RESEARCH ARTICLE

Outcomes in Patients With COVID-19 With Acute Encephalopathy and Coma

An International Prospective Study

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Abstract

Background and Objectives

To report the prevalence of acute encephalopathy and outcomes in patients with severe coronavirus disease 2019 (COVID-19) and to identify determinants of 90-day outcomes.

Methods

Data from adults with severe COVID-19 and acute encephalopathy were prospectively collected for patients requiring intensive care unit management in 31 university or university-affiliated intensive care units in 6 countries (France, United States, Colombia, Spain, Mexico, and Brazil) between March and September of 2020. Acute encephalopathy was defined, as recently recommended, as subsyndromal delirium or delirium or as a comatose state in case of severely decreased level of consciousness. Logistic multivariable regression was performed to identify factors associated with 90-day outcomes. A Glasgow Outcome Scale–Extended (GOS-E) score of 1–4 was considered a poor outcome (indicating death, vegetative state, or severe disability).

Results

Of 4,060 patients admitted with COVID-19, 374 (9.2%) experienced acute encephalopathy at or before the intensive care unit (ICU) admission. A total of 199/345 (57.7%) patients had a poor outcome at 90-day follow-up as evaluated by the GOS-E (29 patients were lost to follow-up). On multivariable analysis, age older than 70 years (odds ratio [OR] 4.01, 95% CI 2.25–7.15),

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

NeuroCovid19 coinvestigators are listed in Appendix 2 at the end of the article.

Glossary

COVID-19 = coronavirus disease 2019; **CRP** = C-reactive protein; **FiO2** = fraction of inspired oxygen; **GCS** = Glasgow Coma Scale; **GOS-E** = Glasgow Outcome Scale–Extended; **ICU** = intensive care unit; **IQR** = interquartile range; **OR** = odds ratio; **PaO2** = partial pressure of oxygen; **PRES** = posterior reversible encephalopathy syndrome; **RCVS** = reversible cerebral vasoconstriction syndrome; **SAPS** = Simplified Acute Physiology Score; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SOFA** = Sequential Organ Failure Assessment.

presumed fatal comorbidity (OR 3.98, 95% CI 1.68–9.44), Glasgow coma scale score <9 before/at ICU admission (OR 2.20, 95% CI 1.22–3.98), vasopressor/inotrope support during ICU stay (OR 3.91, 95% CI 1.97–7.76), renal replacement therapy during ICU stay (OR 2.31, 95% CI 1.21–4.50), and CNS ischemic or hemorrhagic complications as acute encephalopathy etiology (OR 3.22, 95% CI 1.41–7.82) were independently associated with higher odds of poor 90-day outcome. Status epilepticus, posterior reversible encephalopathy syndrome, and reversible cerebral vasoconstriction syndrome were associated with lower odds of poor 90-day outcome (OR 0.15, 95% CI 0.03–0.83).

Discussion

In this observational study, we found a low prevalence of acute encephalopathy at ICU admission in patients with COVID-19. More than half of patients with COVID-19 presenting with acute encephalopathy had poor outcomes as evaluated by GOS-E. Determinants of poor 90-day outcome were dominated by older age, comorbidities, degree of impairment of consciousness before/at ICU admission, association with other organ failures, and acute encephalopathy etiology.

Trial Registration Information

The study is registered with ClinicalTrials.gov, number NCT04320472.

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is dominated predominantly be respiratory symptoms but is notably characterized by a variety of neurologic symptoms with variable severity. The severity of presentation in many cases prompts the consideration of direct neurologic injury. Alteration of consciousness presenting as "acute encephalopathy" is a prominent presentation of severe SARS-CoV-2.[1]

Acute encephalopathy is a potentially life-threatening condition that clinically corresponds to an alteration of consciousness ranging from delirium to coma, most often rapidly evolving over a period of hours to days.[2,3] This entity stems from a pathobiological process in the brain, which itself can be related to various causes such as septic, toxic, hypoxic, or metabolic disorders.

Surprisingly, acute encephalopathy in the setting of coronavirus disease 2019 (COVID-19) during the intensive care unit (ICU) admission has been insufficiently studied.[4-7] Knowledge of the epidemiology and outcomes of adults with severe COVID-19 and acute encephalopathy may help inform clinicians, patients, and their families when goals of care are discussed. To address these gaps, we conducted this international prospective study.

The primary objective of this study was to report the prevalence, characteristics, and outcomes of acute encephalopathy among patients with severe COVID-19 requiring ICU management. The secondary objective was to identify factors associated with 90-day poor outcome.

