Electroencephalographic Abnormalities are Common in COVID-19 and are Associated with Outcomes

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Objective: The aim was to determine the prevalence and risk factors for electrographic seizures and other electroencephalographic (EEG) patterns in patients with Coronavirus disease 2019 (COVID-19) undergoing clinically indicated continuous electroencephalogram (cEEG) monitoring and to assess whether EEG findings are associated with outcomes.

Methods: We identified 197 patients with COVID-19 referred for cEEG at 9 participating centers. Medical records and EEG reports were reviewed retrospectively to determine the incidence of and clinical risk factors for seizures and other epileptiform patterns. Multivariate Cox proportional hazards analysis assessed the relationship between EEG patterns and clinical outcomes.

Results: Electrographic seizures were detected in 19 (9.6%) patients, including nonconvulsive status epilepticus (NCSE) in 11 (5.6%). Epileptiform abnormalities (either ictal or interictal) were present in 96 (48.7%). Preceding clinical seizures during hospitalization were associated with both electrographic seizures (36.4% in those with vs 8.1% in those without prior clinical seizures, odds ratio [OR] 6.51, $p = 0.01$) and NCSE (27.3% vs 4.3%, OR 8.34, $p = 0.01$). A pre-existing intracranial lesion on neuroimaging was associated with NCSE (14.3% vs 3.7%; OR 4.33, $p = 0.02$). In multivariate analysis of outcomes, electrographic seizures were an independent predictor of in-hospital mortality (hazard ratio [HR] 4.07 [1.44–11.51], $p < 0.01$). In competing risks analysis, hospital length of stay increased in the presence of NCSE (30 day proportion discharged with vs without NCSE: HR 0.21 [0.03–0.33] vs 0.43 [0.36–0.49]).

Interpretation: This multicenter retrospective cohort study demonstrates that seizures and other epileptiform abnormalities are common in patients with COVID-19 undergoing clinically indicated cEEG and are associated with adverse clinical outcomes.

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The ongoing Coronavirus disease 2019 (COVID-19) pandemic has had a dramatic worldwide impact; as of January 31, 2021, >102 million cases of COVID-19 have been reported, resulting in >2.2 million deaths.[1] This new disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The most commonly recognized severe clinical manifestations are pulmonary complications, including acute respiratory distress syndrome (ARDS), followed by multisystem organ failure.[2] Neurological manifestations of COVID-19 were first reported in a retrospective case series from Wuhan, China. In 214 patients, 24.8% had central nervous system (CNS) manifestations such as headache, dizziness, impaired consciousness, and acute stroke; 1 patient in the severe group developed clinical seizures during hospitalization.[3] In patients with severe COVID-19 and ARDS, encephalopathy, prominent agitation, and confusion were commonly seen.[4]

Although seizures are a common manifestation of acute severe medical or neurological illness, the extent to which COVID-19 is associated with seizures is unknown. Case reports document meningitis/encephalitis associated with SARS-CoV2 resulting in new-onset seizures,[5] in addition to acute symptomatic seizures or even status epilepticus in critically ill patients.[6,7] However, a retrospective multicenter study from China found no acute symptomatic clinical seizures or status epilepticus in 304 patients with COVID-19 without a past history of epilepsy[8] (although no electroencephalograms [EEGs] were performed, as discussed below).

Subclinical or electrographic seizures are common in hospitalized patients, especially in critically ill populations,[9–11] and can be associated with adverse clinical outcomes.[12–17] This has led to guidelines recommending the use of continuous electroencephalogram (cEEG) monitoring for patients with altered mental status.[18] However, owing to limited resources and concern for contamination, many centers have limited cEEG in patients with COVID-19; hence, large studies on EEG findings are relatively sparse. Notably, in the 2 original retrospective studies from China,[3,8] EEGs were not performed; hence, subclinical seizures and nonconvulsive status epilepticus (NCSE) could not be diagnosed. In the largest study to date of cEEG findings,[19] conducted in a single academic hospital system, electrographic seizures were reported in 7% of patients, demonstrating that seizures are a possible complication of COVID-19. To date, however, there have been no published multicenter studies with sufficient sample size to determine the rate of seizures and other epileptiform abnormalities with statistical confidence across institutions or to investigate their impact on patient outcomes.

The goal of this multicenter retrospective study was to characterize the incidence and risk factors of electrographic seizures, NCSE, and other epileptiform abnormalities in a large cohort of patients with COVID-19 who underwent clinically indicated cEEG. Furthermore, we assessed whether epileptiform abnormalities on EEG are associated with adverse clinical outcomes. Understanding these issues will provide guidance about the necessity and urgency of cEEG in this population.

Patients and Methods

Study Design

We identified retrospectively patients who tested positive for COVID-19 and were referred for cEEG between March 1, 2020 and May 21, 2020 at 9 participating hospitals: Beth Israel Deaconess Medical Center (Boston, MA), Massachusetts General Hospital (Boston, MA), Boston Medical Center (Boston, MA), Brigham and Women's Hospital (Boston, MA), Cleveland Clinic (Cleveland, OH), Emory University (Atlanta, GA), Hospital of the University of Pennsylvania (Philadelphia, PA), Université Libre de Bruxelles – Hôpital Erasme (Brussels, Belgium), and Yale New Haven Hospital (New Haven, CT). Data were collected retrospectively from review of the medical records and EEG reports. Inclusion criteria were age > 18 years old, with EEG studies performed for medically indicated reasons. Any clinical or EEG variables not documented in the medical record or EEG reports were presumed absent. The study was approved by the institutional review board at the respective institutions.

