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Seizures in COVID-19: the relationship between biomarkers and prognosis

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Abstract

Objective To assess the prevalence of seizure, associated risk factors, and prognosis in patients with SARS-CoV-2 infection and identify predictive biomarkers in SARS-CoV-2 patients with seizure.

Methods A cohort of 17,806 patients with SARS-CoV-2 infection admitted to two university hospitals in Adana between March 11, 2020 and January 1, 2021 was analyzed retrospectively. The patients' demographic characteristics, laboratory findings, and systemic and neurological symptoms at admission and on the day of seizure onset were evaluated.

Results Neurological findings were detected in 877 of the 17,806 patients. Of these, 45 patients (0.25%) had seizure (status epilepticus in 4/45 patients, 8.9%). Patients with seizure had a mean age of 55.3 years (range 17–88) and 57.8% were male. Seizure was more common in the 18–44 (24.4%) and ≥ 65 age groups (44.4%) and in those with multiple comorbidity. The case fatality rate for patients with seizure among all SARS-CoV-2 patients was 0.135% (95% CI 80.86–188.71). However, no patient with a previous diagnosis of epilepsy died during SARS-CoV-2 infection. High neutrophil, platelet, and ferritin levels and low lymphocyte and calcium levels on the day of seizure development compared to admission were associated with higher mortality ($p = 0.004$, 0.008, 0.028, 0003, and 0.002, respectively).

Conclusions Seizures are not uncommon during SARS-CoV-2 infection, with a higher risk of mortality in older patients and those with higher inflammatory markers.

Keywords Coronavirus · Seizure · Mortality

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, Hubei Province, China, and in January 2020, the World Health Organization reported that the causal agent had been identified as a novel coronavirus, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Although new variants of SARS-CoV-2 have since appeared, the main symptoms of infection are still fever, headache, dry cough, loss of appetite, and loss of smell or taste. Evidence indicates that SARS-CoV-2 can cause damage to certain organs, such as the respiratory system, kidneys, liver, and heart and can also involve the central nervous system via neurotropic and neuroinvasive spread [3–6]. Neurological findings such as febrile or afebrile convulsions, altered mental status, encephalomyelitis, and encephalitis may be associated with SARS-CoV-2 infection [5, 7]. The reported mortality rate in SARS-CoV-2 infection is 1.79% [8]. However, there is a lack of clear information regarding the prognosis and mortality rates in patients who have seizures during the infection.

The first reported case of seizure during SARS-CoV-2 infection was documented by Moriguchi et al., and the International League Against Epilepsy (ILAE) stated in a summary of three published case reports that information about the risk of new-onset seizures related to SARS-CoV-2 was limited [9, 10]. The literature also includes reports of new-onset focal onset seizures, cluster seizures, and cases of status epilepticus (SE) [11–22]. According to retrospective case series studies conducted in two centers in the United

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States, the prevalence of seizures in patients with SARS-CoV-2 infection and neurological signs was 26% and 27.2% [23, 24]. However, these studies were limited to only the small samples of SARS-CoV-2-infected patients with neurological findings and lacked long-term follow-up and outcome data. In another study examining a hospital database of 40,469 patients with SARS-CoV-2 infection, the frequency of seizure was determined to be 0.6%, but patient-level data could not be analyzed [25]. This made it difficult to establish a strong causal relationship between the neurological symptoms described and SARS-CoV-2 infection. Thus, information about SARS-CoV-2 infection-related seizure consists of isolated cases or case series; to date, no study has been conducted to demonstrate the relationship between seizure risk factors, prognosis, and etiology in patients with SARS-CoV-2 infection.

In this study, we aimed to investigate the incidence, etiologies, risk factors, and prognosis of seizure in patients under treatment for SARS-CoV-2 infection.

Methods

Study population

This study was a retrospective, hospital-based study conducted with patients admitted for SARS-CoV-2 infection to the Health Sciences University Adana Faculty of Medicine City Hospital and Çukurova University Faculty of Medicine Hospital. The study was approved in advance by the Medical Research Ethics Committee of Çukurova University (No: 109/24 and 2021–03-05) and the Turkish Ministry of Health (2021-02-01T13-03-22).

