Ischemic and Hemorrhagic Stroke Among Critically Ill Patients With Coronavirus Disease 2019: An International Multicenter Coronavirus Disease 2019 Critical Care Consortium Study*

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OBJECTIVES: Stroke has been reported in observational series as a frequent complication of coronavirus disease 2019, but more information is needed regarding stroke prevalence and outcomes. We explored the prevalence and outcomes of acute stroke in an international cohort of patients with coronavirus disease 2019 who required ICU admission.

DESIGN: Retrospective analysis of prospectively collected database.

SETTING: A registry of coronavirus disease 2019 patients admitted to ICUs at over 370 international sites was reviewed for patients diagnosed with acute stroke during their stay.

PATIENTS: Patients older than 18 years old with acute coronavirus disease 2019 infection in ICU.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 2,699 patients identified (median age 59 yr; male 65%), 59 (2.2%) experienced acute stroke: 0.7% ischemic, 1.0% hemorrhagic, and 0.5% unspecified type. Systemic anticoagulant use was not associated with any stroke type. The frequency of diabetes, hypertension, and smoking was higher in patients with ischemic stroke than in stroke-free and hemorrhagic stroke patients. Extracorporeal membrane oxygenation support was more common among patients with hemorrhagic (56%) and ischemic stroke (16%) than in those without stroke (10%). Extracorporeal membrane oxygenation patients had higher cumulative 90-day probabilities of hemorrhagic (relative risk = 10.5) and ischemic stroke (relative risk = 1.7) versus nonextracorporeal membrane oxygenation patients. Hemorrhagic stroke increased the hazard of death (hazard ratio = 2.74), but ischemic stroke did not—similar to the effects of these stroke types seen in noncoronavirus disease 2019 ICU patients.

CONCLUSIONS: In an international registry of ICU patients with coronavirus disease 2019, stroke was infrequent. Hemorrhagic stroke, but not ischemic stroke, was associated with increased mortality. Further, both hemorrhagic stroke and ischemic stroke were associated with traditional vascular risk factors. Extracorporeal membrane oxygenation use was strongly associated with both stroke and death.

KEY WORDS: coronavirus disease 2019; extracorporeal membrane oxygenation; hemorrhagic stroke; ischemic stroke; intensive care unit

To date, the coronavirus disease 2019 (COVID-19) pandemic has resulted in over 100 million confirmed cases and 2 million deaths worldwide (1). Although COVID-19 is principally characterized by flu-like symptoms, extrapulmonary manifestations of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (COVID-19) infection can cause significant long-term

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morbidity and death (2). Many have reported that neurologic complications are common in COVID-19 patients (3), but mechanisms for neuronal injury and neurotropism remain unclear.

Evidence for an association between acute stroke and COVID-19 has grown. Although a few have reported reduced acute stroke admissions during the COVID-19 pandemic (4, 5), stroke risk appears to be greater in patients with COVID-19 than in those with influenza (1.6%; 95% CI, 1.1–2.3 vs 0.2%; 95% CI, 0.0–0.6, odds ratio [OR] = 7.6) (6). In one of the earliest studies from Wuhan, 11.4% of 88 patients hospitalized with severe COVID-19 suffered a stroke (7). Since then, many observational studies and case series have examined the frequency of ischemic and hemorrhagic stroke in hospitalized COVID-19 patients. In a recent meta-analysis (n = 108,571 patients), 1.4% had evidence of acute stroke (8), with 38% of those presenting with stroke as an initial reason for hospitalization, rather than presenting with classic COVID-19 symptoms (8). Thus, it is important to separately describe "stroke" as a complication of acute COVID-19 infection to understand associated risk factors and outcomes. However, sparse literature exists on stroke as a complication in COVID-19 patients with acute respiratory distress syndrome (ARDS) in ICUs.

The COVID-19 Critical Care Consortium (CCCC) is an international ICU network that was created to collect multicenter observational data on critically ill patients with confirmed or suspected COVID-19 infection (9). The goal of this CCCC data repository analysis was to determine stroke frequency in a diverse population of COVID-19 patients with severe infection, explore risk factors for stroke, and identify the effect of stroke on outcomes.

METHODS

Trial Registration

Study methods and design, and the rationale behind CCCC have been published previously (9).