Clinical Variables

Clinical information was collected from review of inpatient medical notes, imaging studies, discharge summaries, and EEG reports. Data recorded included baseline demographic data (age and sex), prior history of CNS disorders including epilepsy, suspected clinical seizures as presenting symptoms or during hospitalization (determined by study neurologists based on the medical record), day of first positive test for COVID-19, indications for EEG, laboratory results (blood urea nitrogen [BUN], Creatinine [Cr], alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALK-Ph], D-dimer, fibrinogen, and C-reactive protein [CRP]), brain imaging findings (intracranial lesions were defined as supratentorial infarct, hemorrhage, tumor, or atrophy), length of hospitalization, and in-hospital mortality. All patients in the cohort reached the endpoints of in-hospital death or hospital discharge by the time of the analysis.

EEG-Related Variables

EEG reports were generated by fellowship-trained epileptologists/clinical neurophysiologists utilizing uniform American Clinical Neurophysiology Society intensive care

unit (ICU)–EEG nomenclature. Specifically, interictal abnormalities were classified according to standardized, validated nomenclature,[20,21] and NCSE was defined according to Salzburg criteria for nonconvulsive status epilepticus.[22] Nearly all (190 of 197; 96.4%) of the EEGs were recorded using ≥19 silver/silver chloride electrodes, affixed to the scalp according to the international 10–20 system; the remainder (7 of 197, 3.6%) were completed using a 10-electrode system (Ceribell rapid response EEG; Ceribell, Mountain View, CA) The following factors were assessed from review of final EEG reports: dominant background activity, focal slowing, and presence or absence of: generalized rhythmic delta; lateralized rhythmic delta; sporadic epileptiform discharges (spikes or sharp waves); periodic discharges (lateralized, generalized, or bilateral independent); electrographic seizures; and NCSE. The typical frequency of any periodic patterns was recorded. For some analyses we defined a composite variable, epileptiform abnormalities, to include sporadic epileptiform discharges, lateralized periodic discharges, generalized periodic discharges, electrographic seizures, or NCSE.

Statistical Analysis

Statistical analysis was performed using custom scripts written in Matlab (The Mathworks, Natick, MA) and R (The R Foundation, Vienna, Austria). Results for continuous variables are presented as the median (interquartile range [IQR]). Categorical variables are presented as n (%). Confidence intervals (95% CI) for the incidence of various EEG findings were estimated using the binomial exact calculation. Univariate odds ratios (OR) were calculated to quantify associations between key demographic/clinical variables (Table 1) and EEG findings.

For determining the relationship between key clinical/EEG variables and mortality, hazard ratios (HRs) for predictor variables were calculated using multivariate Cox proportional hazards regression, taking the day of the EEG as $t = 0$. Included variables were chosen a priori based on literature and clinical experience: age; sex; history of prior CNS disorders; intracranial lesions; history of epilepsy; clinical seizure as a presenting symptom; clinical seizure during hospitalization (before EEG); epileptiform abnormalities; electrographic seizures; NCSE; maximal value up to the time of EEG for BUN, ALT, AST, alkaline phosphatase, D-dimer, ferritin, and CRP; hemodialysis or continuous renal replacement therapies before EEG initiation, mechanical ventilation before EEG initiation, and extracorporeal membrane oxygenation before EEG initiation.

For determining the relationship between key EEG variables and length of hospital stay, we performed a competing risk (CR) analysis with death and hospital discharge

TABLE 1. Characteristics of Evaluated Cohort

Characteristic	All Patients (n = 197)
Age, yr	65 (57–73)
Male sex, n (%)	118 (59.9)
Past medical history	
Prior epilepsy, n (%)	32 (16.2)
Prior CNS disorders, including epilepsy, n (%)	67 (34.0)
Renal insufficiency (maximum before/during EEG study)	
Cr, mg/dl	2.4 (1.2–5.6)
BUN, mg/dl	62 (30–104)
HD/CRRT, n (%)	75 (38.1)
Liver dysfunction (maximum before/during EEG study)	
ALT (IU/l)	53 (26–117)
AST (IU/l)	81 (44–166)
ALK-Ph (IU/l)	128 (88–211)
Maximum D-dimer, ng/ml	7520 (2,581, >10,000)
Maximum fibrinogen, mg/dl	723 (566, >740)
Maximum ferritin, ng/ml	1387 (640–3656)
Maximum CRP, mg/l	205 (64, >300)
Mechanically ventilated (during hospital course), n (%)	161 (81.7)
Clinical seizure on admission, n (%)	27 (13.7)
Clinical seizure during hospitalization, n (%)	11 (5.6)
Brain MRI/CT	
New intracranial lesions, n (%)	61 (31.0)
Old intracranial lesions, n (%)	35 (17.8)
No intracranial lesions, n (%)	90 (45.7)
Unknown, n (%)	16 (8.1)

Demographic characteristics, laboratory findings, and brain imaging findings. Age and all laboratory results are reported as the median (interquartile range).

