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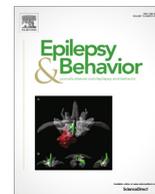
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Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19



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ABSTRACT

Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a myriad of neurological manifestations and its effects on the nervous system are increasingly recognized. Seizures and status epilepticus (SE) are reported in the novel coronavirus disease (COVID-19), both new onset and worsening of existing epilepsy; however, the exact prevalence is still unknown. The primary aim of this study was to correlate the presence of seizures, status epilepticus, and specific critical care EEG patterns with patient functional outcomes in those with COVID-19.

Methods: This is a retrospective, multicenter cohort of COVID-19-positive patients in Southeast Michigan who underwent electroencephalography (EEG) from March 12th through May 15th, 2020. All patients had confirmed nasopharyngeal PCR for COVID-19. EEG patterns were characterized per 2012 ACNS critical care EEG terminology. Clinical and demographic variables were collected by medical chart review. Outcomes were divided into recovered, recovered with disability, or deceased.

Results: Out of the total of 4100 patients hospitalized with COVID-19, 110 patients (2.68%) had EEG during their hospitalization; 64% were male, 67% were African American with mean age of 63 years (range 20–87). The majority (70%) had severe COVID-19, were intubated, or had multi-organ failure. The median length of hospitalization was 26.5 days (IQR = 15 to 44 days). During hospitalization, of the patients who had EEG, 21.8% had new-onset seizure including 7% with status epilepticus, majority (87.5%) with no prior epilepsy. Forty-nine (45%) patients died in the hospital, 46 (42%) recovered but maintained a disability and 15 (14%) recovered without a disability. The EEG findings associated with outcomes were background slowing/attenuation (recovered 60% vs recovered/disabled 96% vs died 96%, $p < 0.001$) and normal (recovered 27% vs recovered/disabled 0% vs died 1%, $p < 0.001$). However, these findings were no longer significant after adjusting for severity of COVID-19.

Conclusion: In this large multicenter study from Southeast Michigan, one of the early COVID-19 epicenters in the US, none of the EEG findings were significantly correlated with outcomes in critically ill COVID-19 patients. Although seizures and status epilepticus could be encountered in COVID-19, the occurrence did not correlate with the patients' functional outcome.

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1. Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has multiple neurological manifestations. Many patients with

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COVID-19 are found to have encephalopathy either related to potential direct viral neuroinvasion or as a consequence of multi-organ dysfunction in the context of critical illness [1].

Over the past few decades, EEG is being utilized to a greater extent in comatose patients in intensive care units, although the effect of seizure recognition and treatment on the overall outcome is debated [2]. Seizures and status epilepticus (SE) have been reported with COVID-19, with new onset or exacerbation of existing epilepsy and the prevalence of seizures in patients with COVID-19 is still unknown. Multiple studies have recognized electroencephalography (EEG) changes in COVID-19, utilizing short- and long-term EEG recording, though no clear EEG pattern is reliably seen in this patient population [3]. Furthermore, the effects of seizures, clinical or subclinical (electrographic), on the functional outcome in critically ill patients with COVID-19 remain unclear.

During the COVID-19 pandemic, Detroit city and Southeast Michigan were among the early epicenters in the United States [4]. We initiated a collaboration of large medical centers and academic institutions in the region to better characterize EEG findings, assess the prevalence of seizures and status epilepticus in patients with COVID-19, and the functional outcomes grouped as recovered, recovered with disability, or deceased.

The primary aim of this study was to correlate the presence of seizures, status epilepticus, and specific critical care EEG patterns in hospitalized patients with COVID-19 who had EEG with their functional outcomes.

2. Materials and methods

This was a retrospective, multicenter cohort study conducted through Henry Ford Health System in Detroit, MI, USA, in collaboration with three other major hospital systems in southeast Michigan that include Beaumont Royal Oak Hospital, Detroit Medical Center, and Michigan Medicine. The study was approved by the institutional review board (IRB) of all the individual participating institutions.