Ethics Approval

All participating hospitals obtained approval from their local institutional review board. Waivers of informed consent were granted for all patients because the study was observational, data recorded in the central repository were deidentified, and there was minimal risk to participants. A complete summary of ethics and regulatory approvals is included in the main CCCC protocol (9).

Study Design and Population

The CCCC registry is currently enrolling COVID-19 patients from over 370 sites spanning 52 countries. All recruiting sites are listed in **Supplementary Information, Part I** (http://links.lww.com/CCM/G612). This study is reported using Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines. The CCCC database was examined for patients admitted to participating ICUs from January 1, to December 21, 2020. Inclusion criteria were as follows: 1) age greater than or equal to 18 years, 2) active symptomatic (determined by attending physician) COVID-19 infection (defined as a laboratory-confirmed COVID-19 infection (real-time polymerase chain reaction and/or next-generation sequencing), 3) admission to the ICU, and 4) known time of acute stroke onset verifying onset during the index ICU admission. All included patients had active COVID-19 requiring ICU admission. Asymptomatic patients with SARS-CoV-2 positive tests and patients with acute stroke prior to ICU admission were excluded.

Data Collection and Outcome Measures

Site investigators and study coordinators used a data dictionary and support from the CCCC coordination center to submit case report forms (**Supplementary Information, Part II**, http://links.lww.com/CCM/G612). Deidentified data from each site were uploaded to the Research Electronic Data Capture (REDCap) electronic database based at Oxford University, United Kingdom (10). Detailed descriptions of data collection, management, and access are available elsewhere (8).

For all enrolled patients, the following information was extracted from the CCCC database: demographics, morphometrics, comorbidities, medications, laboratory values, adverse events/complications, and outcomes. Additional case report forms were completed for patients who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Disease severity was rated with Acute Physiology and Chronic Health Evaluation (APACHE) II (11) and Sequential Organ Failure Assessment (SOFA) scores

at ICU admission (12). The CCCC data quality personnel contacted investigators who reported stroke complications to collect information on stroke type (ischemic, hemorrhagic, and unspecified), laterality, and date of onset.

Cerebrovascular events (strokes) included ischemic stroke, defined as new brain infarction determined by CT or MRI, and hemorrhagic stroke, defined as intra- or extraparenchymal brain hemorrhage confirmed by CT or MRI. Unspecified stroke was defined as a persistent focal neurologic deficit suspected by treating clinicians to be due to brain injury in the absence of definitive neuroimaging. In these cases, clinical reasons or resource limitations prevented neuroimaging. The main study aims were to determine the frequency of each stroke type and model the impact of stroke on hospital mortality. Patient characteristics and treatments associated with ischemic and hemorrhagic stroke were also investigated. Site investigators indicated the main cause of death from the following options: multiple organ failure, respiratory failure, cardiac failure, liver failure, stroke, septic shock, hemorrhagic shock, and other (to be specified with a free text response).

Statistical Analysis

Descriptive variables were grouped by stroke status and included demographic and morphometric characteristics, comorbidities, disease severity scores, ICU variables, and treatments. Continuous variables were summarized as median and interquartile range. Categorical variables were summarized as numbers and percentages.

Survival models were used to investigate the effect of stroke on the competing risks of death and discharge while adjusting for confounders, with separate survival analyses of ischemic and hemorrhagic stroke. Assessed confounders were age, sex, body mass index, and a site-specific random intercept to control for inter-ICU differences. The transition of patients over time was modeled using a multistate survival model with four states: ICU admission, stroke, death, and discharge from hospital (**Supplementary Information, Part III**, http://links.lww.com/CCM/G612). To determine whether ECMO increased the risk of stroke, we added an additional state (ECMO) to the model to account for the time-dependent nature of ECMO (e.g., patients receiving ECMO early in their ICU stay vs patients receiving it relatively late). The multistate model for ECMO and stroke also incorporated the timing of stroke events relative to the timing of ECMO treatment.

For survival analysis, we used parametric Weibull regression models to estimate instantaneous risk. Cumulative survival models were applied to estimate cumulative hazard ratios (HRs) for death, stroke, and discharge with CIs. Survival model results are presented as HRs with 95% credible intervals. We prefer using CIs over *p* values because CIs are more clinically meaningful and show the strength of associations, whereas *p* values do not indicate association strength and are prone to overinterpretation (13). The risk of stroke during the ICU stay, together with the competing risks of death and discharge, is illustrated as cumulative incidence curves. We verified the results of our parametric Weibull survival models using semiparametric Cox models and checked the proportional hazard assumptions of these models. We assessed for influential patients using leave-one-out analysis.