Inclusion criteria are cases where the diagnosis of Covid-19 was confirmed by PCR (polymerase chain reaction) and Co-RADS (Covid-19 Reporting and Data System) methods according to the SARS-CoV-2 diagnosis and treatment guide of the Ministry of Health and seizures developed while being followed up in the hospital with this diagnosis, cases that did not meet these criteria or had missing laboratory and examination parameters during follow-up were excluded.

Patients who were hospitalized in these two university hospitals between March 11, 2020 (when the first COVID-19 case in Turkey was reported) and January 31, 2021 were included. During this time, a total of 17,806 patients were hospitalized with a definitive or presumed diagnosis of SARS-CoV-2 infection according to the Turkish Ministry of Health COVID-19 diagnostic guidelines; neurology consultation was requested for 877 of those patients because of acute neurological findings, and 45 of the patients had one or more seizures during follow-up. Acute epilepsy was defined and managed in accordance with the practical clinical definition from the ILAE [26, 27].

Data collection

Detailed clinical data from the 45 patients with SARS-CoV-2 and seizure were gathered from the patients' records, charts, and discharge summaries. Demographic information, medical history (preexisting comorbidities, stroke, epilepsy, etc.), neurological examination findings, treatment protocols (antiepileptic, hypnosedative drugs, etc.), and outcome (discharge or death) were obtained from the electronic medical records system.

Laboratory tests including complete blood cell count (CBC) with differential, liver and renal function assessment, C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), procalcitonin (PCT), pro-beta natriuretic peptide (pro-BNP), partial pressure of carbon dioxide (PCO_2), electrolyte, and glucose levels were reviewed. Laboratory findings on the first day of hospitalization and on the day of seizure onset were recorded.

In addition, the patients' major systemic conditions, neurological examination findings, and cerebral imaging results on the day of hospital admission and the day of seizure onset were also recorded and reviewed. Parameters were compared between surviving and non-surviving patients.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation or median and minimum–maximum as appropriate. Chi-square test was used to compare categorical variables between the groups. Mann–Whitney U test was used for comparisons of continuous variables between two groups, and Wilcoxon signed-rank test was used for comparisons of paired continuous variables. All analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY) statistical software package. An alpha level of 0.05 was used to determine statistical significance in all tests.

Results

General characteristics of the patients

Of the 17,806 patients diagnosed as having SARS-CoV-2 infection during the study period, 877 (4.9%) required neurology consultation and 45 (0.25%) had one or more seizures. Patients with seizure accounted for 5.13% of all SARS-CoV-2 patients with neurological symptoms, their mean age was 55.3 ± 20.1 (17–88) years, and 57.8% ($n = 26$) were male. The mean time of seizure onset was 9 (1–101)

days after admission, and the mean length of hospital stay was 23.2 (2–124) days. In terms of age distribution, 31.1% of patients with seizures during SARS-CoV-2 infection were in the 18–44 age group, 24.4% were in the 45–64 age group, and 44.4% were in the ≥ 65 age group. Six patients (13.3%) had at least one vascular risk factor such as hypertension (HT) and cerebrovascular disease (CVD), 22 (48.9%) had multiple comorbidities (at least 2 conditions such as diabetes mellitus, HT, coronary artery disease, chronic obstructive pulmonary disease, asthma, and chronic kidney disease), and 7 (15.6%) had a history of epilepsy (5 with sequelae of cerebral palsy) (Table 1).

According to the Turkish Ministry of Health COVID-19 diagnosis and treatment guide, SARS-CoV-2 diagnosis was based on positive PCR test in 44.4% ($n = 20$) of the patients, while 46.7% ($n = 21$) of the patients had negative PCR but were CO-RADS category ≥ 4 on chest computed tomography (CT) examination, and 8.9% ($n = 4$) did not undergo a PCR test but were evaluated as CO-RADS ≥ 4. Nearly all of the patients (97.8%, $n = 44$) had ground-glass densities on chest CT on the day of admission. Only one patient had no signs of pneumonia on chest CT but was PCR-positive.

