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Electroencephalography at the height of a pandemic: EEG findings in patients with COVID-19

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HIGHLIGHTS

- 93 COVID-19 patients received VEEG mostly for coma (60%) or seizure-like spells (38%).
- The most common VEEG findings were diffuse slowing (97%), attenuation (31%), generalized periodic discharges (17%) and generalized sharp waves (15%).
- Seizures were seen in 8% of patients, all with risk factors for seizures.

ABSTRACT

Objective: To characterize continuous video electroencephalogram (VEEG) findings of hospitalized COVID-19 patients.
Methods: We performed a retrospective chart review of patients admitted at three New York City hospitals who underwent VEEG at the peak of the COVID-19 pandemic. Demographics, comorbidities, neuroimaging, VEEG indications and findings, treatment, and outcomes were collected.
Results: Of 93 patients monitored, 77% had severe COVID-19 and 40% died. Acute ischemic or hemorrhagic stroke was present in 26% and 15%, respectively. Most common VEEG indications were encephalopathy/coma (60%) and seizure-like movements (38%). Most common VEEG findings were generalized slowing (97%), generalized attenuation (31%), generalized periodic discharges (17%) and generalized sharp waves (15%). Epileptiform abnormalities were present in 43% and seizures in 8% of patients, all of whom had seizure risk factors. Factors associated with an epileptiform VEEG included increasing age (OR 1.07, p = 0.001) and hepatic/renal failure (OR 2.99, p = 0.03).
Conclusions: Most COVID-19 patients who underwent VEEG monitoring had severe COVID-19 and over one-third had acute cerebral injury (e.g., stroke, anoxia). Seizures were uncommon. VEEG findings were nonspecific.
Significance: VEEG findings in this cohort of hospitalized COVID-19 patients were those often seen in critical illness. Seizures were uncommon and occurred in the setting of common seizure risk factors.

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1. Introduction

Coronavirus disease 2019 (COVID-19) has emerged as the disease caused by the novel coronavirus SARS-COV-2. Typical symptoms of COVID-19 infection include fever, cough, shortness of breath and flu-like symptoms ((CDC), April 6, 2020). Complications may include respiratory failure (Guan et al., 2020; Bhatraju et al., 2020; Goyal et al., 2020; Argenziano et al., 2020), renal failure (Pei et al., 2020; Argenziano et al., 2020) and hypercoagulability (Miesbach and Makris, 2020). Neurologic complications of COVID-19 include, but are not limited to, anosmia, headaches, encephalopathy, encephalitis, paresthesias and stroke (Mao et al., 2020; Romero-Sánchez et al., 2020). While clinical seizures are infrequently reported in large case series, including in one large multicenter study in China (Lu et al., 2020), initial cohort studies did not report findings from electroencephalogram (EEG) monitoring, in part because neurophysiology services were limited to minimize technologists' exposure (Lu et al., 2020; Assenza et al., 2020). EEG monitoring however, can be critical for the detection of nonconvulsive seizures and allows for dynamic monitoring of neurological function (Smith, 2005).

Recent studies examining EEG findings, mostly performed in patients with severe or critical COVID-19, reported generalized background slowing and variable amounts of epileptiform discharges with seizures occurring infrequently (Pellinen et al., 2020; Ashraf and Sajed, 2020; Louis et al., 2020; Pasini et al., 2020; Galanopoulou et al., 2020; Flamand et al., 2020; Lin et al., 2021; Hwang et al., 2022). However, few large studies have systematically examined the interplay between patients' EEG findings, COVID-19 severity, neuroimaging findings, and antiseizure medications. In this study, we describe the clinical, radiographic, and EEG patterns of a cohort of hospitalized patients with COVID-19 who underwent video EEG (VEEG) monitoring at three large New York City (NYC) hospitals at the height of the pandemic – the original US epicenter.

2. Methods

2.1. Cohort identification

We performed a retrospective chart review of adults (≥18 years) who received VEEG monitoring at three Mount Sinai Health System (MSHS) hospitals (The Mount Sinai Hospital, Mount Sinai West, and Mount Sinai Morningside) in NYC from March 15 to May 15, 2020. These hospitals offer long-term VEEG monitoring and were COVID-19 hotspots at the height of the pandemic. Patients were ascertained by reviewing all VEEG reports stored on the Mount Sinai Natus NeuroWorks EEG database (Xltek, Natus Medical Inc., Pleasanton, CA) during the study period and cross-referenced using the Epic electronic medical record (Epic Systems Corp., Verona, WI) to assess their COVID-19 status. Patients with a confirmed positive/presumed positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nasopharyngeal PCR or serum antibody test prior to or within 24 hours of VEEG monitoring were included. Additionally, all patients were classified as having COVID-19 infection as per internal medicine/infectious disease specialist consults.

2.2. Clinical characteristics

The following sociodemographic and clinical characteristics were abstracted: age, sex, race/ethnicity, epilepsy risk factors (e.g. prior history of epilepsy, prior history of stroke or encephalomalacia, prior brain mass), renal impairment, hepatic failure, acute ischemic or hemorrhagic stroke on neuroimaging studies (CT head or MRI brain), presence of antiseizure medications or sedating infusions at the time of VEEG, and cardiac arrest. Race/ethnicity was extracted from the electronic medical record as reported by the patient/surrogate at time of admission and categorized as per prior publications from the Center for Medicare/Medicaid Services Office of Minority Health (Martino et al., 2019). COVID-19 severity was also defined according to hospital standards, whereby mild disease required no oxygen support, moderate disease required nasal cannula, and severe disease required respiratory support by non-invasive (non-rebreather mask, high-flow nasal cannula, continuous or bilevel positive airway pressure) or invasive (intubation with mechanical ventilation) methods for critical illness, unless otherwise specified.