Methods

Study Design and Participants

This prospective observational cohort study was conducted in 31 university or university-affiliated ICUs in 6 countries (France, United States, Colombia, Spain, Mexico, and Brazil) and involved patients admitted between March and September of 2020. Given the epidemic surge during the first wave of COVID-19, all participating centers had patients admitted to mixed ICU types (general and specialty based such as medical or neurologic ICU).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the French Intensive Care Society research ethics committee (number CE_SRLF_2024). Participating centers obtained ethical approval according to the requirements in their countries. The study complied with the Declaration of Helsinki, Good Clinical Practice, and the regulatory requirements of each country. Oral informed consent was requested from all patients as soon as they regained capacity; when not possible, investigators sought consent for participation from surrogates. Patients and their surrogates were informed that they could decline to participate or withdraw from the study at any time. The study is registered with ClinicalTrials.gov, number NCT04320472.

Study Population and Definitions

All patients aged 18 years and older who were tested positive for SARS-CoV-2 on qualitative PCR assay and were admitted to the

participating ICUs were prospectively screened for eligibility. Eligible patients had acute encephalopathy before/at ICU admission, defined as subsyndromal delirium or delirium, or to a comatose state in case of a severely decreased level of consciousness, according to recently established consensus by 10 medical societies.[2]

Delirium was defined according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, by the presence of all the following criteria: (A) disturbance in attention and awareness; (B) evolution over short period (usually hours to a few days) representing a change from baseline attention and awareness and tending to fluctuate in severity during the course of the day; (C) additional disturbance in cognition; (D) disturbances in criteria A and C not explained by another preexisting, established, or evolving neurocognitive disorder and not occurring in the context of a severely reduced level of arousal, such as coma; and (E) evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication, or withdrawal (i.e., because of a drug of abuse), exposure to a toxin, or because of multiple etiologies.[8] Patients presenting with some of the criteria were considered as having a subsyndromal delirium. Comatose state was defined as a Glasgow coma scale (GCS) score <9.[9] Some patients may have had subdelirium or delirium progressing to coma or may have required endotracheal intubation before the ICU admission (for example, respiratory failure as a reason), explaining why some of these criteria may have not always been determined by ICU physicians but also through the prehospital records. No training was specifically conducted for this study among the physicians responsible for the inclusions. Patients sedated and intubated on ICU admission who did not have acute encephalopathy before intubation as defined earlier were not included in this study. Functional outcomes at 90 days were assessed by the Glasgow outcome scale–extended (GOS-E) score (ranging from 1 to 8, with 8 indicating the best score), with scores dichotomized into good (5–8) and poor (1–4; indicating death, vegetative state, or severe disability).[10]

Data Collection

A standardized form was used to prospectively collect data on demographics, medical history, comorbidities, presumed ultimately fatal comorbidity (according to the McCabe score), the Charlson comorbidity index, and details of COVID-19 index episode (setting, date and time of onset, clinical symptoms, criterion for delirium, GCS score, vital signs, and glycemia) and COVID-19–targeted and supportive treatments. Laboratory findings at ICU admission (partial pressure of oxygen in the arterial blood/fraction of inspired oxygen [PaO_2/FiO_2], D-dimer, C-reactive protein [CRP], procalcitonin, lymphocytes, creatinine, and lactate dehydrogenase) and the results of investigations for a final diagnosis of acute encephalopathy were also collected. All diagnoses were confirmed during the ICU and hospital course by the local medical investigator or by the research team after confirming the diagnosis with the local primary investigator. The final diagnosis of acute encephalopathy was categorized as toxic metabolic encephalopathy (septic and/or hypoxic and/or toxic metabolic), CNS infectious/inflammatory complication, CNS ischemic or hemorrhagic complications, or other causes (status epilepticus/posterior reversible encephalopathy syndrome [PRES]/reversible cerebral vasoconstriction syndrome [RCVS]). Toxic metabolic encephalopathy was a default diagnosis, when the various investigations (i.e., brain imaging, lumbar puncture, and EEG) did not allow the identification of an attributable cause. In patients with toxic metabolic encephalopathy, attribution of the cause to septic, toxic metabolic, and hypoxic factors depended on the presence of different elements at presentation (fever and/or inflammation, treatment toxicity and/or metabolic disturbances, and hypoxemia, respectively).