The association of stroke with anticoagulant use was assessed by case-control comparisons. Five controls per case were matched by age (within 2 yr) and ICU days, meaning that controls remained in the ICU but were stroke-free up to the day of their matched case. Results are summarized as ORs with 95% CI. We used the same case-control approach to assess for any association between stroke and selected clinically relevant laboratory variables, including WBC count, troponin I, Pao_2, $Paco_2$, arterial pH, interleukin-6, hemoglobin, D-dimer, and C-reactive protein. Detailed case-control analytic methods are described in Supplementary Information, Part III (http://links.lww.com/CCM/G612).

RESULTS

Stroke Prevalence

Overall, 2,699 COVID-19 patients (median age 59; male 65%) were enrolled, with over 80% from nine countries between January 1, and December 21, 2020 (the United States, Indonesia, Italy, South Africa, Spain, Chile, Colombia, Germany, Canada). Of the patients, 70% required mechanical ventilation and 10.5% ECMO. Overall, 75 patients had stroke as a complication. After excluding nine patients because

the timing of their stroke was unknown and seven because their stroke occurred before ICU admission (Supplementary Information Part II, http://links.lww.com/CCM/G612), the number of strokes ultimately analyzed was 59, for an overall proportion of 2.2%. Nineteen strokes (0.7%) were ischemic, 27 (1.0%) hemorrhagic, and 13 (0.5%) of unspecified type (**Table 1**). Most patients with hemorrhagic stroke experienced intraparenchymal hemorrhage (**Supplemental Fig. 1**, http://links.lww.com/CCM/G612). Stroke laterality is summarized in **Supplemental Table 1** (http://links.lww.com/CCM/G612).

Of 2,699 patients, 283 (10.5%) required ECMO support, predominantly venovenous (94%). In the ECMO cohort, 15 patients (5.3%) had hemorrhagic stroke, three (1.1%) ischemic stroke, and four (1.4%) unspecified type, for an overall stroke rate of 7.7%. Of these, only one ischemic stroke occurred before the ECMO cannulation. Conversely, among 2,415 non-ECMO patients, only 37 (1.4%) had strokes: 12 (0.4%) hemorrhagic, 16 (0.6%) ischemic, and nine (0.3%) unspecified stroke.

Age, sex, and body mass index were similar in the ischemic, hemorrhagic, and stroke-free groups. Although ischemic stroke was more frequent in Black and Latin-American patients, hemorrhagic stroke was more common in White patients (Table 1). Relative to stroke-free patients, patients with stroke had higher SOFA and APACHE II scores and required mechanical ventilation, vasopressor therapy, or ECMO more often. Frequencies of hypertension and chronic cardiac disease were higher for all stroke types compared with those in stroke-free patients.

ECMO support was far more common among patients with hemorrhagic stroke (56%) and slightly more common among ischemic stroke patients (16%) than in stroke-free patients (10%). The location of ECMO cannulation (internal jugular vs femoral) did not influence stroke rate (**Supplemental Tables 2** and **3**, http://links.lww.com/CCM/G612). Cannula size (F) at drainage and return sites were similar in stroke and nonstroke ECMO patients (**Supplemental Fig. 2**, http://links.lww.com/CCM/G612).

Matched Case-Control Analysis

Clinically relevant laboratory values of stroke patients were compared against those of stroke-free patients by matched case-control analysis. The only statistically significant differences were in Pao_2 and platelet count. Higher Pao_2 values taken closest to stroke were significantly associated with hemorrhagic stroke (median 76.4 vs 68.8 mm Hg in controls; OR = 3.8; 95% CI, 1.3–10.9), but not with ischemic stroke (81.5 vs 71.0 mm Hg; OR = 1.6; 95% CI, 0.4–6.2) (**Fig. 1**) (**Supplemental Table 4**, http://links.lww.com/CCM/G612). $Paco_2$ measurements close to the stroke were not associated with either stroke type. We used exploratory analysis to determine if an acute decrease in $Paco_2$ after ECMO cannulation was associated with stroke but identified no statistically significant difference between $Paco_2$ after ECMO cannulation and worst $Paco_2$ value before ECMO initiation (**Supplemental Fig. 3**, http://links.lww.com/CCM/G612). Platelet count on the day of stroke diagnosis was lower among patients with ischemic stroke (94,000/μL) than in matched controls (279,000/μL) (**Supplemental Table 5**, http://links.lww.com/CCM/G612), but similar between hemorrhagic stroke and control patients (238,000 vs 261,000/μL).

