Early Clinical and Electrophysiological Brain Dysfunction Is Associated With ICU Outcomes in COVID-19 Critically Ill Patients With Acute Respiratory Distress Syndrome: A Prospective Bicentric Observational Study*

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OBJECTIVES: Describe the prevalence of acute cerebral dysfunction and assess the prognostic value of an early clinical and electroencephalography (EEG) assessment in ICU COVID-19 patients.

DESIGN: Prospective observational study.

SETTING: Two tertiary critical care units in Paris, France, between April and December 2020.

PATIENTS: Adult critically ill patients with COVID-19 acute respiratory distress syndrome.

INTERVENTIONS: Neurologic examination and EEG at two time points during the ICU stay, first under sedation and second 4–7 days after sedation discontinuation.

MEASUREMENTS AND MAIN RESULTS: Association of EEG abnormalities (background reactivity, continuity, dominant frequency, and presence of paroxystic discharges) with day-28 mortality and neurologic outcomes (coma and delirium recovery). Fifty-two patients were included, mostly male (81%), median (interquartile range) age 68 years (56–74 yr). Delayed awakening was present in 68% of patients (median awakening time of 5 d [2–16 d]) and delirium in 74% of patients who awoke from coma (62% of mixed delirium, median duration of 5 d [3–8 d]). First, EEG background was slowed in the theta-delta range in 48 (93%) patients, discontinuous in 25 patients (48%), and nonreactive in 17 patients (33%). Bifrontal slow waves were observed in 17 patients (33%). Early nonreactive EEG was associated with lower day-28 ventilator-free days (0 vs 16; $p = 0.025$), coma-free days (6 vs 22; $p = 0.006$), delirium-free days (0 vs 17; $p = 0.006$), and higher mortality (41% vs 11%; $p = 0.027$), whereas discontinuous background was associated with lower ventilator-free days (0 vs 17; $p = 0.010$), coma-free days (1 vs 22; $p < 0.001$), delirium-free days (0 vs 17; $p = 0.001$), and higher mortality (40% vs 4%; $p = 0.001$), independently of sedation and analgesia.

CONCLUSIONS: Clinical and neurophysiologic cerebral dysfunction is frequent in COVID-19 ARDS patients. Early severe EEG abnormalities with nonreactive and/or discontinuous background activity are associated with delayed awakening, delirium, and day-28 mortality.

KEY WORDS: acute brain dysfunction; acute respiratory distress syndrome; brainstem; COVID-19; delirium; EEG

COVID-19 disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into a global pandemic since November 2019. Although SARS-CoV-2 primarily targets the respiratory tract with the most severe condition being the acute respiratory distress syndrome (ARDS) (1), other organs are also affected. In particular, neurologic symptoms have been commonly reported, from peripheral (including neurosensory disorders such as anosmia) to CNS involvement (stroke, seizure, and encephalitis) (2–7). In critically ill patients, the prevalence of delirium and abnormal neurologic examination seems especially high (8). Yet, why SARS-CoV-2 infection leads to neurologic symptoms, and whether the virus gains access to the CNS is still pending. Recent neuropathological studies reported vascular and inflammatory lesions most pronounced in the brainstem (9–11).

As brain injury is often a major determinant of functional outcomes in critically ill patients (12), objective tools are necessary to precisely assess its mechanisms and depth. Electroencephalography (EEG) is one of the simplest and most used technique to monitor real-time brain activity at the bedside allowing to assess encephalopathy and epileptogenicity, and to detect focal abnormalities in critically ill patients (13, 14). EEG could also be used as a tool for neuroprognostication, for instance, in cardiac arrest survivors (15) and non-COVID-19 septic patients (16–19). EEG analysis has been reported in COVID-19 patients, but few data are available in critically ill patients, and association between EEG abnormalities and outcomes remains poorly known (20). We aimed to describe the prevalence of cerebral dysfunction evaluated by a clinical and a neurophysiologic approach in critically ill, COVID-19 patients and to assess the relationship between early EEG abnormalities and outcomes.

MATERIALS AND METHODS

Population

We conducted a prospective bicentric observational study between April and December 2020. We included patients admitted in medical ICU of two university hospitals for a severe SARS-CoV-2 infection leading to ARDS (as defined by the Berlin criteria [21]) and requiring invasive mechanical ventilation (IMV) with initial deep sedation (defined as a Richmond Agitation-Sedation Scale (RASS) less than –3 during at least 12 hr). All patients had a positive SARS-CoV-2 polymerase chain reaction (nasopharyngeal swab and/or endotracheal pulmonary specimen). Patients with history of central neurologic disorders were excluded. This study was approved by the "Comité de Protection des Personnes 'Ile de France II'" (n°ID RCB: 2020-01559-30) ethic committee and was registered on clinicaltrials.gouv: NCT04527198. A written informed consent was obtained from each patient or relative.