Renal impairment was defined as having creatinine ≥ 2 mg/dL at the time of VEEG monitoring. Patients with liver failure or significant transaminitis (e.g. ALT > 200 U/L) were identified based on chart review of internal medicine and gastroenterology consult notes. Neuroimaging studies (CT, CT angiography, MRI, MR angiography, and MR venography) performed during the study period were abstracted from radiology reports. We classified imaging findings into prespecified categories of interest: chronic infarcts or encephalomalacia, acute ischemic stroke, acute hemorrhagic stroke or hemorrhagic transformation of ischemic stroke, large vessel occlusion (anterior cerebral, middle cerebral, posterior cerebral or basilar arterial occlusion on arterial imaging), cerebral venous sinus thrombosis, anoxic brain injury, posterior reversible encephalopathy syndrome (PRES) and other findings associated with seizures. Given our objective to correlate VEEG findings to neuroimaging findings, acute (as opposed to chronic) ischemic or hemorrhagic infarcts were only considered if they were identified prior to or within seven days of the start of VEEG monitoring. Unclear neuroimaging findings were resolved after consensus review with two board-certified neurologists.

2.3. EEG data

All VEEGs were performed using the standard 10–20 system. EEG findings were extracted from EEG reports and included background, interictal and ictal findings. EEG findings were coded following standard American Clinical Neurophysiology Society (ACNS) terminology for critical care EEG monitoring (Hirsch et al., 2013). Generalized attenuation was defined as voltage < 20 uV. Additional findings such as focal or generalized slowing or dysfunction severity were abstracted from EEG reports. In cases where the reports did not follow ACNS standards or where the interpretation of a study was unclear, a board-certified epileptologist (LM, JYY, AS, MF, NJ, LB, JY) and fellow (GT) reviewed the raw EEG recording together to make a final determination. For patients who underwent multiple episodes of VEEG monitoring, findings were aggregated and only the most severe findings were coded (i.e., if a patient had a seizure on the first study but not on the second study, the patient was coded as having had a seizure). Likewise, in those cases of an EEG showing evolution over time (i.e., going from moderate to severe slowing over a period of days), only the most severe findings were coded. Medications including antiseizure medications as well as sedating infusions during the period of VEEG monitoring and its immediate vicinity were also abstracted.

2.4. Outcomes

The primary outcomes of interest were the presence of an EEG with epileptiform, rhythmic, and periodic patterns excluding generalized rhythmic delta activity (GRDA), seizures, or status epilepticus. An epileptiform EEG was defined as having focal spikes/sharp waves, generalized spikes/sharp waves, lateralized periodic dis-

charges (LPDs), generalized periodic discharges (GPDs), bilateral independent periodic discharges (BIPDs), multifocal discharges, lateralized rhythmic delta activity (LRDA), brief potentially ictal rhythmic discharges (BIRDs), seizures or status epilepticus. GRDA was excluded as it is commonly regarded as an encephalopathic, rhythmic pattern which is not felt to be associated with seizures (Accolla et al., 2011; Rodriguez Ruiz et al., 2017). The secondary outcomes were discharge disposition, mortality and the Glasgow Outcome Scale (1–5) (Jennett and Bond, 1975) both at discharge and at latest follow-up (October 2020).

2.5. Data and statistical analysis

Descriptive statistics were used to characterize the cohort (demographics, clinical variables, VEEG and neuroimaging findings). T-tests for continuous variable and chi-square tests for categorical variables were conducted to identify subgroup differences. Logistic regression was performed to determine the sociodemographic and clinical factors associated with an epileptiform EEG. The following factors were entered in the regression model: age, sex, COVID-19 severity (mild/moderate vs. severe), known history of seizures or witnessed seizure-like events, hepatic impairment/renal failure (present or absent), lesional brain imaging known to be associated with risk of seizures or epilepsy (e.g. chronic stroke or encephalomalacia, acute ischemic or hemorrhagic infarcts, brain mass, anoxic brain injury, PRES but excluding incidental findings such as pineal gland cyst) and the presence of antiseizure medications or sedating infusions. These factors were included in the model as they have previously been shown to be associated with an abnormal EEG in prior studies (Xinghua et al., 2020). Additionally, logistic regression analyses for the outcome of mortality at discharge were also performed. One regression used the covariates of age, sex, COVID-19 severity (mild/moderate vs. severe), metabolic abnormalities (hepatic or renal failure) as well as the presence of an electrographic seizure on VEEG. A second regression analyses used the covariates of age, sex, COVID-19 severity (mild/moderate vs. severe), metabolic abnormalities (hepatic or renal failure) as well as the presence of any epileptiform abnormality including seizures on VEEG. Analysis was performed using the SAS version 9.4 (Cary, NC).

2.6. Data availability

Researchers with the appropriate credentials, IRB training, and certification can apply to the senior author (JYY) to request access after a data use agreement has been executed with Mount Sinai.

2.7. Standard protocol approvals, registrations, and patient consents

This study was approved by the Mount Sinai COVID-19 institutional review board as part of a larger institutional protocol on the neurological complications of COVID-19. Informed consent for this study was waived given minimal risk to participants. The STROBE cohort reporting guidelines were used in preparation of this manuscript (von Elm et al., 2014).

3. Results

Our final eligible cohort consisted of 93 patients who underwent 115 VEEG studies with confirmed COVID-19 infection. Of the 93 included patients, 86 tested positive for SARS-CoV-2 PCR, 6 were SARS-CoV-2 presumptively positive (presumably due to low level of virus but with clinical picture consistent with COVID-19 infection as per the infectious disease team), and one was antibody positive only. Furthermore, at the time of VEEG, 18% of included patients had developed SARS-CoV-2 antibodies or retested as negative after an initial positive test. All patients in the study were identified as having COVID-19 per clinical and radiographic criteria and were treated per official infectious disease COVID-19 institutional protocols.

3.1. Reasons for VEEG monitoring

As shown in Table 1, the reasons for VEEG monitoring were persistent encephalopathy or coma (60%), witnessed seizure-like movements (38%), focal neurological deficits concerning for seizures (such as gaze preference, 15%), prognostication after cardiac arrest (5%), and syncope (2%). In some cases, especially for patients with repeat monitoring, more than one reason for VEEG monitoring was given.

Table 1
Baseline patient characteristics and neuroimaging findings.