Case-control analysis showed no association between anticoagulant use and stroke. The proportion of patients with hemorrhagic stroke who had undergone anticoagulation was similar to that of matched, stroke-free controls (81% vs 76%) (**Supplemental Table 6*, a*** and ***b***, http://links.lww.com/CCM/G612). Therapeutic (i.e., systemic) anticoagulant use was more common than prophylactic use with hemorrhagic stroke (64% vs 5%), but less commonly observed with ischemic stroke (17% vs 33%) (**Supplemental Table 7**, http://links.lww.com/CCM/G612). However, anticoagulation was not associated with increased odds for either hemorrhagic or ischemic stroke (Supplemental Table 4, http://links.lww.com/CCM/G612). Nevertheless, the number of patients with missing anticoagulation therapy data limits confidence in this analysis (**Supplemental Fig. 4**, http://links.lww.com/CCM/G612).

Survival Model for Death and Discharge

The five-state survival model (ECMO, no ECMO, stroke, discharge, death) revealed that patients had a small probability of having a stroke during their ICU stay that increased gradually over time (**Fig. 2**). Hemorrhagic stroke greatly increased the cumulative hazard of death (HR = 2.74; credible interval, 1.42–5.27), but ischemic stroke did not (**Table 2**). Older age

TABLE 1.
Baseline Demographics and Characteristics for Coronavirus Disease 2019 Patients Who Experienced a Hemorrhagic or Ischemic Stroke in the ICU

Characteristics	Hemorrhagic Stroke (*N* = 27)	Ischemic Stroke (*N* = 19)	No Stroke (*N* = 2,656)
Demographics			
Age, median (IQR) (yr)	58 (48–64)	60 (52–66)	59 (49–68)
Male sex, *n* (%)	17 (63)	12 (63)	1,734 (65)
Body mass index, median (IQR) (kg/m^2)	30 (27–33)	31 (27–37)	29 (25–34)
Ethnicity, *n* (%)			
White	14 (52)	5 (26)	950 (36)
Black	5 (19)	6 (32)	324 (12)
Asian	2 (7)	2 (11)	387 (15)
Hispanic	4 (15)	6 (32)	420 (16)
Other	1(4)	0 (0)	386 (15)
Past medical history, *n* (%)			
Chronic cardiac disease[a]	7 (26)	4 (21)	409 (15)
Chronic kidney disease[b]	3 (11)	2 (11)	252 (9)
Chronic neurologic disorder[c]	1 (4)	4 (21)	160 (6)
Diabetes	9 (33)	11(58)	839 (32)
Hypertension	16 (59)	14 (74)	1,281 (48)
Smoking	7 (26)	6 (32)	682 (26)
ICU variables			
ECMO, *n* (%)	15 (56)	3(16)	262 (10)
Mechanical ventilation, *n* (%)	27 (100)	16 (84)	1,873 (71)
Vasopressor use, *n* (%)	24 (89)	22 (81)	1,756 (66)
Neuromuscular blockade, *n* (%)	23 (85)	14 (52)	1,517 (57)
Tracheostomy, *n* (%)	7 (28)	8 (31)	430 (20)
Sequential Organ Failure Assessment score, median (IQR)	9 (3–11)	6 (4–9)	4 (3–7)
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	21 (14–24)	16 (14–29)	15 (10–21)
Duration/length, median (IQR) (d)			
Mechanical ventilation	18 (10–24)	18 (8–20)	12 (6–22)
ECMO	6 (3–15)	16 (8–17)	16 (8–26)
ICU stay	18 (10–24)	22 (12–30)	12 (6–24)
Hospital stay	18 (4–34)	30 (17-48)	18 (10–32)
Days to event from admission, median (IQR)			
Days to stroke diagnosis[d]	12 (3–24)	12 (1–24)	---
Days to mechanical ventilation	2 (0-3)	2 (0-3)	0 (0-4)
Days to ECMO cannulation	0 (0-1)	2 (1–3)	2 (0-6)
Outcomes, *n* (%)			
Death	20 (74)	7 (37)	925 (37)
Discharge	4 (15)	5 (26)	908 (34)

ECMO, extracorporeal membrane oxygenation, IQR = interquartile range.