ICU and Sedation Management

Patients were managed following current COVID-19 (22) and ARDS guidelines (23). Specific treatments used for SARS-CoV-2 infection are reported. Management of sedation, analgesia, and neuromuscular blockers (NMBs) were protocolized based on the RASS, behavioral pain scale (BPS), and train of four according to guidelines (24). Sedatives and opioids were administered following a nurse-protocolized targeted sedation based on BPS and RASS levels, assessed at least every 4 hours and followed in both participating centers (**Supplementary Fig. 1**, http://links.lww.com/CCM/H26).

Standardized Neurologic Assessment

We assessed acute cerebral dysfunction using a standardized clinical and neurophysiologic approach at two predefined time points. First assessment (T1) was performed in sedated patients, 12–72 hours following the first NMB cessation if patients received paralyzing agents, to rule out any potential lasting effect of NMB and ensure an interpretable clinical examination. Second assessment (T2) was performed 4–7 days after definitive sedative cessation.

Clinical Examination

Standardized clinical neurologic examination was performed by two senior neurointensivists using validated scales: assessment of arousal, awareness and responsiveness using the Full Outline of UnResponsiveness (FOUR) (25) and RASS scores, and assessment of brainstem responses through brainstem reflexes and cranial nerves (pupillary light reflex, corneal reflex, oculocephalic reflex [OCR] to
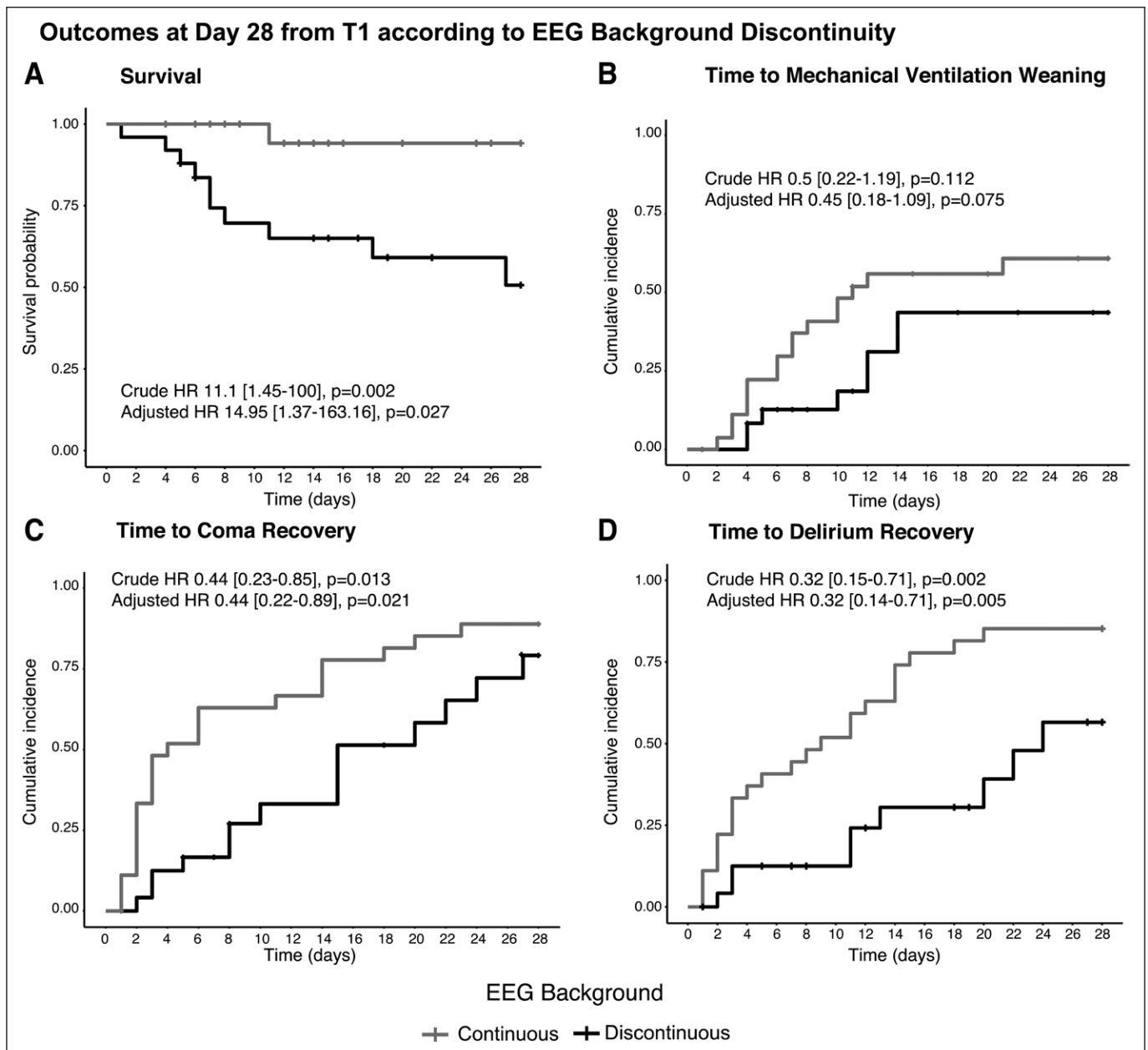
Figure 1. Time-to-event analyses at day 28 from neurologic assessment according to electroencephalography (EEG) background discontinuity survival probability (**A**) and cumulative incidences of mechanical ventilation weaning (**B**), of coma (**C**), and of delirium (**D**) recovery according to EEG background discontinuity. Kaplan-Meier curves were used for visual presentation, and Cox proportional hazards models were used to compute the crude and adjusted hazard ratio (HR) and corresponding 95% CIs on sedatives and opioids infusion rates, cumulative doses, and duration at the time of neurologic assessment. Patients were followed for 28 d from the neurologic assessment or up to ICU discharge, whichever came first.