Patient characteristics	N (%)
Age (mean with range)	63.5 (27–88)
Sex	
Male	58 (62.4)
Female	35 (37.6)
Race/Ethnicity[a]	
White	14 (15)
Black	30 (32)
Hispanic/Latino	27 (29)
Asian/Pacific Islander	6 (6)
Other/unknown	19 (20)
Reason for EEG monitoring[b]	
Persistent encephalopathy or coma	56 (60)
Witnessed seizures or seizure-like movements	35 (38)
Unexplained focal neurologic deficits	14 (15)
Prognostication after cardiac arrest	5 (5)
Syncope	2 (2)
Medical history	
Stroke or encephalomalacia	24 (26)
Epilepsy	8 (9)
Brain mass	4 (4)
Medical comorbidities	
Renal failure	51 (55)
Cardiac arrest[c]	11 (12)
Hepatic failure	5 (5)
COVID-19 severity	
Severe	72 (77.4)
Moderate	19 (20.4)
Mild	2 (2.2)
Seizure activity likely per neurologist[d]	18 (19)
Mental status	
Comatose	53 (57)
Encephalopathic	38 (41)
Normal	2 (2)
Neuroimaging	
Any head imaging	84 (90)
CT head	83 (89)
MRI brain	47 (51)
No head imaging	9 (10)
Neuroimaging findings[e]	
Acute ischemic stroke	22 (26)
Acute hemorrhagic stroke or transformation	13 (15)
Anoxic brain imaging	7 (8)
PRES	2 (2)
Cerebral venous sinus thrombosis	1 (1)
Large vessel occlusion	2 (2)

Abbreviations: EEG = electroencephalogram, CT = computed tomography, LVO = large vessel occlusion, MRI = magnetic resonance imaging, PRES = posterior reversible encephalopathy syndrome.
[a] 3 patients identified as both Hispanic and Black.
[b] Multiple indications could be present for a single patient.
[c] Occurring prior to EEG monitoring.
[d] Based on either clinical history, exam or EEG findings.
[e] Based on the subpopulation of patients who underwent imaging.

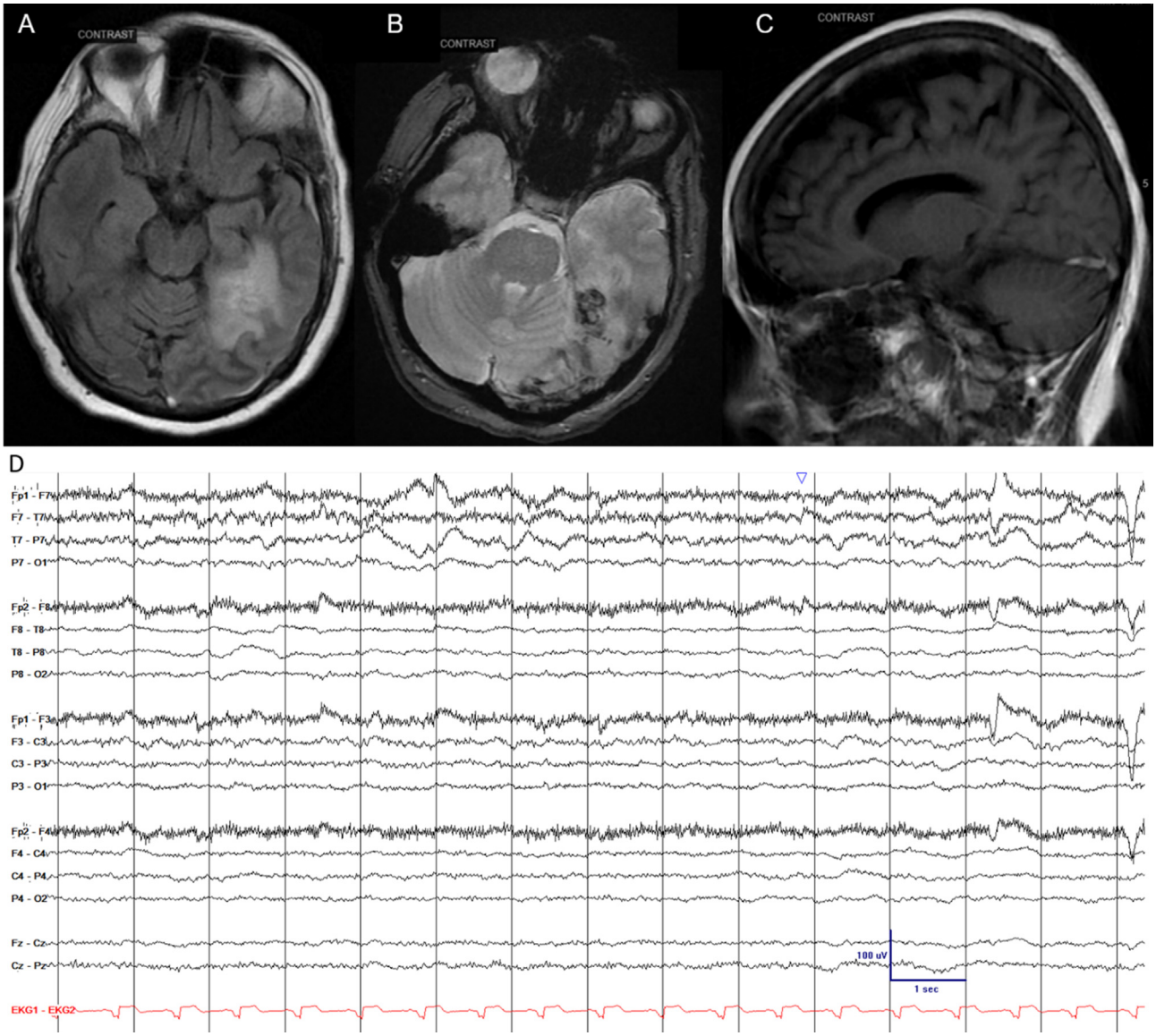

Fig. 1. Findings from a patient with COVID-19 and cerebral venous sinus thrombosis. 71-year-old female presenting with acute confusion and productive cough for 3 days. (A) T2 fluid-attenuated inversion recovery MRI sequence showing left temporo-occipital venous congestion with overlying hemorrhagic transformation seen by gradient echo sequence (B). (C) Hyperintense T1 signal seen in the left transverse and sigmoid sinus consistent with cerebral venous sinus thrombosis. (D) Standard bipolar electroencephalogram (EEG) montage showing generalized slowing as well as focal left temporal slowing.