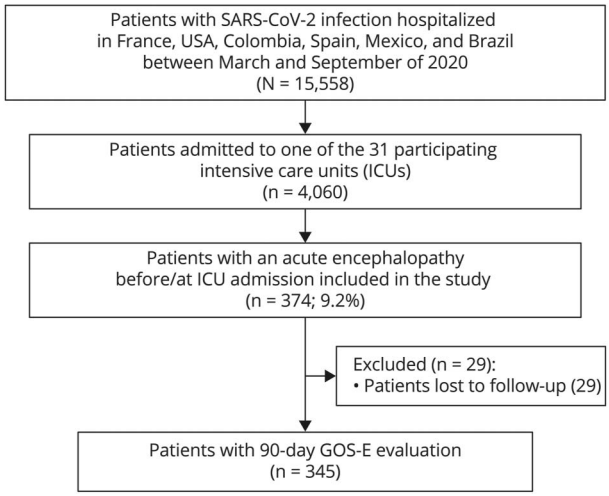
In patients with CNS infectious/inflammatory complication, acute encephalitis was diagnosed according to the International Encephalitis Consortium definition.[11] Patients with PRES or RCVS diagnoses did not overlap with the acute ischemic stroke/intracerebral hemorrhage group. Severity of acute illness and organ failures were captured using the Simplified Acute Physiology Score II (SAPS-II) and Sequential Organ Failure Assessment (SOFA) scores, respectively. The GOS-E score from each patient was determined by a trained physician or a trained research team member (by the local investigator of each participating center) through a telephone interview at 3-month follow-up. The patient's GOS-E score was obtained from the caregivers when the patient's condition did not allow for its evaluation. When investigators were not able to reach the patient or their surrogate after 2 attempts on separate days, during and out of office hours, hospital charts were reviewed to collect the follow-up outcomes. The exact proportions of each of these methods were not collected for this study.

Statistical Analysis

Quantitative variables are described as medians with interquartile ranges (IQRs) and qualitative parameters as numbers (percentages). Prevalence was calculated by dividing the total number of cases with acute encephalopathy by the total number of patients with SARS-Cov-2 infection in the participating ICUs.

We first compared the characteristics of patients lost to follow-up with those whose status was known at day 90, as reported in eTable 1 (links.lww.com/WNL/C744). Differences between 90-day poor outcome and 90-day good outcome groups were assessed with the use of the Wilcoxon rank sum test for quantitative variables and the Fisher exact test for qualitative variables. Logistic regression was used to identify associations between factors listed in eTable 2 (links.lww.com/WNL/C745) and poor 90-day outcome in the 345 patients with 90-day GOS-E evaluation. Continuous variables were assessed for log-linearity before performing the multivariable logistic regression analysis. Non–log-linear variables were transformed into dummy variables according to their inflexion point or median value. The criterion for choosing the dichotomization point among these 2 strategies was guided by the clinical relevance of the variable obtained. Noncollinear variables that yielded p values <0.05 by univariate analysis and clinically relevant variables were considered for the multivariable model. Variables included in the

Figure Patient Flowchart



GOS-E = Glasgow Outcome Scale–Extended; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

multivariable model selection process were as follows: age, male sex, presumed fatal comorbidity, Charlson comorbidity index, temperature at ICU admission, GCS score before or at ICU admission, PaO_2/FiO_2 on admission, worst D-dimer and CRP values between day 1 and day 28 of the ICU stay, vasopressor/inotropic use, renal replacement therapy, and for the final diagnosis of acute encephalopathy. These variables were chosen because they reflect important demographics or variables associated with the severity of COVID-19. Selection of variables was performed using stepwise model selection guided by the Akaike Information Criterion and confirmed by a complementary step-by-step approach. The Hosmer-Lemeshow goodness-of-fit test and area under the receiver operating characteristic curve estimated using the C-statistic were computed on the final models. We identified 69/345 (20%) of observation with at least 1 missing data. Further exploration revealed the absence of particular patterns of missing data and the absence of association between missing data. Accordingly, analyses were conducted under the hypothesis of data missing at random. Associations of factors with 90-day poor functional outcome are reported as odds ratios (ORs) with their 95% CIs obtained after multiple imputation for missing data by means of chained equations (35 imputations and 10 iterations). All tests were 2 sided, and p values <0.05 were considered significant. Analyses were performed using R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

Ethical restrictions apply to the availability of these data regarding participant privacy prohibiting us from making the entire data set publicly available. However, after publication, data will be available to any researcher who provides a methodologically sound study proposal that is approved by the central study team. Proposals can be submitted to the IctalGroup Research Network at the Versailles Hospital (slegriel@ch-versailles.fr). Individual patients and hospitals will not be identifiable in any released data, and all appropriate information governance protocols will be followed.