ALK-Ph = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CNS = central nervous system; Cr = creatinine; CRP = C-reactive protein; CRRT = continuous renal replacement therapies; CT = computed tomography; HD = hemodialysis; MRI = magnetic resonance imaging.

as competing endpoints, in an inverse probability weighted Cox proportional hazards model with epileptiform abnormalities and NCSE as covariates. The inverse probability weights were computed from the propensity for epileptiform abnormalities or NCSE, which was determined using a logistic regression model with epileptiform abnormalities or NCSE as the outcome and covariates as follows: age; sex; prior brain injury or history of neurologic disease; prior history of epilepsy; clinical seizure as presenting symptom; maximal values up to the time of EEG for BUN, ALT, and ferritin; hemodialysis or continuous renal replacement therapies up to the time of EEG, and mechanical ventilation up to the time of EEG. We computed cumulative incidences of discharge for patients with and without epileptiform abnormalities or NCSE (with separate models for each of these EEG findings). Results for the CR analysis are reported as the estimated proportion (and 95% CI) of patients discharged by day 30, in patients with versus without epileptiform abnormalities, and with versus without NCSE.

Mortality survival analysis was conducted using the coxphfit function in Matlab. Competing risks analysis was conducted using the survival, survminer, stats, and the causalCmprsk[23] packages in R.

Results were considered statistically significant at a threshold of 5%, or for differences if the estimated confidence intervals did not overlap. We report estimates with 95% CIs using the format (X [Y, Z]).

Results

Study Cohort

A total of 197 patients with COVID-19 who underwent EEG studies were included from 9 participating centers. Their demographic and clinical characteristics are shown in Table 1. The median age was 65 (IQR 57–73) years; 118 (59.9%) were male and 79 (40.1%) female. A prior history of intracranial neurologic disease was present in 67 (34.0%), including 32 (16.2%) with a prior history of epilepsy. Table 1 also summarizes the laboratory and brain imaging results of these patients. Of the 197 patients, 181 (91.9%) underwent brain computed tomography (CT) and/or magnetic resonance imaging (MRI). Of these, 61 (33.7%) had new intracranial lesions, 35 (19.3%) had old intracranial lesions, and 90 (49.7%) had neither acute nor chronic intracranial lesions. Overall, 111 of 197 patients (56.3%) had a history of CNS disorders or intracranial lesions on neuroimaging, whereas 86 of 197 patients (43.7%) had neither of these.

Incidence of Clinical Seizures

Twenty-seven patients (13.7%) presented to the hospital with witnessed seizures or seizure-like events, and 11 more patients (5.6%) had clinical seizures or seizure-like events during their hospitalization before EEG. Of these 38 patients (19.3% of all 197 subjects), 22 (57.9%) had a prior history of CNS disorders, including 12 (31.6%) with a history of epilepsy. Of the 16 patients without prior history of CNS disorders, the majority had either intracranial lesions (acute or remote) detected on brain CT or MRI (n = 5, 31.2%) or other risk factors for seizures (eg, electrolyte disturbance, anoxic brain injury, sepsis or ARDS; n = 10, 62.5%). Only 1 patient, a 47-year-old man with no significant past medical history, presented with new-onset seizures (a bilateral tonic–clonic seizure) in the setting of COVID-19 pneumonia, but without any intracranial lesions or other identifiable seizure risk factors. Of the 12 patients with a history of epilepsy, 10 presented to the hospital with breakthrough seizures, and 2 developed seizures during their hospitalization. In addition to COVID-

TABLE 2. Summary of Electrographic Seizures

Patients with Electrographic Seizures	Number (Total n = 19)
Etiology	
History of CNS disorders (epilepsy)	9 (6)
Acute or chronic structural brain lesions	14
ARDS	10
Systemic infection/sepsis	9
Renal failure	7
Anoxic brain injury	3
Hyperammonemia	1
Multi-organ failure	1
None of the above	0
Electroencephalographic seizure onset	
Focal	12
Multifocal/bilateral	3
Generalized	4
Clinical correlate	
Motor manifestation	11
No clear correlate	5
Myoclonus	3

ARDS = acute respiratory distress syndrome; CNS = central nervous system.