3.2. Demographics and baseline clinical characteristics

Demographic characteristics are listed in Table 1. Mean age was 63.5 years (SD 13.1, range 27–88) and 62% were male. Race/ethnicity breakdown was as follows: White (15%), Black (32%), Hispanic (29%), Asian/Pacific Islander (6%) and Other/unknown (20%), with 3% identifying as being both Black and Hispanic. Of all patients, 77% had severe COVID-19 infection, 55% had renal impairment or failure, 12% sustained a cardiac arrest prior to VEEG monitoring, and 5% had hepatic failure. Pre-existing seizure risk factors included prior cerebrovascular disease or chronic encephalomalacia (26%), epilepsy (9%), and brain mass (brain tumor or abscess, 4%).

3.3. Neurologic assessments

Fifty-seven percent of patients were described as comatose by a neurologist or critical care physician. In 19% of cases, a neurologist noted that a seizure was likely to have occurred based on the clinical history, neurologic exam and/or VEEG findings.

3.4. Neuroimaging findings

Most patients (90%) had at least one neuroimaging study, most commonly a head CT (89%), brain MRI (51%), or both (49%). Of the 90% who underwent brain imaging, 26% had an acute ischemic infarct on imaging during the same admission either preceding or within a week of the VEEG. Intracranial hemorrhage or hemorrhagic transformation of ischemic infarcts was seen in 15%, anoxic injury in 8%, PRES in 2%, and large vessel occlusion on CT angiogram in 2%. Cerebral venous sinus thrombosis was seen in one patient, who also sustained associated ischemic and hemorrhagic infarctions (Fig. 1).

3.5. VEEG findings

Of the 93 patients included in this study, 64 underwent VEEG recording > 2 h in cumulative duration. The average VEEG duration was 29.3 h (range 0.3–238 h). EEG findings are shown in Table 2. EEGs were abnormal in 98% of patients, most commonly due to

Table 2
EEG findings.

EEG findings[a]	Number (%)
Mean duration in hours (range)	29.3 (0.3, 238)
EEG abnormal	91 (98)
Diffuse slowing	90 (97)
Focal slowing	14 (15)
Attenuation, diffuse	29(31)
Attenuation, focal	3(3)
Focal spikes/sharp waves	13 (14)
LPDs	3 (3)
BIPDs	2 (2)
LRDA	6 (6)
Multifocal	4 (4)
Generalized sharp waves	14 (15)
GPDs	16 (17)
GRDA	12 (13)
BIRDs	0 (0)
Any epileptiform	40 (43)
Seizures[b]	7 (8)
Non-convulsive	5 (5)
Convulsive	3 (3)
Myoclonic	2 (2)
Generalized	4 (4)
Focal	3 (3)
Medications	
Sedating infusions	30 (32)
On antiseizure medications (ASMs)	46 (49)
As a percentage of patients on ASM[c]	
Levetiracetam	40 (87)
Lacosamide	9 (20)
Valproic acid	7 (15)
Phenytoin	3 (7)
Phenobarbital	1 (2)
Clobazam	1 (2)
Lamotrigine	1 (2)
Oxcarbazepine	1 (2)
Clonazepam	1 (2)
Acetazolamide	1 (2)

Abbreviations: ASMs = antiseizure medications, BIPD = Bilateral independent periodic discharges, BIRDs = brief potentially ictal rhythmic discharges, EEG = electroencephalogram, GPD = generalized periodic discharges, GRDA = generalized rhythmic delta activity, LPD = lateralized periodic discharges, LRDA = lateralized rhythmic delta activity.

[a] Most severe findings for each patient throughout all episodes of VEEG monitoring.

[b] Multiple seizure types could apply to each patient.

[c] 46 (49%) patients received treatment with antiseizure medications, not including sedating infusions, which were used in 30 (32%) of patients monitored; table shows the percentages of each non-infusion antiseizure medication used within this subgroup of patients.

background abnormalities. Diffuse slowing was seen in 97% of patients, while 15% had focal slowing. EEG attenuation was seen in 34% of patients, which was generalized in 31% of all patients (defined as voltage < 20 uV) and focal in 3%. GRDA was seen in 13%. Epileptiform features included GPDs (17%), generalized sharp waves (15%), focal spikes or sharp waves (14%), LRDA (6%), multifocal spikes or sharp waves (4%), LPDs (3%), and BIPDs (2%). No BIRDs were detected. Taken together, an EEG with epileptiform, rhythmic, and periodic patterns excluding GRDA, seizures, or status epilepticus was seen in 43% of patients.

Seizures were captured on VEEG in seven patients (8%). Of these patients, three had status epilepticus (two non-convulsive and one both non-convulsive as well as focal convulsive). All patients had epilepsy and/or seizure risk factors: three had seizures/status epilepticus in the setting of anoxic brain injury/severe hypoxemia, two had a history of epilepsy, one had acute renal failure and sepsis with suspected cefepime neurotoxicity and one had hemorrhagic PRES. Of the patients who presented in status epilepticus, one had focal facial twitching and encephalopathy due to cefepime neurotoxicity with EEG findings that were diffuse and non-localizing. The second patient had witnessed convulsive seizures followed by electrographic non-convulsive status epilepticus and coma in the setting of hemorrhagic PRES, of diffuse onset. The third patient had focal right posterior quadrant nonconvulsive status epilepticus after a major hypoxemic event (Fig. 2). Characteristics of patients who had seizures are summarized in Table 3.

3.6. Focal imaging correlates

Of the 15 patients who had focal epileptiform findings on EEG, 10 were found to have associated imaging correlates ($p < 0.0001$, chi-square test of association). Of the 22 patients who had any focal EEG finding (either focal slowing or focal epileptiform findings), 15 had focal imaging correlates ($p < 0.0001$, chi-square test of association).

3.7. Medications

Forty-six patients (49%) were on at least one antiseizure medication and 30 (32%) were on a sedating infusion (e.g., midazolam, propofol, dexmedetomidine, fentanyl) at the time of VEEG monitoring. The most common antiseizure medication was levetiracetam, followed by lacosamide and valproic acid (Table 2).