Results

The patient flow chart is shown in Figure. A total of 15,558 hospitalized patients with SARS-CoV-2 infection were screened, of whom 4,060 were admitted to the participating ICUs over the 6-month study period. Among these patients, 374/4,060 (9.2%) had acute encephalopathy before/at ICU admission: 154 (41.2%) in France/Spain, 111 (29.7%) in the United States, and 109 (29.1%) in Colombia/Mexico/Brazil.

Patient Characteristics and ICU Management

Cohort characteristics and details of early management across study sites are summarized in Tables 1 and 2. The median age was 68 years (IQR 58–74), and 63.9% patients were male. Sixty-two (16.6%) patients had a history of neurologic disease. Overweight and obesity were present in 255/374 (68.2%) patients. The median Charlson comorbidity index was 3 (IQR 2–5), and 16.6% presented with a presumed fatal comorbidity. Most of the patients (79.4%) had dyspnea at presentation and 51.9% had cough. Acute encephalopathy presented as delirium in 81.3% of patients and/or coma in 28.9%; 1 patient could have successively presented with both types of consciousness impairment. Time from first neurologic symptoms to hospital admission and to ICU admission was 0 (IQR −1 to 1) and 0 (IQR −3 to 0) days, respectively.

At ICU admission, the median number of organ failures according to SOFA score was 3 (IQR 3–4). High-flow nasal oxygen and noninvasive ventilation were administered in 46.5% and 15.0% of patients, respectively; endotracheal mechanical ventilation was required in 83.2% of patients. Time from ICU admission to first endotracheal mechanical ventilation was 0 (IQR 0–1) days. Overall, 290/374 (77.5%) patients were given a SARS-CoV-2–specific treatment in various combinations. Patients received a median of 1 (IQR 1–3) treatments, including methylprednisolone (n = 223), azithromycin (n = 123), hydroxychloroquine (n = 82), remdesivir (n = 50), tocilizumab (n = 44), lopinavir/ritonavir (n = 40), convalescent plasma (n = 19), interferon (n = 11), oseltamivir (n = 7), interleukin-2 inhibitor (n = 1), and immunoglobulins (n = 1).

The acute encephalopathy workup performed is summarized in Table 3. The final diagnosis for acute encephalopathy was toxic metabolic encephalopathy in 81.8% of patients. Other causes were CNS ischemic or hemorrhagic complications in 11.2%, CNS infectious/inflammatory complication in 3.5%, and other causes (status epilepticus, PRES, or RCVS) in 3.5% of patients.

Outcomes

Overall, 139/374 patients died during the study, 112 during ICU stay, 23 during hospitalization but after ICU discharge, and 4 during follow-up. Among the in-hospital deaths, 58/135

Table 1 Patient Characteristics in Patients With Severe COVID-19 and Acute Encephalopathy

	All patients (n = 374)
Demographic and patient characteristics	
Age, y	68 (58 to 74)
Male sex (n = 368)	235 (63.9)
Body mass index (n = 353)	28.3 (24.8 to 31.3)
Normal (18.5–24.9 kg/m^2) or underweight (<18.5 kg/m^2)	90 (26.1)
Overweight (25–29.9 kg/m^2)	125 (36.2)
Obese (≥30 kg/m^2)	130 (37.7)
No comorbidity	103 (27.5)
Neurologic comorbidity	62 (16.6)
Presumed ultimately fatal comorbidity	62 (16.6)
Charlson comorbidity index	3 (2 to 5)
Functional signs	
Dyspnea	297 (79.4)
Cough	194 (51.9)
Time from first neurologic signs to hospital admission, d (n = 348)	0 (−1 to 1)
Time from first neurologic signs to ICU admission, d (n = 348)	0 (−3 to 0)
Clinical and laboratory findings before/at ICU admission	
Delirium/subsyndromal delirium[a]	304 (81.3)
No. of criteria for delirium/subsyndromal delirium diagnosis	3 (1 to 4)
GCS score	13 (7 to 14)
Coma, GCS <9[a]	108 (28.9)
PaO_2/FiO_2 at ICU admission, mm Hg/% (n = 295)	110 (77 to 175)
Severity scores on day 1 after hospital admission	
SAPS II score (n = 370)	43 (35 to 50)
Total SOFA score	6 (4 to 8)

Abbreviations: COVID-19 = coronavirus disease 2019; GCS = Glasgow Coma Scale; ICU = neurocritical or intensive care unit; PaO_2 = partial pressure of oxygen; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score.
Data are n (%) or median (interquartile range).
[a] Some patients may have had consecutively experienced both conditions.

(43.0%) occurred after decisions to withhold or withdraw life-sustaining treatments: 36/154 (23.4%) in France/Spain, 21/111 (8.9%) in the United States, and 1/109 (0.9%) in Colombia/Mexico/Brazil. Outcome data at 90 days were available in 345 patients, of whom 146/206 (70.9%) survivors had a good outcome (i.e., GOS-E 5–8).