lateral passive head rotation and cough reflex in response to five tracheal suctioning and grimacing to pain through bilateral, persistent, and strong pressure to the retromandibular region). Each one of the above was scored as present or abolished, and brainstem dysfunction was defined as a Brainstem Responses Assessment Sedation Score (BRASS) (26) greater than or equal to 1 (**Supplementary Table 1**, http://links. lww.com/CCM/H26).

Electroencephalogram Assessment

Standard 20-minute EEG recordings with 11 scalp electrodes (Fp1, Fp2, Fz, C3, C4, Cz, T3, Pz, T4, O1, and O2 in the 10–20 international reference system) were interpreted by certified electrophysiologists blinded from patient's neurologic examination and outcomes. The following EEG patterns were prospectively described: predominant background frequency (Delta 1–4 Hz,

Theta 4–8 Hz, and Alpha 8–12 Hz), background continuity, symmetry and reactivity to standardized nociceptive and auditory stimuli, paroxysmal activity, and seizures.

Data Collection

We also collected demographic characteristics, body weight, medical history and SARS-CoV-2 symptoms, Simplified Acute Physiologic Score II at admission, Sequential Organ Failure Assessment (SOFA) at admission and at T1 and T2, sedative/opioid exposure (duration, cumulative doses, and infusion rates), length of stay, duration of mechanical ventilation, duration of ICU stay, and mortality. Laboratory findings performed at T1 and T2 and results of brain CT/MRI and cerebrospinal fluid analyses, performed at the treating physician discretion, were also collected.

Neurologic Follow-Up

Besides the T1 and T2 assessments, level of consciousness and command following were assessed every 4 hours using FOUR and RASS scales. In patients with an RASS of –3 to +4, delirium (27, 28) was assessed using the Confusion Assessment Method-ICU (CAM-ICU) at least twice a day (29). Medical Research Council (MRC) score motor testing was performed at ICU discharge with a score less than 48/60 defining ICU-acquired weakness.

Coma was defined by RASS scores between –4 and –5 and awakening by two successive RASS scores greater than or equal to –2. Delayed awakening was defined by the absence of awakening 3 days after sedation discontinuation. Delirium was defined as a positive CAM-ICU assessment and classified as hypoactive, hyperactive, or mixed depending on the associated RASS. Each day was recorded as spent in coma, delirium, or neither of both (all assessments in a 24-h period needed to be negative for a patient to be delirium-free and coma-free, and in the case of both coma and delirium, the day was recorded as "with delirium"). Patients were followed from T1 for 28 days or up to ICU discharge, whichever came first.

Outcomes

Primary end points were the prevalences of acute neurologic failure (coma, delayed awakening, and hypoactive/hyperactive/mixed delirium). Secondary outcomes were first the prevalence at T1 and T2 of brainstem dysfunction and EEG abnormalities and second the association between both at T1 and day-28 outcomes.

Statistical Analyses

Continuous variables were summarized using medians and interquartile ranges and compared with Wilcoxon rank-sum test, and categorical variables were reported as proportions and compared with Pearson chi-square or Fisher exact test as appropriate. Univariate associations between brainstem dysfunction, EEG patterns, or sedatives/opioids exposure and outcomes were explored through logistic regression for binary outcome with area under the receiver operating characteristic curve (AUC), and its 2,000 replicates bootstrap 95% CI, and with linear regression for quantitative outcomes, with the R^2, which represents the proportion of variance of the dependent variable explained by the independent variable. We also explored these associations through time-to-event analyses of the cumulative incidence of ICU survival, weaning from IMV, coma recovery for at least 48 hours, and delirium recovery for at least 48 hours (expressed as days free of coma and delirium for at least 48 hr) from T1 to day 14 and day 28 or up to ICU discharge, whichever came first. Kaplan-Meier survival curves were used for visual presentation of the results. Crude hazard ratio (HR) and adjusted HR (aHR) on sedatives/opioids exposure and/or nonneurologic SOFA at T1 were computed using Cox proportional hazards models. All tests were two-sided with p values of less than 0.05 considered as significant. Statistical analyses were performed using R Software, Version 3.6.3 (2020-02-29; https://cran.r-project.org/).