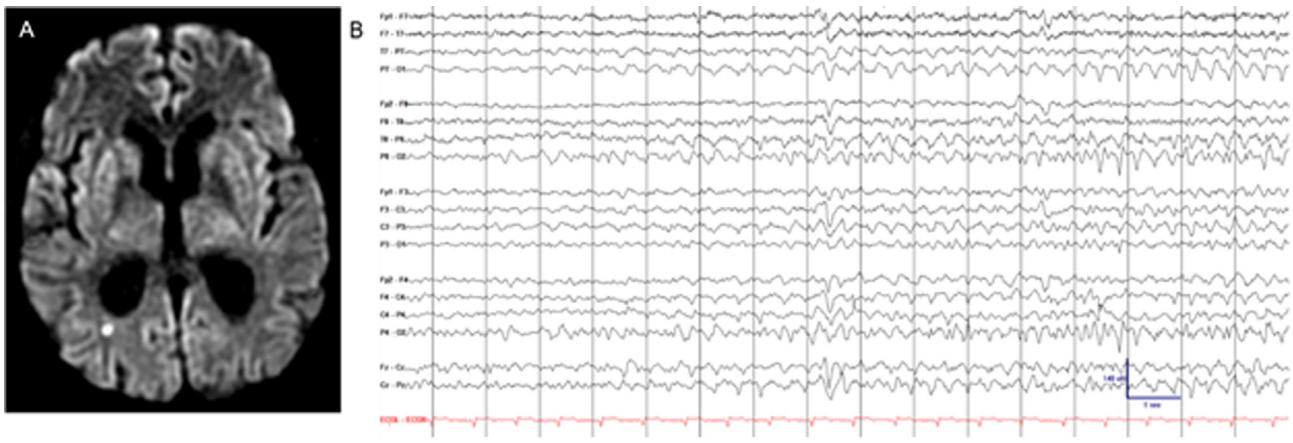

Fig. 2. Findings from a COVID-19 patient post-cardiac arrest with punctate infarction. 47-year-old female with end-stage renal disease, renal transplant, presenting with severe COVID-19 and subsequent respiratory failure and cardiac arrest. (A) Diffusion-weighted MRI showed punctate infarction in the right parietal region. (B) Electroencephalogram (EEG) showed non-convulsive status epilepticus with onset of seizures maximal over the right posterior quadrant.

Table 3
Clinical characteristics of COVID-19 patients with seizures.

Patient	COVID-19 Severity	Seizure risk factors	Clinical features	On ASM's or sedating infusions	Seizure onset on EEG	Seizure type while on EEG (may be several)	Status epilepticus	Glasgow Outcome Scale at Discharge
1	Moderate	Epilepsy	Catatonia	LEV, PHT	Right frontocentral	Nonconvulsive	No	Moderately disabled
2	Severe	Hemorrhagic PRES	Convulsive movements of face and upper body, then nonconvulsive status epilepticus on EEG	LEV, LCM, VPA, anesthetic drip	Generalized	Nonconvulsive	Yes	Severely disabled
3	Severe	Cardiac arrest	None	LEV, LCM, anesthetic drip	Right posterior quadrant	Nonconvulsive	Yes	Vegetative state
4	Severe	Cardiac arrest	Myoclonus	Anesthetic drip	Generalized	Convulsive	No	Dead
5	Moderate	Acute renal failure, cefepime neurotoxicity	Left facial twitching, encephalopathy	LEV, PHT, CLB	Generalized	Focal partial Nonconvulsive	Yes	Dead
6	Moderate	Chronic cortical strokes, epilepsy	Rhythmic tonic clonic activity of head and right arm, then nonconvulsive seizures on EEG	LEV, VPA, PHB	Right posterior temporal	Nonconvulsive	No	Dead
7	Severe	Severe hypoxemia	Myoclonus	LEV, CZP	Generalized with frontal predominance	Convulsive	No	Dead

Abbreviations: CLB = clobazam, CZP = clonazepam, EEG = electroencephalogram, LEV = levetiracetam, LCM = lacosamide, PHB = phenobarbital, PHT = phenytoin, PRES = posterior reversible encephalopathy syndrome, VPA = valproic acid.

Table 4
Factors associated with having an epileptiform EEG, seizures, or status epilepticus.

Variable	OR	95% CI		p-value
Age	1.07	1.03	1.12	0.001
Male	0.44	0.17	1.14	0.09
Severe COVID-19	0.86	0.27	2.77	0.81
Prior epilepsy or witnessed seizure-like movements	1.59	0.51	4.95	0.43
Metabolic abnormalities	2.99	1.10	8.15	0.03
Lesional brain imaging	1.04	0.40	2.70	0.94
Medications	1.58	0.49	5.04	0.44

Any epileptiform findings included the presence of focal or generalized discharges, isolated or periodic, lateralized rhythmic delta activity, multifocal discharges, brief potentially ictal or rhythmic discharges, seizures or status epilepticus. Metabolic abnormalities included the presence of hepatic and renal failure. Lesional brain imaging included imaging findings that could increase the risk of seizures, including chronic infarcts/encephalomalacia, acute ischemic or hemorrhagic infarcts, anoxic brain imaging, posterior reversible encephalopathy syndrome or brain mass, compared to imaging without these findings. Medications included antiseizure medications or sedating infusions compared to not being on medications. Abbreviations: OR = odds ratio CI = confidence interval.

4. Factors associated with having an EEG with epileptiform, rhythmic or periodic patterns excluding GRDA

In the univariate analysis, those with an EEG showing epileptiform, rhythmic or periodic patterns excluding GRDA were significantly older (mean age 68 vs 60), p = 0.0013) as compared to those who did not have epileptiform EEG.

In the multivariable logistic regression, factors associated with having an EEG with epileptiform, rhythmic or periodic patterns excluding GRDA were: Increasing age (OR 1.07 (CI 1.03–1.12), p = 0.001) and the presence of hepatic/renal failure (OR 2.99 (CI 1.10–8.15), p = 0.03) (Table 4). Importantly, witnessed seizure-like events, such as abnormal movements, were not significantly associated with having an epileptiform EEG in our regression analysis. However, of all patients with witnessed abnormal movements, the rate of having an EEG with any epileptiform feature was 43% and the rate of having an EEG with a seizure was 14%. Given that all patients with a history of epilepsy were found to have an epileptiform EEG in our cohort, we were not able to include this factor in a logistic regression as there was a 100% association.