2.1. Participants and EEG recording

A retrospective chart review was performed of all patients with COVID-19, confirmed by nasopharyngeal swab polymerase chain reaction (PCR) test, who underwent EEGs in southeast Michigan between March 12th and May 15th, 2020 (the first two months of the COVID-19 pandemic). EEGs were requested and performed for standard indications (e.g. suspicion for seizures or altered mental status). All patients had at least 21-channel EEG electrodes recording using the international modified 10–20 system. EEGs were performed for a short duration (routine for approximately 20–30 min) or were continuous long-term EEGs (>2 h). Patients with presumed COVID-19 who tested negative were excluded from the study. The patients were evaluated and managed at the four major hospital systems in southeast Michigan (Beaumont Royal Oak Hospital, Detroit Medical Center, Henry Ford Health System, and Michigan Medicine). Hospital admission and COVID-19 testing results data were used to estimate the total number of patients hospitalized during the study period.

2.2. EEG analysis

EEG studies were read by a clinical neurophysiology and/or epilepsy board certified neurologist at each institution and classified according to the American Clinical Neurophysiology Society (ACNS) continuous EEG terminology [5]. The EEG reports were reviewed to abstract study data and, if necessary, the EEG tracings were reviewed to confirm the reported findings. The EEG findings

were categorized into general background pattern, epileptiform discharges, rhythmic and periodic patterns, and clinical seizures and subclinical seizures, according to the Salzburg criteria [6].

2.3. Patient variables and outcomes

Patient medical records were reviewed and data were abstracted regarding demographic information (age, sex, and race), severity of COVID-19 illness (mild/moderate/severe, defined by the diagnostic criteria used per infectious disease teams: mild was only upper respiratory symptoms and/or low grade fever; moderate was with tachypnea > 22 breaths per minute, need for nasal oxygen, high grade fever and leukocytosis; and severe was with endotracheal intubation and/or multi-organ failure), lowest level of consciousness during EEG recording, presence of metabolic disturbances, risk factors for seizures including COVID-19 meningitis or encephalitis, stroke in COVID-19, history of epilepsy and pre-hospitalization seizure control, neuroimaging findings (none, acute, or chronic abnormalities) and location of imaging abnormalities (cortical, white matter, basal ganglia, thalamus, cerebellum, or extra-axial), presence and duration of seizures and status epilepticus, anti-seizure medications (ASMs), indication for EEG, recorded clinical events during EEG, length of stay in the hospital, and length of stay in the intensive care unit (ICU).

The patients were followed up until discharge or August 3rd, 2020 and assessed by the Glasgow Outcome Scale (GOS) [7] at discharge. In addition, the disposition (recovery and discharged home, or disabled and discharged to rehabilitation facility) was collected for all patients. Patients were divided into three recovery outcome groups (recovered, recovered with disability, and deceased). For the four patients still hospitalized, the GOS (3 severely disabled and 1 moderately disabled) on the last follow-up day for the study were all classified in the recovered with disability group.

2.4. Statistical analysis

Descriptive statistics were employed to characterize patient demographics, neuroimaging, EEG findings, and functional outcome information. These statistics included number and percentages for the categorical variables, mean and standard deviation for age and median in interquartile ranges (IQR) for the length of stay variables. For the patients with multiple EEGs performed during their hospitalization, an indication, finding, pattern, or clinical seizure was coded "yes" for that individual patient if they were observed on any EEG. To assess the association between the patient characteristics and functional outcomes, Fisher's exact tests were performed for the categorical variables and Wilcoxon two sample tests were performed for age and the length of stay variables. Logistic regression analyses were used to assess the association between EEG findings and functional outcome, adjusted for severity of COVID-19 disease. Significance was set at p -value = 0.05. The analysis was performed with SAS version 9.4.