RESULTS

Patients From April to December 2020, among the 146 mechanically ventilated patients with COVID-19 ARDS who were admitted in participating centers, 52 patients were included in the study. Compared with eligible patients who could not be included within the 12–72 hours following first NMB cessation time-window, included patients had less comorbid conditions, were less severe at ICU admission, and had higher ICU survival (**Supplementary Fig. 2** and **Supplementary**

Table 2, http://links.lww.com/CCM/H26). Patients were mostly male (81%), with a median age of 68 years (56–74 yr). All patients presented respiratory symptoms at admission, and 12% presented neurologic symptoms of mild encephalopathy with a median Glasgow Coma Scale at ICU admission of 15 (15–15) without any focal sign (Table 1). Patients were mainly sedated with midazolam (98%) and/or with propofol (12%), and analgesia was maintained with sufentanil in all patients. Median lowest Pao_2/Fio_2 ratio within the 24 hours of IMV was 104 (83–118), and almost all patients (98%) received NMB (atracurium), started within 1 hour (0.5–2 hr) of sedation infusion (Table 2).

Standardized Neurologic Assessments

T1 assessment (12–72 hr after the NMB weaning) was performed in all patients after a median delay of 4 days (3–7 d) from intubation and 26 hours (22–44 hr) after NMB cessation. T2 assessment (4–7 d after definitive sedation cessation) was performed in all the 42 patients alive, after a median delay of 17 d (10–24 d) from intubation and median delay from sedatives definitive cessation of 83 hours (73–117 hr). Median sedation duration was 9 days (6–17 d), with a total cumulative dose of 32 mg/kg of midazolam equivalent and 42 µg/kg of sufentanil.

Clinical Assessment

At T1, RASS was –4 (–4 to –5), and FOUR was 5 (5–7). To note, nine patients were RASS-3 (median time of 4 hr [2–6 hr] spent in RASS-3). OCR was abolished in 32 of patients (62%), grimacing to pain in 22 (42%), cough reflex in 12 (23%), and corneal reflex in 4 (7.7%), leading to a prevalence of brainstem dysfunction (defined as a BRASS greater than or equal to 1, Supplementary Table 1, http://links.lww.com/CCM/H26) of 50%, with a median BRASS of 1 (1–2) (Table 2; **Supplementary Figs. 3** and **4**, http://links.lww.com/CCM/H26). At T2, RASS was 0 (–3 to 0) and FOUR 13 (9–16). Brainstem dysfunction was present in 4/42 patients (10%) with absent grimacing to pain in 4 (10%), cough reflex in 2 (5%), and OCR in 7 (17%) (Table 2; Supplementary Fig. 3, http://links.lww.com/CCM/H26).

Neurophysiologic Assessment

EEG was performed in all patients at T1 within 1 hour (0–2 hr) of clinical assessment and in 39 (92%) of the 42 patients alive at T2 within 1 hour (0–3 hr) of clinical assessment. At T1, EEG was mostly symmetric (96%) with a dominant theta (58%) and delta (35%) background rhythm. Background activity was discontinuous and/or suppressed in 25 (patients 48%) and nonreactive in 17 patients (33%). Paroxysmal activity with bifrontal slow waves was observed in 17 patients (33%), and only one patient (1.9%) presented a seizure. At T2, background rhythm was still slowed in 19 patients (49%). Bifrontal slow waves were observed in 12 patients (31%), EEG was nonreactive in 6 patients (15%), and background was discontinuous in 1 (2.6%) (Table 2; Supplementary Fig. 4, http://links.lww.com/CCM/H26). Biological and brain-imaging results are presented in **Supplementary Material 2c** and **Supplementary Table 3** (http://links.lww.com/CCM/H26).

Neurologic and ICU Outcomes

ICU mortality rate was 23% with a median length of stay of 20 days (12–36 d) and a median length of IMV of 18 days (10–34 d). No death was due to withdrawal of life-sustaining therapy decisions. Nine patients (17%) died without awakening from coma. In patients who awoke, median duration of coma was 13 days (8–26 d), and delayed awakening was present in 29 (67%), with a median awakening delay of 4 days (1–13 d). Delirium was present in 32 patients (62%) overall, that is 74% (32/43) of patients who awoke from coma, with a predominance of mixed delirium (62%) and median duration of 5 days (3–8 d). Prevalence of ICU-acquired weakness at ICU discharge was 64% (median MRC of 40 [30–54]).