Respiratory distress (46.7%, $n = 21$) and impaired consciousness (20%, $n = 9$) were the most common examination findings (Table 1). On the first day of hospitalization, 60% ($n = 27$) of the patients underwent neuroimaging (cerebral CT and/or cerebral diffusion magnetic resonance imaging) and cerebral lesions were detected in 33.3% ($n = 15$). These included chronic periventricular ischemia in 17.8% ($n = 8$), acute ischemia in 4.4% ($n = 2$), hydrocephalus in 2.2% ($n = 1$), intracranial tumor in 4.4% ($n = 2$), intracerebral hemorrhage in 2.2% ($n = 1$), and leptomeningeal involvement in 2.2% ($n = 1$). Neuroimaging was normal in the other patients (26.7%, $n = 12$).

Seizure-related findings

Seizure occurred on the first day of hospitalization in 51% ($n = 23$), between 2 and 7 days in 24.4% ($n = 11$), and after day 7 in 24.4% ($n = 11$) of the patients. Of the 45 patients with seizure, 68.9% ($n = 31$) had impaired consciousness and 6.7% ($n = 3$) had lateralizing signs such as right or left hemiparesis, while neurological examination was within normal limits in 24.4% ($n = 11$) of the patients. In 97.8% ($n = 44$) of the patients, chest CT obtained on the day of seizure did not differ from imaging obtained on the day of admission and showed ground-glass densities consistent with SARS-CoV-2 infection.

The timing of seizure onset, associated neurological examination and neuroimaging findings, and outcomes of SARS-CoV-2 patients with seizure are summarized in Table 2. Seizures occurred within the first 2 days in 57.8% of patients ($n = 26$), and these patients were mostly in the

Table 1 Demographic characteristics and systemic and neurological findings on the day of admission in COVID-19 patients with seizure ($N = 45$)

	n	%
Age (years)		
18–44	14	31.1
45–64	11	24.4
≥ 65	20	44.4
Gender		
Male	26	57.8
Female	19	42.2
PCR/CO-RADS classification of confirmed/presumed positive cases		
PCR-negative, CO-RADS ≥ 4	21	46.7
PCR-positive	20	44.4
CO-RADS ≥ 4, PCR not performed	4	8.9
Clinical history		
No comorbidity	4	8.9
CVD ($n = 1$) + HT ($n = 5$)	6	13.3
ASHD/arrhythmia/bypass/etc	2	4.4
Malignancy	3	6.7
Multiple comorbidities	22	48.9
Epilepsy	7	15.6
Systemic lupus erythematosus	1	2.2
Leading clinical finding		
Respiratory distress	21	46.7
Neurological examination findings at admission		
Normal	8	17.8
Impaired consciousness	9	20
Lateralizing signs (right/left hemiparesis)	2	4.4
Cognitive impairment	5	11.1
Cerebral imaging findings at admission		
Imaging not performed	18	40.0
Normal	12	26.7
Chronic periventricular ischemia and atrophy	8	17.8
Acute ischemia	2	4.4
Intracranial hemorrhage	1	2.2
Hydrocephaly	1	2.2
Space-occupying lesion	2	4.4
Leptomeningeal involvement	1	2.2

PCR polymerase chain reaction, *CO-RADS* COVID-19 reporting and data system, *CVD* cerebrovascular disease, *HT* hypertension, *ASHD* atherosclerotic heart disease

18–44 (78.6%; $n = 11$) and ≥ 65 (55%; $n = 11$) age groups. Seizures among patients in the 45–64 age group (63.6%; $n = 7$) most frequently occurred on day 3 or later. Seizures were more frequent in male patients (53.8%; $n = 14$) in the first 2 days. The frequency of seizure were higher in patients with multiple comorbidity both in the first 2 days (53.1%; $n = 17$) and on day 3 (46%; $n = 15$).