Factors Associated With Poor 90-Day Outcome

The results of the univariate analysis, according to 90-day GOS-E status (n = 345), are summarized in Table 3. The Hosmer-Lemeshow goodness-of-fit test (χ^2 p value, 0.19) and area under the receiver operating characteristic curve estimated using the C-statistic were computed on the final models (area under the curve 0.82). By multivariable analysis after imputation for missing data (Table 4), 7 variables were independently associated with 90-day outcome. Age older than 70 years (OR 4.01, 95% CI 2.25–7.15), presumed fatal comorbidity (OR 3.98, 95% CI 1.68–9.44), GCS score <9 before/at ICU admission (OR 2.20, 95% CI 1.22–3.98), vasopressor/inotrope support (OR 3.91, 95% CI 1.97–7.76), renal replacement therapy during ICU stay (OR 2.31, 95% CI 1.21–4.50), and CNS ischemic or hemorrhagic complications as acute encephalopathy etiology (OR 3.22, 95% CI 1.41–7.82) were associated with higher odds of poor 90-day outcome (GOS-E 1–4). Other causes (status epilepticus, PRES, or RCVS) were associated with lower odds of poor 90-day outcome (OR 0.15, 95% CI 0.03–0.83).

Discussion

This international prospective study provides detailed information on the epidemiology and predictors of outcome among critically ill patients with severe COVID-19 and acute encephalopathy or coma. The prevalence of encephalopathy and coma before or at ICU admission was 9.2%. Overall, 36.1% of patients died during hospitalization and 57.7% had a poor 90-day outcome. Determinants of poor outcome were older age, presumed ultimately fatal comorbidity, coma before ICU admission, need for vasopressor/inotrope support or renal replacement therapy during ICU stay, and CNS ischemic or hemorrhagic complications as a cause of acute encephalopathy. Conversely, other causes (status epilepticus, PRES, or RCVS) were associated with good outcome.

We report here a prevalence of 9.2% for acute encephalopathy before or at admission in a population of patients requiring ICU management for SARS-CoV-2 infection. There are numerous studies in the literature, mostly retrospective, that focused on acute neurologic injury in patients with COVID-19. Globally, the prevalence of these neurologic disorders is highly variable, ranging from 2.6% to 84.5%,[12-14] depending on the definitions used; furthermore, the type of disorder ranges from the presence of simple signs such as headache or myalgia to consciousness disorders of varying intensity. Only 1 study reported a similar prevalence rate to our study.[15] Conversely, several authors have reported higher prevalence rates ranging from 36.5% to 84.5%.[1,4,14] These differences could be explained by the retrospective single-center nature or small sample size of these studies. Finally, the international prospective character of our study enhances the external validation of our findings.

The demographic characteristics of our population are quite similar to those of critically ill patients with SARS-CoV-2

Table 2 ICU Management and Main Outcomes in Patients With Severe COVID-19 and Acute Encephalopathy

	All patients (n = 374)	France, Spain (n = 154, 41.2%)	United States (n = 111, 29.7%)	Colombia, Mexico, Brazil (n = 109, 29.1%)
ICU management				
Conventional oxygen therapy	315 (84.2)	148 (96.1)	75 (67.6)	92 (84.4)
High-flow nasal oxygen	174 (46.5)	21 (13.6)	82 (73.9)	71 (65.1)
Noninvasive ventilation	56 (15.0)	16 (10.4)	32 (28.8)	8 (7.3)
Mechanical ventilation	311 (83.2)	126 (81.8)	90 (81.1)	95 (87.2)
Mechanical ventilation duration, d	13 (7–21)	14 (7–23)	11 (4.25–19)	13 (8–19)
Venovenous extracorporeal membrane oxygenation	7 (1.9)	4 (2.6)	3 (2.7)	0
Vasopressor or inotropic support	289 (77.3)	110 (71.4)	90 (81.1)	89 (81.6)
Renal replacement therapy	81 (21.7)	24 (15.6)	24 (21.6)	33 (30.3)
Diagnostic workup				
Brain imaging	149 (39.8)	90 (58.4)	46 (41.4)	13 (11.9)
Lumbar puncture	40 (11.0)	37 (24.0)	3 (2.7)	0
EEG	65 (17.4)	58 (37.7)	7 (6.3)	0
Final diagnosis for acute encephalopathy				
Toxic metabolic encephalopathy (septic and/or hypoxic and/or toxic metabolic)	306 (81.8)	101 (65.6)	101 (91.0)	104 (95.4)
CNS infectious or inflammatory complication	13 (3.5)	10 (6.5)	2 (1.8)	1 (0.9)
CNS ischemic or hemorrhagic complications	42 (11.2)	31 (20.1)	7 (6.3)	4 (3.7)
Other causes[a]	13 (3.5)	12 (7.8)	1 (0.9)	0 (0)
Outcomes				
WLST	58 (15.5)	36 (23.4)	21 (18.9)	1 (0.9)
Time from hospital admission to WLST, d	11 (5, 19)	10 (5, 18)	12 (5, 19)	19 (19, 19)
Length of ICU stay, d	14 (7–24)	13 (8–21)	12 (5–22)	17 (10–28)
Length of hospital stay, d	22.5 (15–37)	23 (16–39)	21 (14–36)	23 (14–36)
ICU mortality	112 (30.0)	38 (24.7)	52 (44.9)	22 (20.2)
Hospital mortality	135 (36.1)	45 (29.2)	63 (56.8)	27 (24.8)
Poor 90-d prognosis (GOS-E 1–4) (n = 345)	199 (57.7)	68 (44.7)	64 (75.3)	67 (62.0)