3. Results

3.1. Patient characteristics

Of the 110 patients with COVID-19 who had EEG, 70 (64%) were male. The mean age was 63 years with a range from 20 to 87 years. The majority of patients were African American ($n = 74$ (67%)) and 27 (25%) were Caucasian. The majority ($n = 77$ (70%)) had severe COVID-19, of which 43 (56%) were in a coma. Almost all the patients (102 of 110, 93%) had acute metabolic abnormalities. The median length of stay in the ICU was 13.5 days (IQR = 3 to 27 days), on a non-ICU floor was 7.5 days (IQR = 2 to 20 days)

and total hospitalization was 26.5 days (IQR = 15 to 44 days), (Table 1).

Twenty-five (23%) patients had a prior history of epilepsy, of which seizures in 21 were controlled and 4 had drug-resistant epilepsy. During hospitalization, 24 (21.8%) of all COVID-19 patients who underwent EEG had clinical seizures, (21 were new-onset seizure and 3 in patients had established epilepsy) and 8 (7%) had new-onset status epilepticus. Two out of the three (66.6%) patients with established epilepsy had status epilepticus. Patients with seizures had a shorter total median length of stay (17.5 days) compared to patients without seizures (29.5 days) ($p = 0.005$).

3.2. Functional outcome

Fifteen patients (14%) recovered without a disability, 46 (42%) recovered with disability, and 49 (45%) patients died in the hospital (Table 1). Recovery was associated with age, with recovered having a lower mean age than patients who died (56.7 vs. 66.1 years; $p = 0.03$). Recovery had a negative correlation with both severity of COVID-19 disease ($p < 0.001$) and level of consciousness ($p < 0.001$). Recovered patients had shorter length of stays in the ICU ($p = 0.002$) and total length of stays ($p = 0.003$) when compared to patients who recovered with disability and patients who died (Table 1).

3.3. EEG and EEG findings

Of the 110 patients with COVID-19, there were 14 patients who had more than one EEG done during their hospitalization (13 with 2 EEGs and 1 with 3 EEGs). For the 125 EEGs performed, the median day on which the EEG was started was day 9 (IQR = 3 to 17.5 days) with a total range from day 0 to day 58 of the hospitalization. There were 48 (38%) short-term EEGs performed with a median duration of 23 min (IQR = 21 to 30 min) and 77 (62%) were long-term EEG with a median duration of 24.7 h (IQR = 20 to 45.2 h). Out of 110 patients, 61 (55%) had at least one EEG for altered mental status and 51 (46%) for witnessed or suspected seizure.

Table 1
Patients and hospital information.

Variable	Response	All Patients (N = 110)	Recovered (N = 15)	Recovered/Disabled (N = 46)	Death (N = 49)	p-value
Age	N	110	15	46	49	0.030
	Mean (SD)	63.0 (12.8)	56.7 (12.9)	61.7 (14.3)	66.1 (10.5)	
	Min, Max	20, 87	25, 73	20, 84	35, 87	
Severity of the COVID-19 illness	Mild	7 (6%)	4 (27%)	2 (4%)	1 (2%)	<0.001
	Moderate	26 (24%)	9 (60%)	15 (33%)	2 (4%)	
	Severe	77 (70%)	2 (13%)	29 (63%)	46 (94%)	
Level of consciousness	Coma	43 (39%)	0 (0%)	17 (37%)	26 (53%)	<0.001
	Stupor	21 (19%)	1 (7%)	11 (24%)	9 (18%)	
	Lethargy/confusion	30 (27%)	9 (60%)	13 (28%)	8 (16%)	
	Awake	16 (15%)	5 (33%)	5 (11%)	6 (12%)	
Prior history of epilepsy	No	85 (77%)	12 (80%)	31 (67%)	42 (86%)	0.285
	Yes, controlled	21 (19%)	3 (20%)	12 (26%)	6 (12%)	
	Yes, intractable	4 (4%)	0 (0%)	3 (7%)	1 (2%)	
Seizure with COVID-19	Yes	24 (22%)	4 (27%)	6 (13%)	14 (29%)	0.115
	No	86 (78%)	11 (73%)	40 (87%)	35 (71%)	
Presence of status epilepticus	Yes	8 (7%)	1 (7%)	2 (4%)	5 (10%)	0.687
	No	102 (93%)	14 (93%)	44 (96%)	44 (90%)	
ICU length of stay, days	N	110	15	46	49	0.002
	Median	13.5	0	16.5	16	
	IQR	3, 27	0, 13	2, 20	8, 30	
Total length of stay, days	N	110	15	46	49	0.003
	Median	26.5	14	30	25	
	IQR	15, 44	10, 25	22, 45	14, 51	