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

[d]Days to stroke diagnosis: days from hospital admission to stroke.

(HR = 1.45) and ECMO use (HR = 1.78) increased both the instantaneous and cumulative hazard of death (Table 2). Male sex was associated with an increased instantaneous (HR = 1.22; credible interval, 1.06–1.40), but not cumulative hazard of death. Despite elevated mortality (74%) in patients with hemorrhagic stroke (Table 1), stroke was the cause of death in only 15% of patients. Instead, multiple organ failure was the leading cause of death in stroke patients (**Supplemental Table 8**, http://links.lww.com/CCM/G612).

ECMO and Stroke

The multistate survival model showed that the risk of all stroke types increased quickly during the first 4 weeks after ICU admission (plateauing at approximately 25 d) (**Fig. 3**). Patients who required ECMO had a higher risk of all stroke types, with clear divergence of the curves at the beginning of the ICU stay. However, the cumulative probabilities were low for ischemic and unspecified (1.0–1.5%) compared with hemorrhagic stroke (6%). Cumulative probabilities for hemorrhagic (relative risk [RR] = 10.5) and ischemic stroke (RR = 1.7) were higher at 90 days for ECMO-supported than for non-ECMO–supported patients (**Supplemental Table 9**, http://links.lww.com/CCM/G612). Further information on ECMO patients are described in **Supplementary Information, Part IV** (http://links.lww.com/CCM/G612).

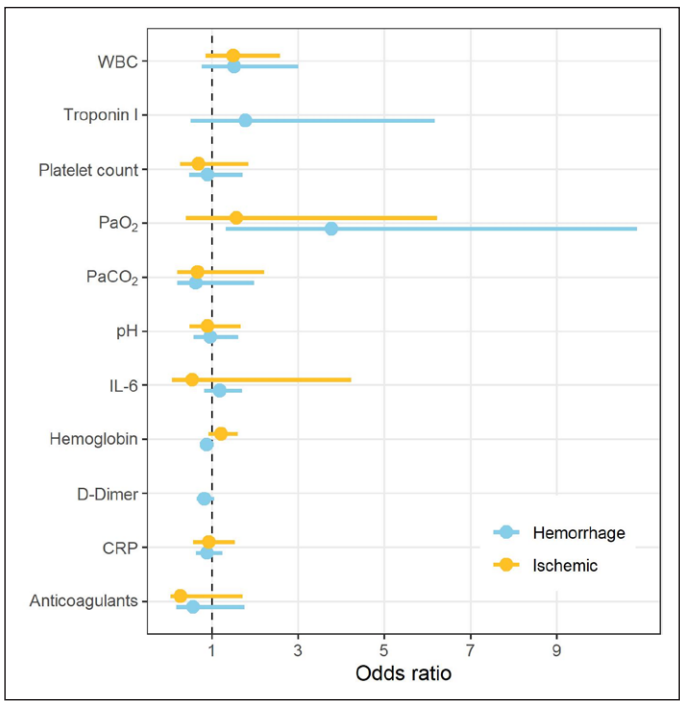

Figure 1. Matched case-control analysis on associations between relevant clinical variables and each type of stroke. For D-dimer, C-reactive protein (CRP), and platelet, the highest value was recorded prior to stroke was used in analysis; for full WBC count, troponin I, platelet count, Pao_2, $Paco_2$, pH, and hemoglobin, the value closest to stroke was used. The plot shows the odds ratio (*dot*) and 95% CI (*horizontal line*). See Supplemental Table 4*b* (http://links.lww.com/CCM/G612) for 95% CI for each odds ratio. IL-6 = interleukin-6.