Abbreviations: COVID-19 = coronavirus disease 2019; GOS-E = Glasgow Outcome Scale–Extended; ICU = neurocritical or intensive care unit; WLST = withdrawal of life-sustaining treatment.
Data are n (%) or median (interquartile range).
[a] Status epilepticus, posterior reversible encephalopathy syndrome, or reversible cerebral vasoconstriction syndrome.

infection in the first and second waves of the pandemic. We note a predominance of male sex in a population of middle-aged or elderly patients who were overweight and had various comorbidities.[16-19] Similar to the COVID-ICU network[20] population, which included all types of critically ill patients with severe COVID-19, our participants demonstrating acute encephalopathy received twice as much noninvasive management in the initial phase of disease, with 46.5% receiving high-flow nasal oxygen and 15.0% noninvasive ventilation, even though overall 83.2% of patients eventually required mechanical ventilation.

The spectrum of etiologies for acute encephalopathy reported in our study is consistent with the few other studies addressing this question. We note a large representation of encephalopathy presenting not only as delirium but also encompassing coma. Toxic metabolic encephalopathy manifested as various presentations depending on the coexistence of hypoxemia or toxic or metabolic complications. As in the study by Frontera et al.,[6] we found a high predominance of septic and hypoxemic causes directly related to SARS-CoV-2 infection. The second cause relates to CNS ischemic or hemorrhagic complications, most commonly ischemic stroke.[21] Infectious or inflammatory causes that may

Table 3 Diagnostic Workup and Final Diagnoses in Patients With Severe COVID-19 and Acute Encephalopathy Before/at ICU Admission ICU Admission

	All patients (n = 374)
Investigations for a cause of acute encephalopathy	
Brain imaging	149/374 (39.8)
CT scan or MRI	145 (38.8)/59 (15.8)
Normal	76/149 (51.0)
Lumbar puncture	40/374 (11.0)
CSF white cell count, per mm^3	2 (1–4)
CSF pleocytosis	10 (25.0)
CSF protein, g/L	0.42 (0.29–0.78)
CSF glucose, mmol//L	4.2 (3.8–5.5)
CSF negative RT-PCR for SARS-CoV-2	32/32 (100)
EEG	65/374 (17.4)
Sequential	61 (16.3)
Continuous	8 (2.1)
No. of sequential EEGs per patient	1 (1–2)
Duration of continuous EEG monitoring, d	3.5 (2.25–4.0)
Slowing background	43/54 (79.6)
Asymmetry	3/54 (5.6)
Periodic patterns	11/54 (20.4)
Rhythmic pattern	4/54 (7.4)
Seizure or status epilepticus	3/54 (5.6)
Frontal pattern	8/54 (14.8)
Final diagnosis for acute encephalopathy	
Toxic metabolic encephalopathy	306 (81.8)
CNS infectious or inflammatory complication	13 (3.5)
COVID-associated acute encephalitis[a]	10 (2.7)
Acute necrotizing encephalopathy	1 (0.3)
Acute disseminated encephalomyelitis	2 (0.5)
CNS ischemic or hemorrhagic complications	42 (11.2)
Ischemic stroke	24 (6.4)
Intracerebral hemorrhage	2 (0.5)
Ischemic stroke and intracerebral hemorrhage	5 (1.3)
Subarachnoid hemorrhage	4 (1.1)
Extradural and/or subdural hematoma	4 (1.1)
Cerebral venous sinus thrombosis	2 (0.5)
Bleeding tumor	1 (0.3)
Other causes	13 (3.5)
Status epilepticus	10 (2.7)
PRES	2 (0.5)
RCVS	1 (0.3)