Abbreviations: N: number, IQR: interquartile range, SD: Standard deviation, BMNT: Beaumont Hospital, HF: Henry Ford Hospital, UM: Michigan Medicine, WSU: Wayne State University/Detroit Medical Center Hospital.

Almost all of the EEGs (91%) had background slowing/attenuation on EEG, 30 (27%) had focal slowing/attenuation, 26 (24%) had rhythmic and periodic discharges, and 15 (14%) had sporadic epileptiform discharges. For the rhythmic or periodic patterns, 23 (21%) of the patients had generalized periodic discharges with triphasic morphology per ACNS guideline (or triphasic waves), 20 (18%) had generalized rhythmic delta activity (GRDA), and 10 (9%) had GPDs. Only 6 (5%) patients had lateralized periodic discharges (LPDs), 1 (1%) patient had bilateral-independent periodic discharges (BIPDs), and another one (1%) had lateralized rhythmic delta activity (LRDA).

During EEG recording, five patients had focal-onset clinical seizures, 5 patients had generalized clinical seizures, and 3 had electrographic-only seizures. Only 7 patients had recorded events with no EEG changes (Table 2).

The EEG findings associated with the recovery were background slowing/attenuation (recovered 60% vs recovered with disability 96% vs died 96%, $p < 0.001$) and normal background (recovered 27% vs recovered with disability 0% vs died 1%, $p < 0.001$) (Table 2). However, these differences were no longer significant after adjusting for severity of COVID-19 disease ($p = 0.119$).

3.4. Brain imaging findings

Not all the patients with COVID-19 had brain imaging studies performed during the initial surge of pandemic. Of the 110 patients, 67 patients underwent brain imaging (Head CT scan or brain MRI) which included 7 patients with new-onset seizures and 7 patients with status epilepticus. A total of 23 patients (34%) had acute changes and 25 (37%) had remote imaging abnormalities; while 29 (43%) had cortical and the remaining had subcortical abnormalities that included changes in the white matter and subcortical structures. Of the patients with new-onset seizures, 5 had acute changes and 4 had some cortical involvement. In addition, in those with status epilepticus, 6 showed acute changes and 5 had cortical involvement. Given the limited imaging data in our patient cohort, further correlation of findings was beyond the scope of this study.

Table 2
Comparing EEG findings.