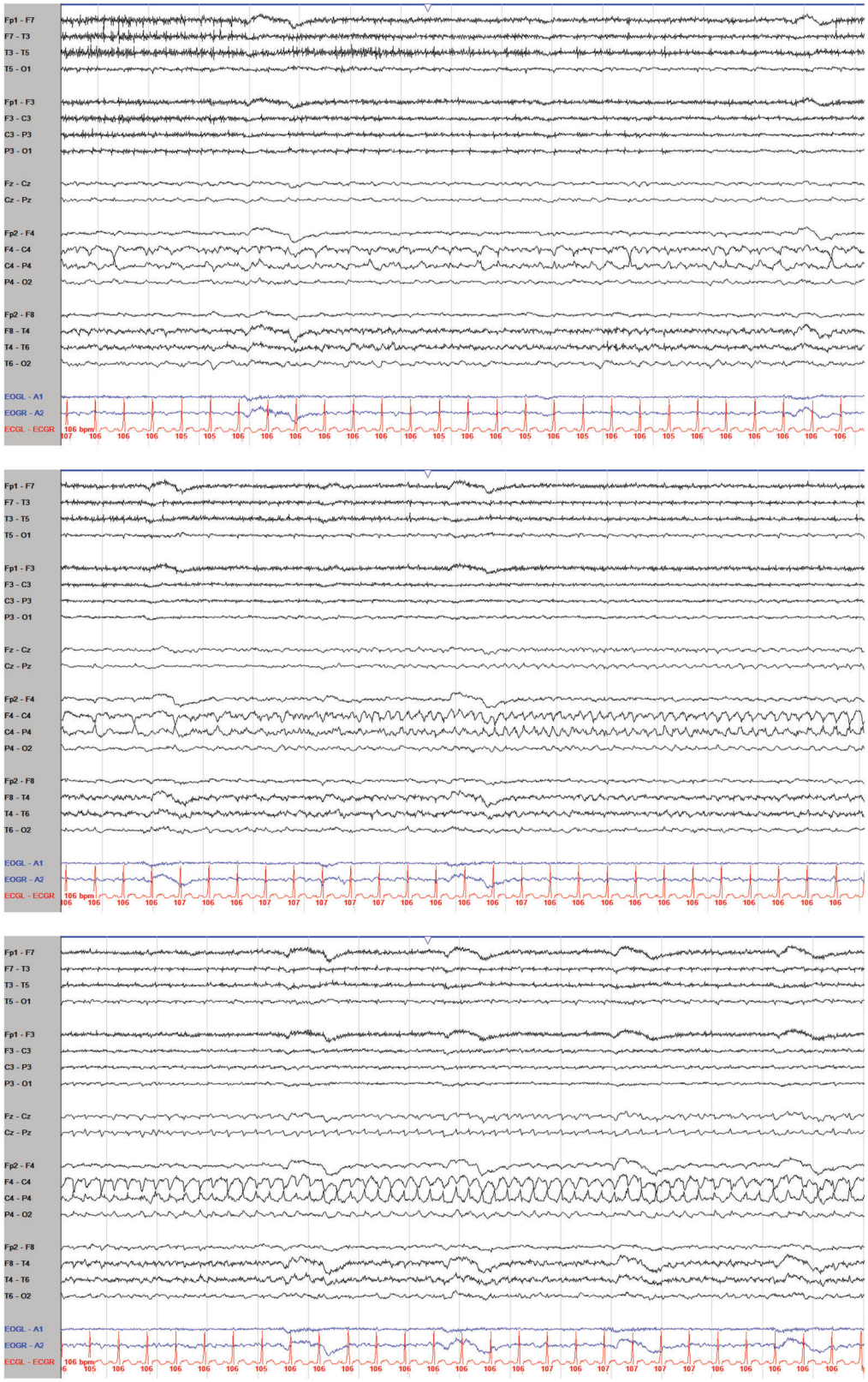

FIGURE 1: Examples of electrographic seizures in Coronvirus disease 2019 (COVID-19) patients. Examples of 19-channel electroencephalogram from a 63-year-old man with no prior history of central nervous system disorders or epilepsy, presenting with acute respiratory distress syndrome attributable to COVID-19 and multi-organ failure, who then developed multifocal electrographic seizures after cardiac arrest. An electrographic seizure from the right central region is shown. Anatomical bipolar montage. High-pass filter 1 Hz, low-pass filter 70 Hz. Scale bars indicate sensitivity and time scale.

TABLE 3. Risk Factors for Electrographic Seizures, NCSE, and Other EEG Findings

EEG Finding	Variable	Odds Ratio	*p*	Prevalence of EEG Finding, n/Total n (%)	
Epileptiform abnormalities	Old intracranial lesion on imaging	2.34	0.03	Yes	23/35 (65.7)
				No	73/162 (45.1)
	Maximal CRP during hospital course	1.48	0.01	–	–
	Time from admission to first positive COVID test	1.46	<0.05	–	–
Electrographic seizures	Clinical seizure during hospitalization	6.51	0.01	Yes	4/11 (36.4)
				No	15/186 (8.1)
	Maximal fibrinogen level	0.53	<0.01	–	–
NCSE	Clinical seizure during hospitalization	8.34	0.01	Yes	3/11 (27.3)
				No	8/186 (4.3)
	Old intracranial lesion on imaging	4.33	0.02	Yes	5/35 (14.3)
				No	6/162 (3.7)
	Maximal fibrinogen level	0.59	0.04	–	–
Sporadic EDs	Old intracranial lesion on imaging	2.12	<0.05	Yes	16/35 (45.7)
				No	46/162 (28.4)
	Maximal CRP	1.64	<0.01	–	–
LPDs	Clinical seizure during hospitalization	7.60	<0.01	Yes	4/11 (36.4)
				No	13/186 (7.0)
GPDs	Clinical seizure as presenting	0.20	0.03	Yes	2/27 (7.4)
				No	48/170 (28.2)
	Maximal CRP	1.46	0.04	–	–
	Time from admission to first positive COVID test	1.45	0.04	–	–
LRDA	D-dimer at start of EEG	2.66	0.04	–	–
	Maximal AST	1.39	0.04	–	–
	Maximal ALT before/during EEG	1.53	0.03	–	–

The table shows univariate odds ratios for significant predictors for EEG findings; for binary measures it also shows the prevalence of EEG findings in the presence versus absence of those findings.
ALT = alanine transaminase; AST = aspartate transaminase; COVID = Coronavirus disease; CRP = C-reactive protein; EDs = epileptiform discharges; EEG = electroencephalogram; GPDs = generalized periodic discharges; LPDs = lateralized periodic discharges; LRDA = lateralized rhythmic delta activity; NCSE = nonconvulsive status epilepticus.