Abbreviations: COVID-19 = coronavirus disease 2019; ICU = neurocritical or intensive care unit; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstriction syndrome; RT-PCR = reverse transcriptase-PCR.
Data are n (%) or median (interquartile range).
[a] According to the International Encephalitis Consortium definition[11]: possible in 6, probable or confirmed in 4.

have been due to the neuroinvasive character of the virus were much less common. Finally, more circumstantial presentations, such as status epilepticus,[22] PRES,[23] and RCVS have also been found.[24] Taken together, this evidence strongly supports a large proportion of indirect involvement of SARS-CoV-2 in acute encephalopathy, whether presenting as delirium or coma.[4,5,12,25,26]

Our results for mortality are similar to the reported 35% rate of in-hospital death in the study by Frontera et al.,[5] in a fairly similar population. The rate is also rather similar to that reported in studies of ICU patients.[20] In this study, we found that 57.7% of patients had a poor 90-day outcome as defined by a GOS-E score of 1–4. Functional impairment is usually reported as physical, cognitive, and mental health effects in the overall population of patients with COVID-related impairment. Symptoms related to functional impairment vary in frequency and time of onset, but are characterized by the persistence of psychiatric disorders such as anxiety, depression, and post-traumatic stress symptoms, leading to alterations in quality of life and thus to a global functional impairment.[27,28] However, our methodology did not allow us to explore this hypothesis.

Of interest, we found an important heterogeneity in ICU management, diagnostic workup, and withdrawal of life-sustaining treatment decisions across the participating countries, reflecting the different practices of healthcare systems and the heterogeneity of cultural backgrounds across countries. The decision to withdraw life-sustaining treatment may have resulted in worse outcomes in setting of a self-fulfilling prophecy and an uncertainty of outcomes during the first wave of the pandemic.

We identified 7 factors that were independently associated with 90-day functional outcome and which can be categorized into 4 main categories: comorbidities (age older than 70 years, presumed fatal comorbidity); intensity of impairment of consciousness before or at admission to ICU (GCS score <9); association with other organ failures during ICU stay

Table 4 Multivariate Logistic Regression Analysis of Factors Associated With the 90-Day Poor Outcome (After Multiple Imputation for Missing Data)

	Multivariate analysis MICE	
	OR	95% CI
Age older than 70 y	4.01	2.25–7.15
Male sex	1.25	0.73–2.13
Presumed ultimately fatal comorbidity	3.98	1.68–9.44
Body temperature >37.0°C at ICU admission	0.75	0.44–1.27
Glasgow coma scale score <9 before or at ICU admission	2.20	1.22–3.98
PaO_2/FiO_2 ratio <150 during ICU stay	1.77	0.95–3.30
Vasopressor/inotrope support during ICU stay	3.91	1.97–7.76
Renal replacement therapy during ICU stay	2.31	1.21–4.50
Final diagnosis: Toxic metabolic encephalopathy	Reference	
Final diagnosis: CNS infectious/inflammatory complications	1.62	0.44–5.98
Final diagnosis: CNS ischemic or hemorrhagic complications	3.22	1.41–7.82
Final diagnosis: Other causes[a]	0.15	0.03–0.83

Abbreviations: FiO_2 = fraction of inspired oxygen; ICU = neurocritical or intensive care unit; MICE = Multiple Imputation by Chained Equations; OR = odds ratio; PaO_2 = partial pressure of oxygen; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstriction syndrome.
[a] Status epilepticus, posterior reversible encephalopathy syndrome, or reversible cerebral vasoconstriction syndrome.

(vasopressor/inotrope support and renal replacement therapy); and cause of acute encephalopathy itself (CNS ischemic or hemorrhagic complications or other causes).

The burden of comorbidities in the vital outcome of patients with COVID-19 is one of the best demonstrated factors to date. In a recent meta-analysis comprising 31,089 patients with COVID-19, Zadori et al.[29] identified previous cerebrovascular disease, chronic obstructive pulmonary disease, cardiovascular disease, hypertension, diabetes mellitus, and malignancy as independent predictors of poor outcome (i.e., defined need for ICU admission or hospital death). In a large prospective cohort study in 4,244 critically ill patients with COVID-19, older age, obesity, and a history of diabetes mellitus, in addition to acute respiratory distress syndrome severity, were the main predictors of hospital death.[20] Our findings are, therefore, aligned with previous reports of patients with SARS-CoV-2 infection.