4.1. Secondary outcomes

Patient outcomes are shown in Table 5**.** The mean Glasgow Outcome Scale was 2.4 (SD 1.2). Of all the 93 patients included, 38% had died by the time of discharge, and 40% by the time of last follow-up in October 2020. Of those patients who were not deceased by the time of discharge, 8% were alive but in a vegetative state, 38% were severely disabled, 15% moderately disabled and 2% had made a good recovery by discharge. In terms of discharge disposition, 37% were discharged to a subacute facility, ventilator-weaning facility, or nursing home, 13% to an acute rehabilitation facility, 9% to home with home services and 1% to home without any needs.

Two multivariable logistic regressions for the outcome of mortality at discharge were performed adjusted for age, sex, COVID-19 severity, metabolic abnormalities (liver and/or renal failure) and either having seizures on EEG (Table 6) or having any epileptiform ability on EEG (Table 7). For the first regression, both severe COVID-19 (OR = 5.30, 95 %CI 1.36–20.86, p = 0.02) as well as the presence of metabolic abnormalities (OR = 3.85, 95 %CI 1.48–10, p = 0.01) were significantly associated with mortality at discharge

Table 5
Patient outcomes.

Outcome	Number (%)
Discharge disposition	
Home	1 (1)
Home with services	8 (9)
Acute rehabilitation	12 (13)
Subacute rehabilitation or vent-weaning facility	34 (37)
Dead (at time of discharge)	35 (38)
Dead (at time of chart review)	37 (40)
Other (hospital transfer etc.)	3 (3)
Glasgow Outcome Scale	
Dead (1)[a]	35 (38)
Vegetative state (2)	7 (8)
Severely disabled (3)	35 (38)
Moderately disabled (4)	14 (15)
Good recovery (5)	2 (2)
Mean Glasgow Outcome Scale (SD)	**2.4 (1.2)**

SD = standard deviation.
[a] This number increased to 37 (40%) by the time of last chart review.

Table 6). The presence of an electrographic seizure on EEG approached (OR = 7.77, 95 %CI 0.94–64.15, p = 0.06) but did not reach statistical significance, likely due to the low number of electrographic seizures present in our cohort. Similarly, in the second regression, using the covariate of any epileptiform finding on EEG rather than just electrographic seizures, only severe COVID (OR 3.98, 95 %CI 1.16–13.7, p = 0.03) and the presence of metabolic abnormalities (OR 3.46, 95 %CI 1.34–8.94, p = 0.01) were significantly associated with mortality at discharge (Table 7).

5. Discussion

We report a cohort of 93 patients who underwent VEEG monitoring at the height of the COVID-19 pandemic in NYC. To our knowledge, this represents one of the largest EEG monitored cohorts reported thus far during the pandemic. The primary outcome of interest was an EEG with any epileptiform abnormality or seizures, which was seen in 43% and 8% of patients, respectively. The most common reason for VEEG monitoring was persistent encephalopathy or coma (60%), followed by abnormal movements concerning for seizures (38%). The most common electrographic abnormality was diffuse background slowing (present in 97% of studies).

The most frequent epileptiform discharges were GPDs, which are generally considered non-specific markers of cortical irritability and can be seen in a variety of states, including anoxic injury, toxic-metabolic encephalopathy, renal and hepatic failure, sepsis, cefepime neurotoxicity, among others (Husari and Johnson, 2020; Sully and Husain, 2018). However, GPDs can also indicate an increased tendency towards seizures, which increases according to the frequency of discharges (Beniczky et al., 2013; Husari and Johnson, 2020).

Seizures were relatively infrequent (8%), and occurred in COVID-19 patients with additional concomitant risk factors for seizures, including comorbid epilepsy, severe hypoxemic events, cefepime neurotoxicity and acute hemorrhagic PRES. Although we did not observe a specific electrographic signature of COVID-19, neuromonitoring with VEEG provided critical assistance in ruling out non-convulsive seizures, which can be common in critically ill populations.

A recent New York University study examined continuous EEG recordings from 111 patients between March 1, 2020 and April 30, 2020, most of whom were critically ill or comatose (Pellinen et al., 2020). Compared to our cohort, they observed a similar prevalence of seizures among patients with severe COVID-19 (7% vs 8%). However, we observed a higher overall prevalence of epileptiform discharges (43% vs 32%), including focal discharges (14% vs 11%), generalized discharges (15% vs 5%), and GPDs (17% vs 9%). This may be due to the lower proportion of patients in our study on sedative infusions (32% vs 60%) as well as inter-institutional variability in EEG classification despite using the same ACNS nomenclature (Gaspard et al., 2014). However, the predominance of generalized sharp waves and generalized epileptiform discharges observed in our cohort is comparable to the findings from another New York study at Montefiore (Galanopoulou et al., 2020), which detected sporadic epileptiform discharges (but no seizures) in 41% of patients using primarily a reduced montage EEG with smaller numbers or routine and continuous EEG recordings. Our findings are also consistent with other New York based studies including one from Columbia University where 14% had GPDs with a similar number (8%) having electrographic seizures on continuous recordings (Waters et al., 2021), as well as from a large cohort of 192 patients at Northwell using a mixture of continuous and routine recordings where the overall presence of epileptiform discharges was 39.6% with a prevalence of GPD's of 19.3% and seizures of 4.1% (Hwang et al., 2022). Our results also mirror

Table 6
Factors associated with mortality, using covariate of electrographic seizure on EEG.

Variable	OR	95% CI		p-value
Age	1.02	0.99	1.06	0.22
Male	0.94	0.36	2.42	0.90
Severe COVID-19	5.30	1.36	20.86	0.02
Metabolic abnormalities	3.85	1.48	10	0.01
Electrographic seizure on EEG	7.77	0.94	64.15	0.06

Abbreviations: CI = confidence interval, COVID-19 = Coronavirus disease 2019, EEG = electroencephalogram,OR = odds ratio.

Table 7
Factors associated with mortality, using covariate of any epileptiform abnormality on EEG.

Variable	OR	95% CI		p-value
Age	1.01	0.98	1.05	0.49
Male	0.93	0.36	2.40	0.88
Severe COVID-19	3.98	1.16	13.7	0.03
Metabolic abnormalities	3.46	1.34	8.94	0.01
Any epileptiform abnormality on EEG	1.59	0.58	4.33	0.37

Abbreviations: CI = confidence interval, COVID-19 = Coronavirus disease 2019, EEG = electroencephalogram, OR = odds ratio.

Table 8
Summary of major studies discussing EEG findings in patients with COVID-19 during the initial surge of the pandemic.

