and Boston Medical Center, Boston, MA.*

3 *Department of Medicine (Infectious Diseases), Boston University School of Medicine and Boston Medical Center, Boston, MA.*

4 *Department of Critical Care Medicine, Mercy Hospital, St. Louis, MO.*

5 *Department of Neurology, Lahey Hospital and Medical Center, Burlington, MA.*

6 *Department of Neurology, Tufts University School of Medicine, Boston, MA.*

7 *Department of Neurosurgery, Tufts University School of Medicine, Boston, MA.*

8 *Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN.*

9 *Department of Neurology, Mayo Clinic, Rochester, MN.*

10 *Mayo Clinic Alix School of Medicine, Rochester, MN.*

11 *Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN.*

12 *Society of Critical Care Medicine, Mount Prospect, IL.*

13 *Center for Advanced Analytics, Baptist Health South Florida, Coral Gables, FL.*

14 *Atrium Health Navicent, Macon, GA.*

15 *Abbott Northwestern Hospital, Allina Health, Minneapolis, MN.*

16 *Center for Clinical Informatics Research and Education, MetroHealth Medical Center, Cleveland, OH.*

17 *Department of Pulmonary and Critical Care Medicine, MetroHealth Medical Center, Cleveland, OH.*

18 *Department of Anesthesiology and Medical Center, UT Southwestern Medical Center, Dallas, TX.*

19 *Wake Forest University School of Medicine, Winston-Salem, NC.*

20 *Atrium Health Wake Forest Baptist Network, Winston-Salem, NC.*

21 *Section of Pulmonary, Critical Care, and Environmental Medicine, Tulane University School of Medicine, New Orleans, LA.*

22 *Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Brookline, MA.*

23 *Department of Surgery, St. Joseph Mercy, Ann Arbor, MI.*

24 *Department of Medicine, Section of Pulmonary, Allergy, and Critical Care Medicine, Boston University School of Medicine and Boston Medical Center, Boston MA.*

25 *Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN.*

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For information regarding this article, E-mail: anna.cervantes@bmc.org

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