DISCUSSION

We used a large, international dataset to investigate ischemic and hemorrhagic strokes in critically ill COVID-19 patients. Our consortium collects data from 52 diverse countries, which should render our results externally valid across a broad range of healthcare settings. Although the primary cause of death in COVID-19 patients is respiratory failure from ARDS, neurologic complications have frequently been reported (14). One particularly alarming complication of COVID-19 is acute stroke (15, 16), including in young patients with no/few traditional vascular risk factors. The incidence of stroke has been reported to be higher for patients with COVID-19 than for those hospitalized with acute influenza (6). In two recently published meta-analyses, the overall frequency of acute stroke in all COVID-19 patients was 1.1–1.4% (8, 17). However, these studies neglected to report strokes separately for patients in the ICU, where organ dysfunction is likely more severe, compared with asymptomatic patients with positive SARS-CoV-2 test. It is important to highlight that all included patients in our study had severe COVID-19 infection, requiring ICU admission. Therefore, stroke in this study represents a complication of COVID-19, rather than asymptomatic patients with positive SARS-CoV-2 test who had acute stroke. In our analysis, acute stroke was uncommon (2.2%) in COVID-19 ICU patients. Additionally, the numbers of ischemic and hemorrhagic strokes were similar, contrary to prior studies in which ischemic strokes were predominant (8, 17). The number of hemorrhagic strokes may have been higher in our study in part because of more aggressive anticoagulation use in severely affected ICU patients (18) who require treatments such as ECMO, which can be associated with hemorrhagic complications (19, 20). The finding that only hemorrhagic stroke was strongly associated with increased mortality (74%) suggests that it might indicate more severe disease. However, information on

withdrawal of life-sustaining therapy (WLST) was not available, limiting the interpretation of this finding. Patients with the most severe ARDS are typically selected for ECMO, making it difficult to differentiate whether ECMO itself, rather than the severity of illness, increases the risk of hemorrhagic stroke. It is important to note that most strokes occurred early in the course within 1–2 weeks (Fig. 2) regardless of ECMO status, which may indicate the high early stroke risk during acute infection and inflammation.

Multiple factors have been implicated as causes of stroke in COVID-19 patients, including an acquired coagulopathy, dysregulation of the immune system, manifested by a hyperactive cytokine-release, endothelial dysfunction with inflammation and thrombosis, direct infiltration into the nervous system with angiotensin-converting enzyme-2 receptor uptake of COVID-19 virus, hypoxemia, and systemic metabolic derangements in ICU patients (18, 21). We used a matched case-control analysis to identify differences in ICU laboratory values between stroke and stroke-free patients. Pao_2 levels closest to an acute stroke were associated with hemorrhagic stroke (OR = 3.8), although median values were within the normal range (76.4 vs 68.8 mm Hg in controls), leading to uncertainty regarding the clinical significance. However, all patients (100%) with hemorrhagic stroke were mechanically ventilated compared with 84% in ischemic stroke and 70% in without stroke (Table 1), which may suggest an association between hemorrhagic stroke and critical illness. Ischemic stroke patients had fewer platelets than did controls, potentially because thrombocytopenia in COVID-19 patients could be a manifestation of a consumptive coagulopathy with features of disseminated intravascular coagulation or the use of ECMO, leading to thromboembolic events. Another explanation is that some may develop heparin-induced thrombocytopenia with thrombosis (HITT) or a coagulopathy with pathophysiologic features overlapping those of HITT (22). Ischemic stroke in the context of thrombocytopenia has been described in patients with immune thrombocytopenia (23).

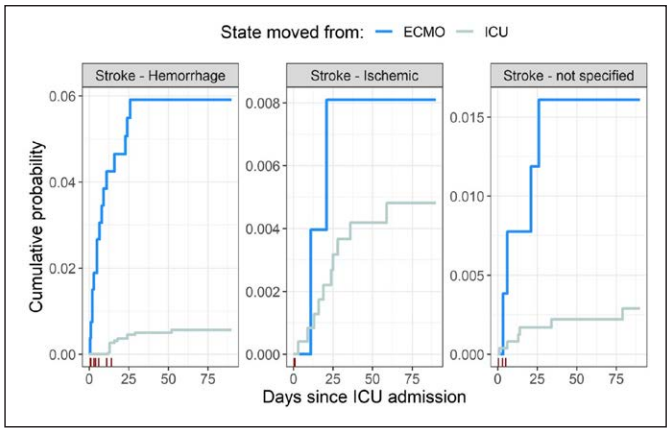

Figure 2. Plot of patient probabilities for each of the five states (ICU, extracorporeal membrane oxygenation [ECMO], stroke, discharge, and death) over time (days since ICU admission).