Reference	Site	Study Period	N	Epileptiform discharges, %	Electrographic seizures, %	EEG type	Mortality, %	Seizure predictors/correlates	Predictors of outcome
Tantillo et al.	New York, NY, USA	March 15 – May 15, 2020	93	43.0 (any ED or seizures)	7.5	Routine and LTM	37.6	Pre-existing epilepsy, anoxia, cardiac arrest, PRES, cefepime neurotoxicity	COVID-19 severity, metabolic abnormalities
(Danoun et al., 2021)	Southeast Michigan, USA	March 12 – May 15, 2020	110	13.6 (sED), 23.6 (prED)	11.0	Routine and LTM	44.5	NR	COVID-19 severity, age, level of consciousness
(Galanopoulou et al., 2020)	New York, NY, USA	March 1 – April 15, 2020	22	40.9 (sED), 18.2 (prED)	0.0	Routine, LTM, Rapid-EEG	NR	NR	NR
(Hwang et al., 2022)	New York, NY, USA	March-June, 2020	192	39.6 (any ED or seizures)	4.2	Routine, LTM, Rapid-EEG	37.5	Pre-existing epilepsy, acute structural lesions	Coma, ventilatory support
(Lambrecq et al., 2021)	Paris, France	March 30 – June 11, 2020	78	5.1 (sED), 7.7 (prED)	1.3	Over 20 minutes, NR	9.0	NR	NR
(Lin et al., 2021)	Multicenter (USA and Belgium)	March 1 – May 21, 2020	197	48.7 (any ED or seizures)	9.6	LTM	37.1	Preceding clinical seizure, maximal fibrinogen level, old intracranial lesion	Electrographic seizure, maximum ferritin level
(Louis et al., 2020)	Cleveland, OH	April 20 – May 20, 2020	22	13.6	9.1	Routine and LTM	27.3	NR	None
(Pellinen et al., 2020)	New York, NY, USA	March 1 – April 30, 2020	111	31.5 (any ED or seizures)	7.2	LTM, Rapid-EEG	44.1	Pre-existing epilepsy, preceding clinical seizure	NR
(Skorin et al., 2020)	Santiago, Chile	May 1 – June 15, 2020	62	14.9 (sED), 3.2 (prED)	4.2	Routine and LTM	27.4	NR	Cancer, EEG performed at third week of hospitalization
(Waters et al., 2021)	New York, NY, USA	March 1 – June 30, 2020	79	7.6 (sED), 6.3 (prED)	7.6	LTM	26.5	Pre-existing epilepsy, PRES, metastatic cancer, intracranial hemorrhage	NR

Abbreviations: ED = epileptiform discharges; LTM = long-term monitoring electroencephalogram (>2 hrs); NR = not reported; prED = periodic or rhythmic epileptiform discharges; PRES = posterior reversible encephalopathy syndrome; Rapid-EEG = Rapid Response EEG (eight-channel headband EEG; Ceribell Inc., Mountain View, CA); rEEG = routine electroencephalogram, sED = sporadic epileptiform discharges.

those in other parts of the United States including a study in Michigan which reported high rates of generalized periodic discharges with triphasic morphology (21%), GRDA (18%) and non-triphasic GPDs (9%) and a comparable incidence of electrographic seizures (11%) on routine and continuous recordings (Danoun et al., 2021) as well as a study from the Cleveland Clinic (Louis et al., 2020), which reported GPDs and seizures in 32% and 9% of patients who underwent primarily continuous as well as routine EEG. In all of these studies, the most common reason for EEG monitoring was severely abnormal mental status followed by paroxysmal motor events concerning for seizures, and the proportion of patients on antiseizure medications was high (27–55%). Overall, the high rate of diffuse slowing and the low rate of seizures observed in our cohort are consistent with the findings of two recent systematic reviews of EEG findings in COVID-19 patients (Antony and Haneef, 2020; Roberto et al., 2020). Similar findings showing the preponderance of diffuse slowing and low rate of electrographic seizures were also reported in case series from Chile and Italy (Skorin et al., 2020; Pasini et al., 2020). The incidence of seizures in a cohort of 168 pediatric patients in Italy was determined to be 3% (5 patients), with four of these patients having a pre-existing history of epilepsy or febrile seizures (Garazzino et al., 2020). More recently, a multicenter study of 197 patients with an incidence of seizures of 9.6%, had an overall prevalence of any epileptiform discharges of 49%, with the most frequent epileptiform abnormalities being GPDs (25%) (Lin et al., 2021). Our study therefore further serves to confirm the incidence and prevalence of seizures and epileptiform findings in this population. For a summary of seminal studies about COVID-19 and EEG findings, please see Table 8.

Our study demonstrated a higher burden of acute stroke (26% for acute ischemic stroke and 15% for hemorrhagic stroke or transformation), than what has been previously reported in the literature (1–3%), including the recently reported cerebrovascular cohort from our own Mount Sinai Health System (Mao et al., 2020; Romero-Sánchez et al., 2020; Dhamoon et al., 2020). This is likely due to the fact that our study population was reflective of the subpopulation of critically ill patients with encephalopathy (often coma) and abnormal movements who underwent both VEEG studies and brain imaging, rather than the *overall* population of hospitalized COVID-19 patients. Both encephalopathy and cerebrovascular events have been observed more frequently in patients with severe COVID-19 (Mao et al., 2020), who made up the majority of our cohort. In many cases, infarcts were attributed to COVID-19-associated microthrombosis as well as ischemic events in the setting of global hypoxia or hypotension, reflecting the critical nature of these patients. Importantly, many were punctate infarctions noted incidentally on MRIs performed for persistently altered mentation. Notably, our cohort had a higher utilization of MRI compared to prior studies (Pellinen et al., 2020), which facilitated the detection of punctate infarcts likely due to microthrombosis that might not be a cause of cortical irritability. The high percentage of hemorrhagic strokes or hemorrhagic transformation of ischemic infarcts may also be related to derangements in coagulation or may further reflect the sequelae of the broad anticoagulation policy being followed at the time. Our stroke prevalence, however, is similar to the EEG series reported at New York University who found a prevalence of 24% for acute stroke and 17% for hemorrhagic stroke. The high prevalence of vascular events in this critically ill population compared to seizures further underscores the need for expe-

dited brain imaging to determine the cause of COVID-19-associated encephalopathy.