Association of Brainstem Dysfunction and EEG Patterns With ICU Outcomes

Twenty-five patients (96%) without brainstem dysfunction awoke from coma versus 18 patients (69%) with brainstem dysfunction ($p = 0.024$). Median delay of awakening was 2 (0–8) versus 9 (2–19) days ($p = 0.019$), respectively (**Supplementary Table 4**, http://links.lww.com/CCM/H26). Brainstem dysfunction was associated with lower ventilator-free days (VFDs) (0 d [0–12 d] vs 18 d [0–24 d]; $p = 0.004$), coma-free days (CFDs) (6 d [0–16 d] vs 23 d [6–25 d]; $p = 0.021$), and delirium-free days (DFDs) (5 d [0–14 d] vs 18 d [2–25 d]; $p = 0.015$) at day-28 from T1, whereas mortality (31% vs 12%; $p = 0.09$) did not differ between the groups.

TABLE 1.
Population Characteristics

Demographic Characteristics	n = 52
Age (yr)	68 (56–74)
Male sex	42 (81)
BMI (kg/m²)/obesity (BMI > 30 kg/m²)	27.8 (25.5–29.8)/15 (29%)
Knaus score	
A–no limitation	23 (44)
B–moderate limitation	24 (46)
C–severe limitation	5 (9.6)
MaCCabe score	
1–no chronic disease	42 (81)
2–chronic disease with at least 5 yr of expected survival	10 (19)
Comorbidities	34 (65)
Diabetes	15 (29)
Hypertension	13 (25)
Cardiac history	7 (13)
Cancer history	10 (19)
Respiratory history	4 (7.7)
Renal history	5 (9.6)
Immunodepression	9 (17)
Characteristics at ICU Admission	
COVID-19 symptoms	
Respiratory	52 (100)
Neurologic	6 (12)
Positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction	52 (100)
First symptoms to ICU delay (d)	10 (7–13)
Glasgow Coma Scale at hospital admission	15 (15–15)
Simplified Acute Physiology Score II at ICU admission	48 (35–69)
Sequential Organ Failure Assessment-total at ICU admission	5 (4–8)
Lowest Pao_2/Fio_2 within 24 hr of IMV	104 (83–118)
Treatments Received	
High-flow nasal canula oxygenotherapy before IMV	35 (67)
Prone positioning during IMV	47 (90)
Neuromuscular blocking agent	50 (96)
Renal replacement therapy	21 (40)
Extracorporeal membrane oxygenation	3 (5.8)
Dexamethasone	46 (88)
Anticoagulant: reinforced prophylactic / therapeutic	29 (56)/23 (44)
Anti-interleukin-6/remdesivir/other	6 (12)/3 (5)/2 (4)

BMI = body mass index, IMV = invasive mechanical ventilation.

TABLE 2.
Standardized Neurologic Assessments

Assessment	T1, $n = 52$	T2, $n = 42$
Assessment Conditions		
Delays		
ICU admission to assessment (d)	4 (3–7)	17 (10–25)
Neuromuscular blockade offset to assessment (hr)	26 (22–44)	NA
EEG to clinical assessment (hr)	1 (0–2)	1 (0–3)
Nonneurologic Sequential Organ Failure Assessment	6 (4–9)	3 (2–6)
Sedatives/opioids drugs		
Midazolam	51 (98)	0 (0)
Propofol	6 (12)	0 (0)
Sufentanil	52 (100)	2 (5)
Sedatives/opioids infusion rate (mg/kg/hr)		
Midazolam	0.11 (0.07–0.19)	NA
Propofol	2.0 (1.5–2.7)	NA
Midazolam and propofol (midazolam equivalent)	0.11 (0.07–0.23)	NA
Sufentanil	0.17 (0.09–0.23)	0.07 (0.07–0.07)
Sedatives/opioids cumulative dose (mg/kg)		
Midazolam	12 (8–18)	29 (15–42)
Propofol	23 (2–40)	40 (13–95)
Midazolam and propofol (midazolam equivalent)	13 (8–20)	32 (20–48)
Sufentanil	17 (10–26)	42 (30–73)
Sedatives/opioids duration (d)	4 (3–7)	9 (6–17)
Clinical Assessment		
Richmond Agitation-Sedation Scale score	–4 (–5 to –4)	0 (–3 to 0)
Full Outlined of Unresponsiveness score	5 (5–7)	13 (9–16)
Brainstem Response Assessment Sedation Scale score	0 (0–1)	0 (0–0)
Brainstem reflexes		
Absent oculocephalic reflex	32 (62)	7 (17)
Absent corneal reflex	4 (8)	0 (0)
Absent pupillary reflex	0 (0)	0 (0)
Absent cough reflex	12 (23)	2 (5)
No grimacing to pain	22 (42)	4 (10)
Electrophysiology Assessment		
EEG dominant frequency		
Alpha	4 (7)	20 (51)
Theta	30 (58)	17 (44)
Delta	18 (35)	2 (5)
EEG symmetry	50 (96)	38 (97)
EEG unreactive	17 (33)	6 (15)
EEG discontinuous and/or suppressed background	25 (48)	1 (3)
Bifrontal slow waves	17 (33)	12 (31)
Seizure	1 (2)	0 (0)

EEG = electroencephalography, NA = not applicable.