The prognostic factors identified in our study are applicable to patients with COVID-19 requiring ICU management. Furthermore, the cause of acute encephalopathy was independently associated with prognosis in our population. This point is interesting because we could establish that prognosis differs according to 2 of the categories. Thus, while the occurrence of other causes (status epilepticus, PRES, or RCVS) are associated with a favorable outcome, a vascular cause underlying the SARS-CoV-2 infection incurs a worse prognosis. This finding is likely explained by the functional nature of involvement of the former, which is expected to be reversible in case of rapid and appropriate symptomatic management.[30,31] Conversely, neurologic vascular injury has been reported to be associated with SARS-CoV-2 involvement in the CNS.[25,32,33] The frequency of vascular injury reported and its etiologic spectrum—largely dominated by acute ischemic stroke, is aligned with previously published data.[5] It should also be noted that ischemic or intracerebral hemorrhage commonly present with acute encephalopathy.[27] All these vascular presentations may be related to direct viral involvement through the formation of endothelial lesions and in situ thromboinflammation.[34] They may also result from coagulopathy mechanisms indirectly responsible for arterial or venous thrombotic complications or immediate or secondary hemorrhagic complications.[35] This event, hypothesized to be the main pathophysiologic mechanism responsible for clinical manifestations of the viral attack, is thus one of the major determinants of the vital and functional damage in patients presenting with acute encephalopathy.[36,37]

Our study has several limitations. First, the international nature of the study is a potential source of heterogeneity in the decision for ICU admission and management (including care limitation decisions), especially because of differences in the healthcare systems across countries. No training was specifically conducted for this study among the physicians responsible for the inclusions. However, we believe that this is also an important strength of this work, allowing better representation of the spectrum of this neurologic presentation, regardless of the modalities of management. Second, it is possible that we are underreporting some neurologic complications such as seizures and strokes because we did not require the participating centers to obtain imaging, lumbar puncture, or EEG. The heterogeneity of assessments and diagnostic tests (such as CT, MRI, and lumbar puncture) between different countries may have affected the underlying etiology evaluation and diagnoses in our cohort. Third, our study lacks an external validation for the diagnosis of acute encephalopathy and for other diagnoses reported in this study. Fourth, our study does not address the risk factors associated with acute encephalopathy because it would have required a different study design through including detailed data collection in patients without acute encephalopathy in the study. Fifth, we acknowledge the potential of missing some patients with encephalopathy due to failure to screen in the setting of critically affected healthcare structures during the first wave of COVID-19. Sixth, 29 patients were lost to follow-up, limiting a complete evaluation of 90-day follow-up outcomes with the risk of attrition bias. We observed a higher proportion of comorbidities at baseline in patients lost to follow-up suggesting an underestimation of 90-day mortality rates. This hypothesis is potentially offset by a lower severity as indicated by a lower SAPS-II score and a lower proportion of organ failure during the ICU stay. In any case, a risk of attrition bias cannot be formally ruled out. Seventh, the small sample size of our population and the inherent constraints of

the multivariate logistic regression model selection process most likely caused wide OR CI s and a risk of overfitting. Moreover, the use of a stepwise selection could have arbitrary discarded variables from the final model due to a level of nonsignificance, resulting to an erroneous final model. To minimize these issues, to reduce the risk of bias, and to report more efficient estimates, we performed a multivariate model after handling missing data by Multivariate Imputation by Chained Equations. Finally, we have included patients whose acute encephalopathy is heterogeneous, varying from presentations directly or indirectly related to SARS-CoV-2 infection, sometimes totally functional or symptomatic (as in the case of toxic metabolic encephalopathy or even in the case of status epilepticus) or, on the contrary, with a structural injury as in the case of stroke. Furthermore, the observed differences in diagnostic workup, ICU management, and withdrawal of life-sustaining treatment decisions across the participating countries could be another source of bias in the analysis of our results. However, our approach is in line with the nosological framework recently defined by a joint statement involving 10 societies.[2] Thus, our definition is contemporary and provides important information on this disease in accordance with up-to-date recommendations. This approach also allows us to study the association between the prognosis and different neurologic disorders of COVID-19, thus providing important information in the case of syndromic disease such as acute encephalopathy.

In this observational multicenter study, we found a low prevalence (9.2%) of acute encephalopathy before or at admission in critically ill patients with COVID-19. Acute encephalopathy was associated with poor 90-day outcome. Determinants of poor outcome were dominated by older age, presence of comorbidities, intensity of impairment of consciousness before or at admission to ICU, the association with other organ failures, and the cause of acute encephalopathy itself.

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