Unsurprisingly, pre-existing epilepsy was associated with an increased risk of seizures in the context of COVID-19. This may be due to several factors. Patients with epilepsy have a predisposition to seizures that can be exacerbated by acute infection and medical stressors, as well as by the multiple metabolic derangements that have been associated with COVID-19, including renal failure (Pei et al., 2020). Indeed, our analysis demonstrated that all patients with pre-existing epilepsy had at least one EEG with an epileptiform finding, and further found that metabolic abnormalities were significantly associated with an increased odds of an EEG with epileptiform abnormalities, although not seizures themselves. Although many neurophysiology laboratories have scaled down activities to minimize unnecessary staff exposure, patients with epilepsy warrant a higher clinical suspicion of breakthrough seizures as a cause of prolonged encephalopathy and may benefit more from VEEG monitoring.

Multiple mechanisms have been proposed to link seizures and COVID-19, including factors associated with critical illness (e.g., hypoxia, hypoperfusion, electrolyte disturbances, multiorgan failure), inflammation-induced endothelial dysfunction (leading to hypercoagulability and increased incidence of cerebrovascular disease), neuroinvasive disease traveling to the brain via the olfactory bulb (leading to encephalitis and frontal lobe dysfunction) as well as systemic inflammation secondary to cytokines, all of which may occur during the most severe part of the disease or as a parainfectious phenomenon, as detailed in a recent review (Ellul et al., 2020). At a more general level, the sequelae of critical illness, including renal failure, prolonged time for clearance of anesthesia and the neurologic damage secondary to hypoxemia (Romero-Sánchez et al., 2020), cannot be overstated. Given the limited number of seizures in this cohort, we were unable to provide evidence to support any particular mechanism by which COVID-19 causes seizures.

Prior case reports and series have described selective frontal dysfunction as a possible biomarker of COVID-19 encephalopathy (Vellieux et al., 2020; Pasini et al., 2020; Flamand et al., 2020), with a recent systematic review noting that about half of focal slowing and status epilepticus cases were of frontal origin (Antony and Haneef, 2020). Additionally, frontal EEG abnormalities and periodic discharges have been described to be more prominent in patients with COVID-19 related encephalopathy in a recent series of 9 patients from Paris, France (Lambrecq et al., 2021). While this is a provocative hypothesis, further studies are needed to support a unique clinical-pathological correlation between selective frontal involvement and COVID-19. Although our study was not powered to detect localization-related findings, only 2/7 (28%) of patients with seizures in our cohort had onsets in the frontal lobe or diffuse onsets with frontal predominance, and while the cohort reported at New York University reported 11% of patients had focal non-periodic discharges and 24% had focal slowing, they did not specifically comment on frontal predominance.

It may be worthwhile to consider the predominance of electrographic frontal dysfunction as a by-product of non-specific neuronal injury from systemic derangements, which are known to manifest prominently in the frontal lobe. For example, generalized EEG patterns commonly seen in critically ill patients with toxic-metabolic encephalopathy (GRDA and GPD, especially those with triphasic morphology) are often frontally predominant. While this process is incompletely understood, it is hypothesized to be mediated by thalamocortical circuits and their interplay with the brainstem arousal system, disruption of which may occur during encephalopathic states of critical illness or metabolic dysfunction, leading to epileptiform activity, often during arousal or stimulation (Hirsch et al., 2004). Data from our cohort suggests that the ictal and epileptiform activity captured by VEEG studies are inextricably linked to neurological complications of critical illness including hypoxemia and metabolic abnormalities as well as new or underlying structural brain disease.

In support of the hypothesis linking our EEG findings in patients with COVID, are numerous studies showing baseline EEG abnormalities in critically ill patients with a recent study of 1123 critically ill adults showing GPDs, GPDs with triphasic morphology and LPDs in 29% of all patients and in 51% of those patients who had seizures (Newey et al., 2018). Prior studies have also indicated that seizures in critically ill patients are mostly nonconvulsive in nature and occur more frequently in patients with acute brain lesion such as CNS infections, intracerebral hemorrhage and anoxic brain injury (Newey et al., 2018). In a separate prospective study looking at CEEG findings in 98 critically ill patient with sepsis and alteration of mental status, periodic patterns were detected in 25% of patients, while the prevalence of nonconvulsive seizures was 11%, all of which began with periodic discharges and the majority of which were generalized, mirroring our own findings (Gilmore et al., 2015).

Our study has several limitations. First is the retrospective nature of the study, which is subject to several biases. This was minimized by frequent consensus review of neurologic findings regarding VEEG and neuroimaging reports. Furthermore, although we considered over 100 VEEG studies across three different hospitals within our health system, the sample size is still relatively small. This is at least partially due to reduced VEEG utilization to minimize unnecessary EEG technologist exposure. As a result, many COVID-19 were not monitored despite profound mental status disturbances. Especially during the most acute phase of the illness when encephalopathy was commonly attributed to active infection and medical instability, VEEG monitoring was often deferred, which may have reduced our yield for seizures or epileptiform activity. Nevertheless, the large proportion of patients whom at some point experienced severe COVID-19 (77%) likely allows sufficient exploration of this population. Additionally, the threshold to obtain VEEG monitoring may have differed between hospitals and clinical units in our cohort, introducing selection bias. A reduced montage EEG was sometimes used for rapid screening purposes, as has been described in several other reports (Galanopoulou et al., 2020), however this device was not uniformly available at all three hospitals, so these recordings were not included in our analysis.

6. Conclusion

The results of our study, including the high burden of epileptiform discharges, demonstrate that COVID-19 can cause significant neuronal dysfunction. However, this uncommonly progressed to seizures in the absence of additional risk factors, such as pre-existing epilepsy, major acute changes in brain imaging, severe sepsis, or significant hypoxia. We did not find any specific electrographic signature apart from the electrographic sequelae of critical illness most commonly including diffuse slowing, attenuation and generalized epileptiform discharges. Therefore, patients with encephalopathy or abnormal movements in the setting of severe COVID-19 should trigger an investigation for an underlying cause, beginning with brain imaging and then proceeding to VEEG mon-

itoring if structural lesions or additional clinical risk factors are present.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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