19 infection, 6 of 12 patients with epilepsy had other triggering factors including electrolyte disturbance, sepsis, and withdrawal of antiseizure medications.

Clinical Indication for EEG Studies

EEGs were performed on median day 7 (IQR day 2–18) of hospitalization, and patients remained on cEEG for a median of 25 hours (IQR 19–48 hours). The most commonly reported reason for ordering EEGs was to exclude nonconvulsive seizures/NCSE as a potential etiology of altered mental status (120 patients; 60.9%); among these, 11 also had abnormal movements, 4 had focal neurological deficits, 2 had myoclonus, and 1 had gaze deviation. EEGs were ordered to evaluate whether abnormal movements or other transient symptoms concerning for seizures were ictal in etiology in 51 patients (25.9%), and to monitor for continuing

TABLE 4. Summary of EEG Features

EEG Features	n	Prevalence, % (95% CI)
Patients with EEGs, n	197	
Mechanically ventilated during EEGs, n	149	
Background		
Normal/alpha	11	
Theta	63	
Theta-delta	31	
Delta	73	
Burst suppression	11	
Generalized suppression	8	
Focal slowing/background asymmetry	52	26.4 (20, 33)
GRDA	36	18.3 (13.1, 24.4)
LRDA	11	5.6 (2.8, 9.8)
Epileptiform abnormalities	96	48.7 (41.6, 55.9)
Sporadic EDs	62	31.5 (25.1, 38.4)
LPDs	17	8.6 (5.1, 13.5)
GPDs	50	25.4 (19.5, 32.1)
Seizure, electrographic	19	9.6 (5.9, 14.7)
NCSE	11	5.6 (2.8, 9.8)

The table shows the prevalence of various EEG features (with 95% confidence intervals for epileptiform features).
CI = confidence interval; EDs = epileptiform discharges; EEG = electroencephalography; GPD = generalized periodic discharge; GRDA = generalized rhythmic delta; LPD = lateralized periodic discharge; LRDA = lateralized rhythmic delta activity; NCSE = nonconvulsive status epilepticus.

subclinical seizures after witnessed clinical seizures in 18 patients (9.1%). Other less common indications included monitoring the response to therapy for seizures, monitoring sedation levels, or for prognostication.

Incidence and Risk Factors for Electrographic Seizures

Electrographic seizures occurred in 19 of 197 patients (9.6%, 95% CI [5.9–14.7]%), with 11 (5.6 [2.8–9.8]%) diagnosed with NCSE. Among patients with electrographic seizures, 12 of 19 (63.2%) had their seizures detected within the first 5 days of admission; in the remaining 7, seizures were detected ≥10 days after admission. Among the 19 subjects with electrographic seizures, 14 (73.7%) had either a history of a CNS disorder (including 6 with history of epilepsy) or acute/chronic intracranial lesions. Thus, in the 111 patients with either a history of CNS disorders or intracranial lesions, the rate of electrographic seizures was 12.6 [7.1–20.3]%. In contrast, in the 86 patients without a history of CNS disorders or intracranial lesions, 5 (5.8 [1.9–13.0]%) had electrographic seizures. These 5 patients had other acute metabolic risk factors for developing seizures (ARDS, sepsis, renal failure, or severe anoxia). The electrographic seizure characteristics, including localization and clinical correlates, are summarized in Table 2, and a typical electrographic seizure is shown in Figure 1. Notably, 5 of 19 patients (26.3%) with electrographic seizures had no motor manifestations of their seizures.

On univariate testing of the demographic and clinical patient characteristics (Table 1), significant risk factors for seizures (summarized in Table 3) included the presence of a clinical seizure during hospitalization before EEG hook-up; this was associated with both electrographic seizures (36.4% of patients with a clinical seizure during hospitalization before EEG hook-up vs 8.1% without; OR = 6.51, p = 0.01) and NCSE (27.3% vs 4.3%; OR = 8.34, p = 0.01). Another risk factor for NCSE specifically was the presence of an old intracranial lesion on neuroimaging (14.3% vs 3.7%; OR = 4.33, p = 0.02). Interestingly, the maximum fibrinogen level during the hospital course was inversely correlated with both electrographic seizures (OR = 0.53, $p < 0.01$) and NCSE (OR = 0.59, p = 0.04).

EEG Findings and Association with Clinical Features

Epileptiform EEG abnormalities were common in this patient population; 96 of 197 (48.7%; 95% CI [41.6–55.9]%) patients had epileptiform abnormalities (including electrographic seizures and NCSE) on EEG. Details of various EEG findings are summarized in Table 4. We examined the associations between clinical variables and interictal EEG findings (Table 3). Significant univariate associations ($p < 0.05$) for any epileptiform abnormalities were noted for the presence of an old intracranial lesion (OR = 2.34); maximal CRP value during hospitalization (OR = 1.48); and the day after admission on which the first positive COVID-19 testing was done (OR = 1.46; suggesting that delayed positive COVID-19 testing was associated with a greater risk of these findings). For associations between clinical variables and specific epileptiform EEG abnormalities, see Table 3.