Table 2 Seizure-related data and outcomes of COVID-19 patients with seizure (N=45)

	n	%
Time of seizure onset		
Day 1	23	51.1
Day 2–7	11	24.4
After day 7	11	24.4
Summary neurological status on day of seizure onset		
Impaired consciousness	31	68.9
Right/Left Hemiparesis	3	6.7
Normal	11	24.4
Cerebral imaging findings on day of seizure onset		
Imaging not performed	11	24.4
Normal	15	33.3
Cerebral edema	1	2.2
Ischemic stroke	3	6.7
Intracranial hemorrhage	2	4.4
Space-occupying lesion	2	4.4
Chronic ischemia	11	24.4
Follow-up time (length of hospital stay)		
1–7 days	12	26.7
8–21 days	16	35.6
≥ 22 days	17	37.8
Outcome		
Death	24	53.3
Discharge	21	46.7

Compared to imaging at admission, neuroimaging on the day of seizure (76%; n=34) revealed signs of cerebral involvement in 42% of the patients (n=19; admitting findings plus acute ischemia in one patient and intracranial hemorrhage in one patient). Cerebral imaging could not be performed in 24% of the patients (n=11) because they were connected to mechanical ventilation in the intensive care unit.

A single seizure was observed in 6.7% (n=3) of the patients, while 93.3% (n=42) of the patients had two or more seizures within 24 h (SE in 8.9%, n=4). Medical treatment was administered according to the ILAE recommendations for first seizure management (Epilepsy Foundation, 2015) [27].

Prognostic factors of the patients

After treatment, 53.3% (n=24) of the patients died, while 46.7% (n=21) of the patients recovered and were discharged (Table 2). All patients with a previous diagnosis of epilepsy survived to discharge.

Some hemogram and biochemical parameters on the day of admission and the day of seizure onset were found to be associated with prognosis in patients who developed seizure during SARS-CoV-2 infection. At admission, non-surviving patients had lower creatinine levels and higher blood glucose, BUN, fibrinogen, CRP, pro-BNP, and PCT levels compared to surviving patients ($p < 0.05$, Table 3).

On the day of seizure onset, nonsurviving patients had lower lymphocyte and calcium levels and higher white blood cell (WBC), neutrophil, glucose, LDH, aspartate aminotransferase (AST), BUN, ferritin, creatinine, CRP, pro-BNP, D-dimer, and PCT levels compared to surviving patients ($p < 0.05$, Table 4).

Platelet, magnesium, alanine aminotransferase (ALT), and pCO_2 values did not differ significantly between the groups.

The patients' neutrophil, platelet, and ferritin values were significantly higher while lymphocyte and calcium values were significantly lower on the day of seizure onset

Table 3 Laboratory findings on the day of admission in COVID-19 patients with seizure (N=45)

Parameter (normal range)	Outcome				p	Total	
	Death		Discharge				
	Mean ± SD	Median	Mean ± SD	Median		Mean ± SD	Median (Min–Max)
Glucose (74–106 mg/dL)	190.7 ± 116.1	144.5	129.1 ± 51.1	117.0	0.048	162 ± 95.9	125 (76–480)
BUN (17–43 mg/dL)	68.9 ± 47.6	61.5	29.5 ± 22.4	23.0	0.000	50.5 ± 42.5	38 (5.7–223)
Ferritin (23.5–336 g/L)	959.7 ± 2444.4	303.2	182.6 ± 204.3	105.0	0.018	597 ± 1815.5	198.1 (8.2–11,997)
Creatinine (0.67–1.17 mg/dL)	2 ± 3.7	1.0	3.6 ± 13.2	0.6	0.006	2.8 ± 9.3	0.8 (0.3–61)
Fibrinogen (180–350 mg/dL)	546.6 ± 222.9	527.3	403.7 ± 162.9	393.3	0.029	481.6 ± 208.5	467.3 (116–900)
CRP (0–5 mg/dL)	149.5 ± 126.4	123.0	43.1 ± 50.8	19.0	0.000	99.8 ± 111.4	62.8 (3.7–478)
Pro-BNP (0–133 g/L)	4486.3 ± 8616.1	2190.0	2461.3 ± 7119.1	198.0	0.007	3586.3 ± 7903.6	1120 (70–35,000)
Procalcitonin (0–0.65 µg/L)	3.5 ± 12.2	0.3	0.4 ± 1.2	0.1	0.006	2.1 ± 9	0.1 (0–60)