T1 assessment was performed in sedated patients, 12–72 hr after neuromuscular blockade weaning for patients receiving paralyzing agents, whereas T2 assessment was performed 4–7 d after definite sedation cessation. Statistics presented: median (interquartile range); n (%). Midazolam equivalent dose is computed assuming that 10 mg of propofol would be equal to l mg of midazolam (30, 31).

EEG patterns at T1 were also significantly associated with outcomes. Discontinuous background was associated with lower VFD (0 [0–14] vs 17 [0–22]; $p = 0.010$), CFD (1 [0–14] vs 22 [12–26]; $p < 0.001$), DFD (0 [0–9] vs 17 [12–25]; $p = 0.001$), and higher mortality (40% vs 4%; $p = 0.001$) at day 28 from T1 (Table 2), whereas bifrontal slow waves were associated with higher CFD (25 [10–26] vs 8 [0–22]; $p = 0.009$) and DFD (19 [10–26] vs 6 [0–17]; $p = 0.006$). Nonreactive EEG was associated with lower VFD (0 [0–14] vs 16 [0–22]; $p = 0.025$), CFD (6 [0–13] vs 22 [2–26]; $p = 0.006$), DFD (0 [0–9] vs 17 [0–25]; $p = 0.006$), and higher mortality (41% vs 11%; $p = 0.027$). Similar results were observed in time-to-event analyses for both brain stem dysfunction and EEG patterns (**Supplementary Table 5**, http://links.lww.com/CCM/H26).

Investigation of the Role of Sedation

In order to assess the potential confounding effect of sedation, we first investigated bivariate associations at T1 between brainstem dysfunction or EEG patterns and sedatives/opioids exposure, and between each outcome and sedatives/opioids exposure. Among these, only opioids infusion rate was significantly higher in patients with brainstem dysfunction (0.21 μg/kg/hr [0.14–0.26 μg/kg/hr] vs 0.11 μg/kg/hr [0.07–0.18 μg/kg/hr]; $p = 0.004$; Supplementary Table 3, http://links.lww.com/CCM/H26). Yet, neither sedation infusion rate, cumulative dose, nor duration was significantly associated with outcomes. Conversely, clinical features and electrophysiology patterns of brain dysfunction significantly outperformed sedatives/opioids exposure for explaining the variance of day-28 CFD and DFD (R^2 between 11% and 22%; $p < 0.05$ vs $R^2 \leq 1\%$; $p > 0.05$), as well as in predicting mortality (AUC ≥ 0.7; $p < 0.05$ for discontinuous or nonreactive EEG vs AUC < 0.7; $p > 0.05$ for sedatives/opioids exposure) (**Table 4**).

Second, we adjusted time-to-event analyses on sedatives/opioids exposure. Whether adjusted on infusions rates, cumulative doses or duration alone (**Supplementary Table 6**, http://links.lww.com/CCM/H26), or all at the same time (**Supplementary Table 7**, http://links.lww.com/CCM/H26), discontinuous and nonreactive EEG backgrounds remained independently associated with lower cumulative incidences of survival at day 28 (aHR, 14.95 [1.37–163.16]; $p = 0.027$ and 3.74 [1.06–13.17]; $p = 0.04$, respectively). Brain stem dysfunction and discontinuous EEG background were also significantly associated with a lower cumulative incidence of delirium recovery (aHR, 0.37 [0.15–0.89]; $p = 0.026$ and 0.32 [0.14–0.71]; $p = 0.005$, respectively) within 28 days of T1 assessment (Fig. 1; **Supplementary Fig. 5** and Supplementary Table 5, http://links.lww.com/CCM/H26), whereas bifrontal slow waves were associated with a higher cumulative incidence of delirium recovery (aHR, 2.84 [1.35–5.96]; $p = 0.006$) at day 28.

Finally, after adjusting for nonneurologic SOFA at T1 in addition to sedatives/opioids exposure, brainstem dysfunction remained independently associated with day-14 coma and delirium recovery, nonreactive EEG with day-28 survival and discontinuous EEG with day-28 survival, coma, and delirium recovery, suggesting that clinical features and electrophysiology patterns of brain dysfunction association with outcomes were independent of organ dysfunction (**Supplementary Table 8**, http://links.lww.com/CCM/H26).