Patient Outcomes

Death occurred in 73 of 197 patients (37.1% overall). Multivariable Cox proportional hazards regression identified electrographic seizures as significantly associated with

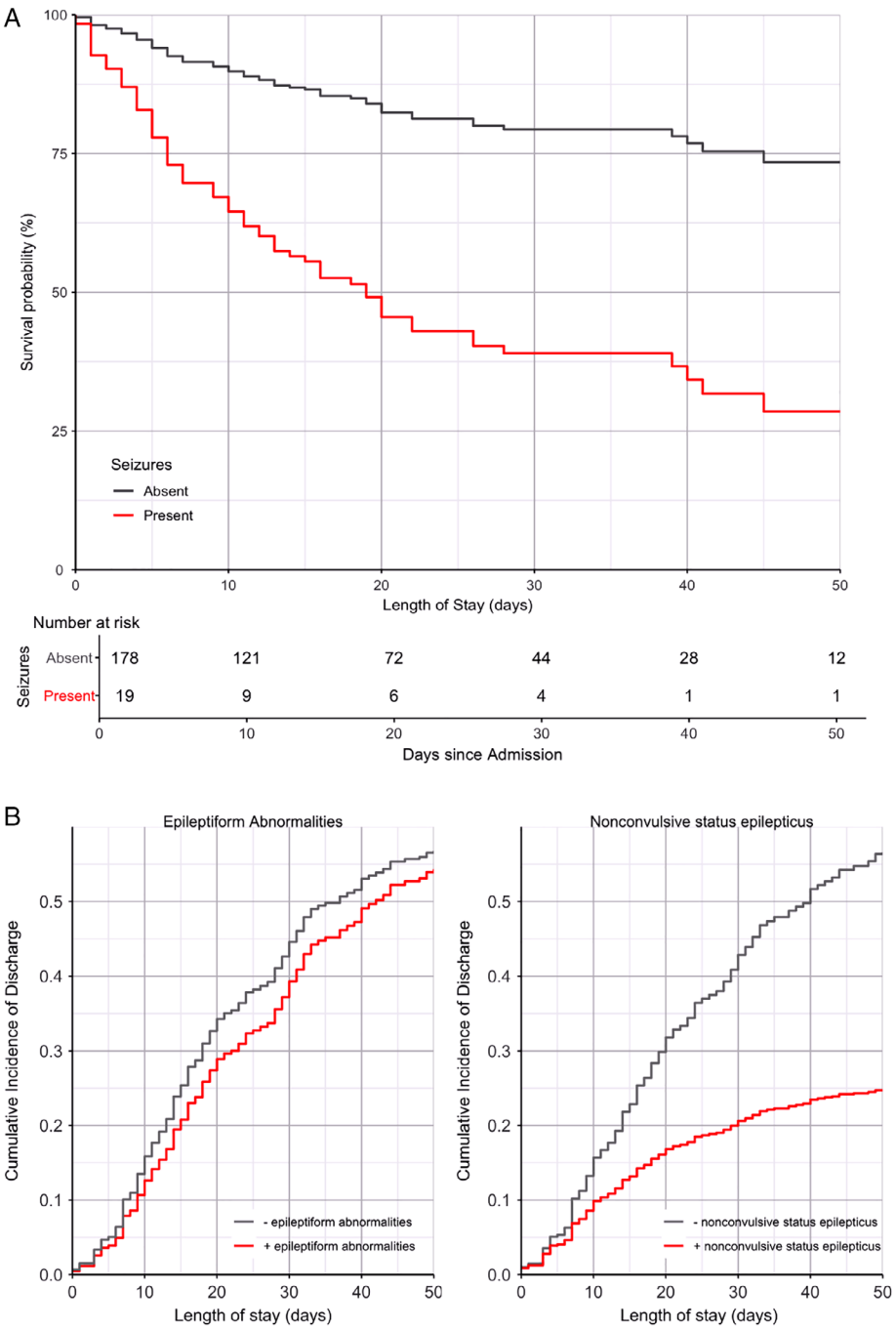

FIGURE 2: Association of electroencephalographic (EEG) findings with mortality and length of stay. (A) Survival curves for the proportion of patients alive over time as a function of presence versus absence of electrographic seizures on EEG; hazard ratio for mortality = 4.06, $p < 0.01$. (B) Cumulative incidence of discharge without death (competing risk analysis) for patients with versus without epileptiform abnormalities (left) or nonconvulsive status epilepticus (NCSE) (right) on EEG (likelihood of discharge by 30 days in patients without vs with EEG abnormality: 0.45 [0.36–0.53] vs 0.39 [0.26–0.47] for epileptiform abnormalities; 0.43 [0.36–0.49] vs 0.21 [0.03–0.33] for NCSE).

mortality (HR 4.07 [1.44–11.51], $p < 0.01$); survival curves are shown in Figure 2A. Death occurred in 63 of 178 (35.4%) patients without electrographic seizures versus 10 of 19 (52.7%) patients with electrographic seizures. A higher maximal ferritin level was also independently associated with increased mortality ($p < 0.05$; Table 5), and older age trended ($p = 0.08$) toward increased mortality. Of note, clinical seizures as a presenting symptom were not associated with increased mortality (HR 0.57 [0.32–1.41], $p > 0.2$).