As expected, patients with stroke were sicker than stroke-free patients and had higher SOFA and APACHE II scores and higher rates of mechanical ventilation, vasopressor infusion, and ECMO. Past medical history of chronic neurologic and kidney disease was more common in patients with ischemic stroke, suggesting that COVID-19 patients with premorbid conditions are more susceptible to acute neurologic complications.

The association between hemorrhagic stroke and ECMO is important. Among patients supported with ECMO, ~8% experienced a stroke in this study, 68% of them hemorrhagic. The proportion of hemorrhagic stroke (5.3%) was similar to that reported by the Extracorporeal Life Support Organization (ELSO) registry for ECMO patients with COVID-19 (6%) (24). The number of strokes appears to be higher in COVID-19 when compared with those with venovenous ECMO support without COVID-19, where ischemic stroke occurred in 1.4% and hemorrhagic stroke in 3.1% from the ELSO registry analysis of 15,872 patients (19). Based on prior reports, we analyzed whether an acute decrease in $Paco_2$ (25) or cannula size (26) was associated with ischemic or hemorrhagic strokes in COVID-19 patients, but uncovered no associations. However, the number of patients supported with ECMO in this study may make it underpowered to rule out associations between these aspects of ECMO management and the complication of stroke during ECMO. The fact that ECMO was associated with an increased risk of stroke suggests that attention should be paid to potential modifiable factors, particularly anticoagulation management, as these patients often present with coagulation disorders and other clinical features—from elevated laboratory markers and subclinical microthrombi to thromboembolic events, bleeding, and disseminated intravascular coagulation (18). In this context, the best strategy is unclear, and in most cases, the choice and dose of anticoagulation should be

TABLE 2.
Hazard Ratios (95% CI) From Weibull Survival Model (Instantaneous Hazard) and Cumulative Regression Model (Cumulative Hazard) for Death and Discharge

Variables	Instantaneous Hazard		Cumulative Hazard	
	Death HR (95% CI)	Discharge HR (95% CI)	Death HR (95% CI)	Discharge HR (95% CI)
Male	1.22 (1.06–1.40)	0.87 (0.77–1.00)	1.10 (0.96–1.27)	0.89 (0.79–1.01)
Age (+10 yr)	1.45 (1.37–1.54)	0.79 (0.75–0.83)	1.36 (1.29–1.44)	0.89 (0.85–0.93)
Body mass index (+ 5 kg/m^2)	0.99 (0.94–1.04)	0.94 (0.89–0.98)	0.96 (0.90–1.02)	0.99 (0.96–1.03)
Extracorporeal membrane oxygenation	1.17 (0.90–1.53)	0.45 (0.35–0.57)	1.26 (1.03–1.55)	0.77 (0.63–0.93)
Hemorrhagic stroke	7.75 (4.61–12.59)	1.39 (0.55–3.06)	4.99 (2.62–9.52)	0.48 (0.21–1.06)
Ischemic stroke	1.62 (0.60–3.63)	1.16 (0.49–2.44)	1.01 (0.43–2.40)	1.12 (0.57–2.19)

HR = hazard ratio.
Extracorporeal membrane oxygenation during course of ICU stay.

tailored case-by-case, focusing on the estimated risks of bleeding and thrombosis. Because ECMO patients have a RR of hemorrhagic stroke more than 10 times that of non-ECMO patients, systematic, protocolized neurologic monitoring is warranted (27).

Last, and unsurprisingly, hemorrhagic stroke greatly increased the risk of death and reduced the rate of hospital discharge. Ischemic stroke and nonspecified stroke type did not affect mortality risk but did increase the length of hospital stay. Older age, use of ECMO, and hemorrhagic stroke were each independently associated with increased cumulative hazard of death, hemorrhagic stroke showing the strongest hazard (HR = 2.74). This is consistent with venovenous ECMO patients without COVID-19 showing higher in-hospital mortality in those with hemorrhagic stroke (73%) compared with those with ischemic stroke and without stroke (68% and 36%, respectively).