Variable	Response	All patients (N = 110)	Recovered (N = 15)	Recovered/Disabled (N = 46)	Death (N = 49)	p-value
Findings of EEG	Focal seizure	7 (6%)	0 (0%)	5 (11%)	2 (4%)	0.294
	Generalized seizure	4 (4%)	0 (0%)	0 (0%)	4 (8%)	0.112
	Convulsive status epilepticus	1 (1%)	0 (0%)	0 (0%)	1 (2%)	NA
	Non-convulsive status epilepticus	4 (4%)	0 (0%)	2 (4%)	2 (4%)	>0.99
	Sporadic epileptiform discharges	15 (14%)	2 (13%)	5 (11%)	8 (16%)	0.802
	Rhythmic and periodic discharges	26 (24%)	4 (27%)	13 (28%)	9 (18%)	0.453
	Background slowing/attenuation	100 (91%)	9 (60%)	44 (96%)	47 (96%)	<0.001
	Normal	5 (5%)	4 (27%)	0 (0%)	1 (2%)	<0.001
Rhythmic or periodic patterns	None	64 (58%)	9 (60%)	28 (61%)	27 (55%)	0.865
	LPD	6 (5%)	1 (7%)	3 (7%)	2 (4%)	0.735
	GPD	10 (9%)	0 (0%)	3 (7%)	7 (14%)	0.217
	BIPD	1 (1%)	0 (0%)	1 (2%)	0 (0%)	NA
	LRDA	1 (1%)	1 (7%)	0 (0%)	0 (0%)	NA
	GRDA	20 (18%)	3 (20%)	8 (17%)	9 (18%)	>0.99
	Plus Modifier	8 (7%)	0 (0%)	4 (9%)	4 (8%)	0.772
	Triphasic waves	23 (21%)	1 (7%)	12 (26%)	10 (20%)	0.306
Clinical seizures ²	No seizures	98 (89%)	13 (87%)	43 (93%)	42 (86%)	0.488
	Focal clinical	5 (5%)	1 (7%)	3 (7%)	1 (2%)	0.445
	Generalized clinical	5 (5%)	1 (7%)	0 (0%)	4 (8%)	0.119
	Subclinical/electrographic	3 (3%)	0 (0%)	1 (2%)	2 (4%)	>0.99
Recorded events with no EEG changes		7 (6%)	0 (0%)	2 (4%)	5 (10%)	0.415

¹3 patients had both altered state and witnessed seizure.²1 patient had focal clinical seizure on first EEG, but no clinical seizure on second EEG.

4. Discussion

In this large multicenter cohort study, we report outcomes of EEG findings in 110 patients with COVID-19 in Southeast Michigan, who underwent full montage EEG recording (standard 21-channel) during their hospitalization. Most patients (70%) had severe COVID-19, and 43% of patients were comatose.

We found that of all the established EEG findings, having a normal EEG background was associated with recovery and good outcome except one patient, an 83-year-old man who had a normal EEG on day 12 of admission and had progression of pneumonia leading to respiratory failure, followed by hospice care and died on day 29 of admission. Background slowing and attenuation were associated with poor outcomes (disability and death). However, these associations were no longer significant after taking into account the severity of COVID-19.

Given the small number of patients with normal EEG findings, it was difficult to separate the effects of the EEG findings and severity of COVID-19 disease on the recovery outcomes. Of the 4 patients who had normal EEG findings and recovered, 3 had mild and 1 had moderate COVID-19. The one patient who had a normal EEG finding and died, had moderate COVID-19.

A prior systematic review of 177 patients reported that EEG findings are nonspecific in COVID-19, with a majority (63.8%) of the cases having generalized slowing, 3.5% with normal EEG, and 19.2% with epileptiform activity [3]. Status epilepticus was reported in 4.5% of the patients [3], comparable to 5% of patients in our study (4% nonconvulsive, 1% convulsive). Compared to a cohort study from New York City, our cohort exhibited similar rates of clinical seizures at 10% (12/110) of the patients which is comparable to that study of clinical seizures in 7% of the patients [8]. Furthermore, in those who had reported seizures in our cohort, 87.5% (21/24) had no prior history of epilepsy and 12.5% (3/24) had history of epilepsy that was under good control. This is in contrast to the New York cohort, in which seizures were reported to be rare in the absence of a pre-existing epilepsy diagnosis [8]. It remains to

be seen if these new-onset seizures in those without prior history of epilepsy, would eventually lead to a diagnosis of epilepsy.

In 7% of the clinical events reported as seizures by the treating team during EEG recording, there was no epileptiform EEG correlate. Thus, one should consider other possibilities or paroxysmal events in critically ill patients in the ICU in addition to seizures. Benbadis et al. [9] previously demonstrated that 73% of paroxysmal motor events captured on EEG in critically ill patients were nonepileptic in nature. These include tremor-like movements, semi-purposeful movements, nonepileptic myoclonus, transient eye, mouth and head movements as well as psychogenic nonepileptic seizures.