We also analyzed time to discharge, with death as the competing event, for each predictor of interest. The median (range) length of hospitalization overall was 26 (1–124) days, and the length of stay after initiation of

TABLE 5. Risk Factors for In-Hospital Mortality (Multivariate Analysis)

Risk Factors	Mortality (n = 197)		Multivariate Analysis Mortality Hazard Ratio	*p*
Electrographic seizure			4.07	<0.01
No	63 of 178 (35.4%)			
Yes	10 of 19 (52.6%)			
Maximum ferritin, ng/ml, median (interquartile range)	Dead	Alive	1.39	0.04
	2,491 (952–4,778)	1,031 (434–2,637)		
Age, yr, median (interquartile range)	Dead	Alive	1.32	0.08
	66 (60–74)	65 (55–72)		

This table lists variables found to be statistically significant risk factors for in-hospital mortality in multivariate Cox regression analysis, with associated mortality rates. Cox regression analysis was conducted on the full cohort of all 197 patients.

EEG was 15 (0–94) days. In competing risk analysis (Fig 2B), the estimated probability of hospital discharge by 30 days after the time of initiating EEG monitoring was significantly lower for patients with NCSE versus those without (0.21 [0.03–0.33] vs 0.43 [0.36–0.49]). The probability of discharge by 30 days also tended to be lower in patients with epileptiform discharges versus those without, although this was not statistically significant (0.39 [0.26–0.47] vs 0.45 [0.36–0.53]).

Discussion

COVID-19 has emerged as a global pandemic with significant morbidity and mortality. Here, we present the results of a multicenter study of continuous EEG findings in COVID-19 by characterizing the incidence of and risk factors for various EEG findings in a retrospective cohort of 197 hospitalized patients with COVID-19 who underwent clinically indicated cEEG at 9 institutions in North America and Europe. We found that seizures occur in 9.6% of monitored COVID-19 patients and can occur in patients without any prior neurologic history and without any significant structural abnormalities on neuroimaging. Epileptiform abnormalities overall are common, occurring in almost 50% of monitored patients. EEG findings are associated with clinically relevant outcomes, including mortality and length of stay.

Initial studies suggested that COVID-19 poses minimal risk for seizures during acute illness, despite the fact that a large proportion of patients are in a critical condition with known risk factors for developing seizures.[3,8] However, EEGs were often not performed in these patients owing to concern for exposure and limited resources. Given that patients with severe COVID-19 often have hypoxia, multi-organ failure, metabolic derangements, and sometimes acute brain injury owing to cerebrovascular incidents or anoxic brain injury, the possibility of subclinical seizures or NCSE needs to be considered. Subsequent single-center case reports identified electrographic seizures and NCSE in critically ill COVID-19 patients,[6,7] raising further concerns.

In our cohort of COVID-19-positive patients evaluated with cEEG, although 19.3% of patients presented with clinical seizures or seizure-like events immediately before or during hospitalization, the majority of these patients had a history of prior CNS disorders or had other metabolic risk factors for seizures. Only 1 patient presented with new-onset seizure (a bilateral tonic–clonic seizure in the setting of COVID-19 pneumonia) but without any acute or remote intracranial lesions or other identifiable seizure risk factors. Thus, although seizures in the setting of COVID-19 are not uncommon, a directly epileptogenic process (eg, via meningoencephalitis) is unlikely.

We observed epileptiform abnormalities in 48.7% of patients, electrographic seizures in 9.6%, and NCSE in 5.6%. In comparison, the largest prior study of EEG findings in COVID-19,[19] evaluating 111 patients undergoing cEEG in a single academic system, reported epileptiform abnormalities in 31.5% of patients, seizures in 7.2%, and NCSE in 1.8%. These lower numbers observed in the prior study could be attributable to differences in disease characteristics or unique features of the underlying population, in the threshold for initiating cEEG, or in identification/classification of specific EEG findings.

With regard to cEEG findings in other conditions, prior studies have reported electrographic seizures in approximately 20–30% of all patients undergoing cEEG monitoring.[9,10] More directly comparable to the current population, however, seizures have been reported in approximately 10% of patients admitted to the medical ICU (MICU) without a known primary acute neurologic injury[24,25] in both retrospective[24,26] and prospective[25] studies; in patients with severe sepsis specifically, seizures were reported in 11–16%. Of note, a prior history of epilepsy or remote brain injury was present in 27% of patients in 1 of the prior studies,[26] suggesting that the study population was similar to that in the present study. In contrast, a study evaluating patients with a verified discharge diagnosis of encephalitis[27] reported electrographic seizures in 41% of patients. Our results in COVID-19 patients are thus similar to those observed in other critically ill patients with a similar severe primary non-neurologic systemic illness, such as sepsis, suggesting that seizures in COVID-19 might be related to the severity of disease and its systemic effects rather than specifically to neurotropic activity.

Among COVID-19 patients with electrographic seizures, 26.3% had no motor correlate to their seizures. Even in those patients with no prior history of CNS disorders and with no structural lesions (acute or chronic) on neuroimaging, electrographic seizures were seen in 5.8%. These data support the necessity of cEEG for identifying seizures in this population. Furthermore, almost 50% of patients had epileptiform abnormalities on EEG, suggesting that significant cerebral dysfunction leading to cortical hyperexcitability might be present more commonly in COVID-19 than is generally appreciated or clinically apparent.