DISCUSSION

The main findings of this prospective observational study are the high frequency of acute brain dysfunction and EEG abnormalities in COVID-19 critically ill patients with ARDS. More importantly, early discontinuous and/or nonreactive EEG backgrounds were associated with both mortality and neurologic outcomes. Finally, patients frequently exhibited a brain stem dysfunction that was also associated with short-term neurologic outcomes.

Our results are coherent with the literature reporting a particularly high rate of protracted coma and delirium (8, 30), predominantly of hyperactive or mixed motoric subtype (31), in contrast with non-COVID-19 patients (32), also we potentially underestimated the prevalence of acute encephalopathy as nonincluded eligible patients had more comorbid conditions and were more severe than the included patients. Nevertheless, our results raise the question of the long-term impact of COVID-19–related delirium, as both ARDS and delirium are detrimental to long-term cognition (33–35) and reports of lasting cognitive symptoms in postacute COVID-19 are accumulating (36).

Predicting subsequent delirium to set up preventive and therapeutic strategies is thus of prime interest, and our findings indicate that an early standard EEG, widely

TABLE 3.
ICU Outcomes According to EEG Continuity and Reactivity at T1

Populations	Overall n = 52	EEG Continuity			EEG Reactivity		
		Absent (n = 25)	Present (n = 27)	p	Absent (n = 17)	Present (n = 35)	p
Outcomes at ICU discharge							
ICU mortality	12 (23)	11 (44)	1 (4)	< 0.001	7 (41)	5 (14)	0.042
ICU length of stay (d)	20 (12–36)	23 (11–36)	20 (14–36)	0.707	19 (14–33)	20 (12–37)	0.740
Invasive mechanical ventilation duration (d)	18 (10–34)	17 (10–33)	18 (10–35)	0.728	17 (13–33)	18 (10–35)	0.922
Coma							
Awakening							
Number of patients	43 (83)	16 (64)	27 (100)	< 0.001	12 (71)	31 (89)	0.133
Delayed, n = 43	29 (67)	12 (75)	17 (63)	0.416	10 (83)	19 (61)	0.279
Delay (d), n = 43	4 (1–13)	6 (1–17)	2 (0–10)	0.579	9 (4–12)	2 (0–13)	0.392
Duration (d)							
All patients	13 (8–26)	14 (10–24)	13 (6–28)	0.667	13 (11–24)	13 (6–28)	0.661
Awakened patients only, n = 43	13 (8–26)	17 (11–25)	13 (6–28)	0.546	17 (12–24)	12 (6–28)	0.343
Delirium, n = 43							
Delirium	32 (74)	12 (75)	20 (74)	0.946	11 (92)	21 (68)	0.139
Type of delirium							
Hyperactive	4 (12)	0 (0)	4 (20)	0.110	0 (0)	4 (19)	0.091
Hypoactive	8 (25)	5 (42)	3 (15)		5 (45)	3 (14)	
Mixed	20 (62)	7 (58)	13 (65)		6 (55)	14 (67)	
Duration (d), n = 32	5 (3–8)	8 (5–8)	3 (2–6)	0.026	6 (4–8)	4 (3–8)	0.484
Outcomes at day 28 from assessment							
Mortality	11 (21)	10 (40)	1 (4)	0.001	7 (41)	4 (11)	0.027
Ventilator-free days (d)	6 (0–20)	0 (0–14)	17 (0–22)	0.010	0 (0–14)	16 (0–22)	0.025
Coma-free days (d)	14 (0–25)	1 (0–13)	22 (12–26)	< 0.001	6 (0–13)	22 (2–26)	0.006
Delirium-free days (d)	12 (0–22)	0 (0–9)	17 (12–25)	0.001	0 (0–9)	17 (0–25)	0.006

EEG = electroencephalography.
Statistics presented: median (interquartile range); *n* (%). Statistical tests performed: Mann-Whitney *U* test; Fisher exact test; and χ^2 of independence.

available and noninvasive, could be helpful to do so. EEG abnormalities have been described in up to 96.1% of COVID-19 patients (37), ranging from seizure to focal or diffuse periodic/rhythmic discharges or slowing (38), the most frequent being frontal slowing or discharge, associated with severe cases (39). Although we found a similar rate of patients with bifrontal slowing (one-third), these were associated with a better outcome than other pathologic patterns in our study,

in accordance with a recent study in which intermittent slow waves were associated with survival (40). Interestingly, these anterior slow waves were observed regardless of the EEG timing, in contrast with the other pathologic patterns, which dwindled during the stay. Most of the previous studies were retrospective (20), included heterogeneous populations in terms of COVID-19 severity and features (40), whereas we prospectively focused on an homogenous cohort of

TABLE 4.
Univariate Associations Between Day-28 Outcomes and Brainstem Dysfunction, EEG Patterns, and Sedatives/Opioids Exposure