There have been conflicting data on the incidence of electrographic seizures in patients with COVID-19. No electrographic seizures were reported in three case series including 22, 36, and 10 patients with COVID-19 infection undergoing EEG monitoring from New York, France, and United Kingdom, respectively [10–12]. One limitation of the first study is the reliance on limited 8-channel montage, which may miss seizures. No clinical seizures were observed in a large series from China including 304 patients with COVID-19 infection; however, EEG was not obtained in any of these patients [13]. On the other hand, the last series reported the occurrence of electrographic seizures in 7–25% of monitored patients [8,14–16] consistent with the findings in our cohort (electrographic seizures in 11% of patients and SE in 7% of patients). These rates also match the reported rates of electrographic seizures in the setting of sepsis due to various etiologies which range from 11–17% [17,18]. There is no evidence so far indicating any greater increase in electrographic seizures specifically with COVID-19 infection.

Similar to previous series, background slowing or attenuation was the most common EEG finding in our cohort, noted in 91% of patients. This was followed by focal slowing or attenuation, observed in 27% of patients. These findings align with previously reported findings from multiple case series [2,8,10–12,14–16]. Multiple etiologies can cause diffuse EEG slowing including hypox-

ia, toxic, metabolic and medication effect such as from anesthetics. Both GPDs with triphasic morphology and GRDA, seen in 21% and 18% of our cohort, respectively, are patterns most commonly seen in the setting of metabolic encephalopathy, though there have been few reports of association between triphasic wave pattern and nonconvulsive status epilepticus [19–24]. Meanwhile, sporadic interictal epileptiform discharges were noted in 14% of patients, which is largely in concordance with most reported rates in COVID-19 patients, apart from Galanopoulou et al.'s [10] report of occurrence of epileptiform discharges in 40.6% of patients. However, one major limitation of that study is the reliance on limited channel EEG recordings in the majority of patients. Most of the recorded discharges in their study were bilateral symmetric frontal discharges (which may be confused with eye movement artifacts on limited channel recordings), and no seizures were recorded in any of their patients despite the frequent occurrence of epileptiform discharges [25].

During the time of the study, there were 57,000 reported patients with COVID-19 in the state of Michigan, and a total of 4100 were hospitalized in the four major hospitals participating in the study, with up to 23% on mechanical ventilation and in-hospital mortality rate of up to 18%. Of them, 110 patients (2.68%) had EEG which represents the described findings of EEG and seizures as rare, presenting in a small minority of all the COVID-19 patients.

Limitations of the study include the retrospective nature, and a limited number of COVID-19 patients having seizures recorded on EEG could result in type II errors when finding no correlations between the presence of seizures and outcomes. We understand that the delay to obtaining EEG could have missed seizures occurring early in the course of the illness (median time from hospitalization to EEG was 9 days); however, EEGs were triaged and prioritized. A very small number of patients admitted with COVID-19 had EEG which makes the result limited in terms of ability to generalize to all patients with COVID-19. Short-term EEGs, obtained in 38% of patients, can miss up to 50% of seizures, particularly in comatose patients, those with a prior history of seizures, and those with epileptiform discharges on EEG [26–28]. In addition, multiple factors determine patient outcomes during long hospitalization; EEG provides a single time point. Finally, follow-up data after discharge were not available, so long-term seizure and functional outcomes could not be assessed. There has been so far only one published case report of the development of status epilepticus after recovery from COVID-19 infection [29]; so a prolonged follow-up will help better the long-term neurological complications of COVID-19.

5. Conclusion

Our study corroborates that there were no statistically significant EEG findings that correlated with functional outcomes in critically ill COVID-19 patients, after adjusting for severity of COVID-19 disease. Although seizures and status epilepticus could be encountered in COVID-19, the occurrence did not correlate with the patient outcome. While the COVID-19 pandemic continues, multicenter, prospective studies could help improve the understanding of acute seizures and status epilepticus in people with COVID-19, and further aid in better management of seizure and long-term functional outcomes.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

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Declarations of interest

None of the authors has any conflict of interest to disclose.

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