This study had limitations. Foremost, the data were principally collected by chart review by a wide variety of researchers without central adjudication, and CT and MRI reports and images were not available for review. To offset this drawback, we contacted regional primary investigators to confirm the type and date of stroke for validation. Missing data were a major limitation, as we did not include variables with more than 30% missing data in our statistical models. Different centers and countries exhibit significant heterogeneity in routine stroke surveillance, and some centers lack certain neuroimaging resources as well as ECMO. This makes it possible and even probable that the actual rate of any stroke (i.e., if every study patient underwent neuroimaging) is higher among critically ill COVID-19 patients than detected and reported by investigators in the consortium. Even hospitals with advanced neuroimaging may have limited resources during pandemic surges. Furthermore, neuroimaging might not be performed in a timely manner in patients administered sedatives and paralytics, potentially rendering stroke detection more difficult. The lack of adjudication also limits our ability to differentiate hemorrhagic conversion of ischemic stroke from hemorrhagic stroke. Although hypoxic ischemic brain injury was presented in Supplemental Figure 1 (http://links.lww.com/CCM/G612), this variable was not part of the main case report form. As this was collected in the "other" section, it may be associated with reporting bias. Also, although a CT study can detect hemorrhage with high sensitivity, it has low sensitivity for the detection of early cerebral ischemia and posterior fossa infarcts, which may underestimate the frequency of ischemic stroke or hypoxic ischemic brain injury. The matched case-control analysis results also should be interpreted with caution as the database had low power for many variables. The results from the comparative analyses should be carefully interpreted with the low frequency of strokes. The case report forms did not include information on the timing of a decision to transition to palliative care during the critical care course but only on a disposition status

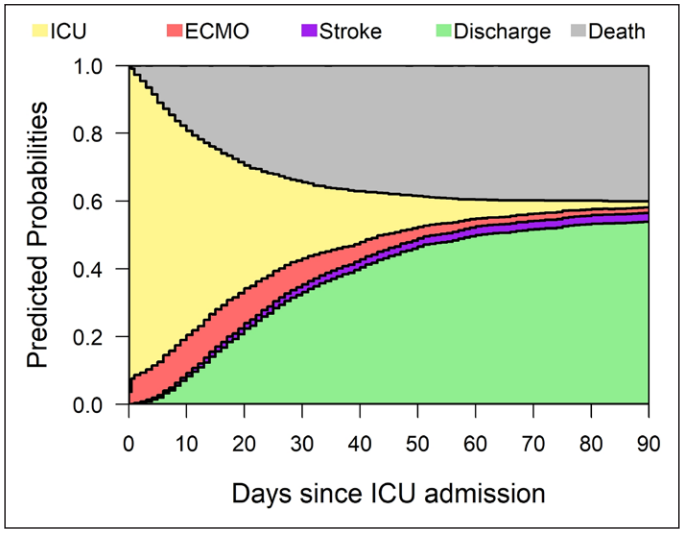

Figure 3. Cumulative probability of hemorrhagic, ischemic, and unspecified strokes for patients with versus without extracorporeal membrane oxygenation (ECMO) support in ICU. Note that the scale on *y*-axis for hemorrhagic stroke is 10 times larger indicating a common occurrence of hemorrhagic stroke with ECMO patients.

of palliative discharge. Also, information on WLST was not collected and hence was not accounted in the reported mortality in our study. This is of particular concern as WLST can dramatically impact the mortality rates in patients with hemorrhagic stroke (28), limiting the interpretation of our results showing increased mortality with hemorrhagic stroke without such data. Because strokes frequently lead to considerations of goals of care, and the degree to which such ethical considerations influenced the impact of stroke on mortality cannot be determined with precision from the available data. Finally, we had a category referred to as unspecified stroke type, limiting the analysis for each type of stroke. However, unspecified stroke reflects a clinical diagnosis of stroke when neuroimaging was not available with resource limitations.

CONCLUSIONS

In an international registry of critically ill COVID-19 patients, acute stroke was infrequent, affecting 2.2% of patients. Although hemorrhagic stroke was associated with increased mortality, ischemic stroke was not, similar to the effects of these stroke types seen in non–COVID-19 ICU patients. Both hemorrhagic stroke and ischemic stroke were associated with traditional vascular risk factors. The use of ECMO was a strong risk factor for both stroke and death. In light of these observations, further study is warranted on the use of anticoagulation and the protocolized use of neurologic monitoring for ECMO patients.

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