Dependent Variable Independent Variable	Mortality Area Under the Receiver Operating Characteristic Curve (95% CI)	p	Coma-Free Days R^2	p	Delirium-Free Days R^2	p
Brainstem dysfunction	0.64 (0.49–0.8)	0.101	0.11	0.015	0.13	0.008
Discontinuous EEG	0.77 (0.66–0.89)	0.009	0.22	0.001	0.22	< 0.001
Nonreactive EEG	0.7 (0.53–0.86)	0.02	0.13	0.008	0.16	0.004
Bifrontal slow waves	0.65 (0.53–0.77)	0.09	0.1	0.021	0.14	0.007
Sedatives infusion rate	0.67 (0.52–0.83)	0.204	0.01	0.421	0.01	0.584
Opioid infusion rate	0.62 (0.44–0.81)	0.398	0.01	0.414	0	0.637
Sedative cumulative dose	0.49 (0.29–0.68)	0.651	0	0.723	0	0.994
Opioid cumulative dose	0.5 (0.3–0.7)	0.829	0.01	0.623	0	0.828
Sedative and opioid duration	0.54 (0.36–0.72)	0.839	0	0.79	0	0.911

EEG = electroencephalography.

Area under the receiver operating characteristic curve with 95% CI and *p* from logistic regressions between day-28 mortality (dependent variable) and each independent variable (brainstem dysfunction, EEG patterns, and sedative/opioid exposure variables). R^2 (measure of explained variance) and corresponding *p* values from liner regressions between coma-free days and delirium-free days and each independent variable.

critically ill patients. Interestingly, a study in a similar population reported a high prevalence of low voltage, rapid rhythm, and bifrontal slow EEG activity but did not assess the relationship of EEG patterns with outcome (8). A recent retrospective study of 33 critically ill COVID-19 patients found that nonreactive EEG was associated with unfavorable neurologic outcome (20). Our study confirms prospectively that EEG helps predicting mortality and neurologic outcomes. Although our conclusions are limited to COVID-19 patients due to the lack of control population, these results are reminiscent of the EEG abnormalities previously reported in septic-sedated critically ill patients, with a roughly similar prognostic value (16–19), as it is also the case for the brainstem dysfunction (26, 41). As EEG rhythms arise from complex corticosubcortical interactions through thalamocortical loops receiving inputs from the brainstem, these results together with brain-imaging (42, 43) and neuropathological studies (9–11, 44, 45) suggest common pathophysiological pathways involving subcortical structures shared by COVID-19 and non-COVID-19 septic patients (46). Rather than stemming from a direct tropism of SARS-CoV-2, COVID-19–related acute brain injury would result from multifactorial unspecific mechanisms associating neuroinflammatory processes triggered by systemic inflammatory response (47) such as cytokine release syndrome (48) and endothelial activation (49) with other well-recognized risk factors of delirium such as metabolic disorders, organ dysfunction, and sedation (50). Regarding the latter, we found that acute brainstem dysfunction and EEG patterns remained associated with subsequent occurrence of delirium and ICU mortality, after adjustment on either sedatives/opioids infusion rates, cumulative doses, or duration. Although we tried to minimize sedation exposure with a goal-directed nurse-protocolized sedation protocol as recommended (24), these findings do not rule out any contribution of sedation, as it is well-established that deep sedation is a risk factor of delirium and death (51–54). These multivariate analyses indicate, however, that EEG and clinical assessment of brainstem responses have a prognosis value per se, mainly because they enable to detect brain-insulting processes despite deep sedation. Another limitation of our study is the use of benzodiazepine, which is recognized as an independent factor of delirium and delayed awakening, as a first-line sedative agent. This is, however, in agreement with recent studies showing that midazolam was used in two-third of patients with severe COVID-19

(31) with the need of higher dose and longer infusion than in non-COVID-19 ARDS (55). The risk of propofol infusion syndrome in patients with severe ARDS could account for the reluctance to use propofol as a first-line sedative agent, which has also been associated with delirium occurrence. Some patients also received interleukin-6 inhibitors, but we could not determine if this treatment had a neuroprotective effect due to the limited number of patients. Finally, almost all patients were treated with NMB due to the severity of ARDS, potentially limiting the generalizability of our results to the most severe patients. Yet, we believe that they are clinically relevant as critically ill adults with COVID frequently have moderate-to-severe ARDS requiring prolonged deep sedation and NMB (56).

CONCLUSIONS

Clinical and neurophysiological brain dysfunctions are frequent in critically ill COVID-19 patients with ARDS. Early nonreactive and/or discontinuous EEG backgrounds are associated with delayed awakening, delirium, and day-28 mortality. An early multimodal neurological assessment could help identifying patients at risk of delirium, who could then be elective to preventive strategies.

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