During the COVID-19 pandemic, determining which patients are at increased risk for seizures might help to optimize utilization of limited cEEG resources and minimize exposure of staff. The present study identified risk factors for electrographic seizures/NCSE, including clinically suspected seizures during hospitalization and the presence of an old intracranial lesion on neuroimaging. These are not unexpected, because clinical seizures before EEG are associated with electrographic seizures on EEG,[12] and patients with prior neurologic injury are known to be at higher risk for nonconvulsive seizures.[9] Of note, the study by Pellinen and colleagues[19] also reported a suspected clinical seizure before EEG as a risk factor for electrographic seizures. Interestingly, in our study, the maximal fibrinogen level was inversely associated with the risk of seizures; this could reflect the possibility that COVID-19 provoked seizures in patients with epilepsy even in the absence of a significant systemic inflammatory response. Another possible explanation is that patients with clinical seizures were connected to cEEG because of suspicion of nonconvulsive seizures but did not have severe COVID-19, whereas patients with severe disease were connected for other reasons (eg, severe persistent encephalopathy). Risk factors for epileptiform abnormalities included the presence of an old intracranial lesion and higher maximal CRP level. Patients with severe COVID-19 infection were noted to have increased inflammatory response, including increased CRP levels, compared with those with non-severe infection,[3] and the epileptiform abnormalities could reflect neurologic dysfunction attributable to either direct effects of the inflammatory response on the brain or the effects of multi-organ failure owing to the systemic inflammatory response.

Importantly, we found that EEG findings were associated with clinically meaningful outcomes. Specifically, in multivariate analysis, electrographic seizures were associated with increased overall mortality of patients with COVID-19. These data are consistent with previous studies regarding the association between electrographic seizures/NCSE and worse outcomes in critically ill populations.[12–17] However, it is unclear whether electrographic seizures are a modifiable risk factor for mortality or simply a biomarker of severe brain injury leading to mortality. In addition, in the competing risks analysis, NCSE was associated with a significantly lower likelihood of discharge within 30 days after EEG onset; the presence of epileptiform abnormalities also trended towards a lower likelihood of discharge within 30 days. Taken together, these data suggest that COVID-19-related cerebral dysfunction might make a substantial contribution to the adverse clinical outcomes noted in this disease. Alternatively, the EEG findings might influence care in a manner that prolongs stay (eg, via addition of sedating antiseizure medications).

Notably, in contrast to EEG seizures, clinical seizures as a presenting symptom were not associated with significant changes in mortality (on the contrary, they trended toward decreased mortality); this could be because this often occurred in patients with a prior history of epilepsy who are predisposed to seizures, and thus might be less indicative of severe disease with CNS impairment that might lead to cEEG in patients without such a prior history. In other words, seizures as a presenting symptom might reflect cortical hyperexcitability even in the presence of otherwise mild disease, whereas seizures on EEG (which were not associated with seizures as a presenting symptom) might reflect the effects of severe COVID-19 systemic disease.

This study has several limitations. First, this was a retrospective study, and all data, including EEG findings, were abstracted from the electronic medical records and EEG reports. Second, the 197 patients included were all

hospitalized inpatients, who were preselected based on their clinical need for cEEG. Relatedly, both the mechanical ventilation rate (81.7%) and the mortality rate observed in this study (37.1%) were high, suggesting that these patients typically had severe disease. It is likely that if all patients with COVID-19 were to be included, the incidence of clinical and electrographic seizures would be lower. Nevertheless, our findings also suggest that many patients with encephalopathy who do not undergo cEEG might be having seizures that go undetected. We also did not account for specific classes of medical and neurologic comorbidities, the impact of seizure-specific treatment effects (eg, antiseizure medications), or COVID-19-specific treatment effects.

Future studies could address these weaknesses. A prospective study is needed in this population to investigate further the risk of developing seizures or other epileptiform abnormalities and to clarify the relationship between such findings and clinical outcomes after a longer follow-up period. Such studies should ensure that biomarker data are collected at least at specified intervals in all subjects to facilitate analyses of the impact of time-varying biomarker fluctuations on outcomes.

In conclusion, we found that seizures were not uncommon in patients with COVID-19 undergoing cEEG, particularly in patients with a prior history of neurologic disease or significant abnormalities on neuroimaging. Furthermore, epileptiform abnormalities were common, occurring in almost 50% of monitored patients, indicating that the impact of COVID-19 on cerebral physiology might be greater than is generally appreciated. Notably, seizures were associated with increased mortality, and NCSE was associated with prolonged length of stay, both of which suggest that the neurologic complications of COVID-19 might be an important contributor to the observed disease mortality and morbidity. These findings thus strongly support the need for more careful neurologic assessment, including cEEG in many patients, and long-term follow-up in these patients.

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Author Contributions

M.M.S., M.B.W., I.K., C.N., N.G., E.J.G., and L.J.H. contributed to the conception and design of the study. All authors (M.M.S., M.B.W., L.L., S.D., S.S.M., A.A.-F., N.A., P.B., L.F., I.K., J.W.L., C.N., J.P., M.A., C.C., N.G., D.M.G., E.J.G., J.J., J.A.K., E.Y.K., H.S.L., S.T., S.Z., and L.J.H.) contributed to the acquisition and analysis of data. L.L., M.M.S., M.B.W., S.D., and S.S.M. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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