BUN blood urea nitrogen, *CRP* C-reactive protein, *Pro-BNP* pro-b type natriuretic peptide, *Mean ± SD* mean ± standard deviation

$p < 0.05$

Table 4 The patients' laboratory findings on the day of seizure onset

Parameter (normal range)	Outcome					Total	
	Death		Discharge				
	Mean ± SD	Median	Mean ± SD	Median	p	Mean ± SD	Median (Min–Max)
WBC (3.6–10.2×10^4/L)	12 ± 4.4	11.7	9.4 ± 4.9	7.7	0.026	10.8 ± 4.8	10.6 (1–21.8)
Neutrophils (43.5–73.5%)	87.3 ± 9.2	90.3	70.2 ± 17.7	75.8	0.000	79.3 ± 16.2	84.5 (32.4–97.1)
Lymphocytes (15.3–43.3%)	7 ± 7.2	4.6	19 ± 15.3	11.4	0.000	12.6 ± 13	9.6 (0.9–57.8)
Glucose (74–106 mg/dL)	209.9 ± 113.5	177.5	131 ± 52	120.0	0.008	173.1 ± 97.7	131 (76–480)
Calcium (8.8–10.6 mg/dL)	8 ± 1	7.9	8.7 ± 0.6	8.9	0.003	8.3 ± 0.9	8.4 (6.3–10.7)
LDH (5–248 U/L)	698 ± 568.7	541.5	315.9 ± 164.1	254.0	0.001	519.7 ± 467.4	399 (20–2833)
AST (5–50 U/L)	137.2 ± 387	39.0	33.6 ± 21.5	24.0	0.017	88.8 ± 285	33 (10–1938)
BUN (17–43 mg/dL)	91.1 ± 74.8	66.0	27.5 ± 21	21.0	0.000	61.4 ± 64.4	39 (5.7–259)
Ferritin (23.5–336 g/L)	1714.5 ± 2637.7	741.2	205 ± 232.2	105.0	0.000	1010 ± 2059.4	290 (8.2–11,299)
Creatinine (0.67–1.17 mg/dL)	2.2 ± 3.7	1.0	0.8 ± 0.6	0.6	0.019	1.5 ± 2.8	0.7 (0.3–18.4)
CRP (0–5 mg/dL)	111.9 ± 80.2	89.7	47.7 ± 55	20.6	0.001	82 ± 76.1	61 (3.7–344)
Pro-BNP (0–133 g/L)	$5323.9 \pm 11,163.1$	1800.0	663.7 ± 1261.1	155.0	0.009	2993.8 ± 8070.9	828.5 (70–#####)
D-dimer (90–500 g/L)	5547.4 ± 7994.3	1900.0	1407.3 ± 2447.1	595.0	0.004	3718.1 ± 6472.4	1260 (0.2–#####)
Procalcitonin (0–0.65 µg/L)	3.2 ± 5.6	1.1	0.4 ± 1.2	0.1	0.000	1.9 ± 4.3	0.3 (0–19.7)

WBC white blood cells, *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *Pro-BNP* Pro-b type natriuretic peptide, *Mean ± SD* mean ± standard deviation

$p < 0.05$

compared to admitting values ($p = 0.004$, 0.008, 0.028, 0003, and 0.002, respectively).

The non-surviving patients' mean age was 59.2 (20–76) years and the mean length of hospital stay was 32.3 (5–124) days. Cerebral lesions were detected on imaging in 50% ($n = 12$) of non-surviving patients, while the most common metabolic problems were hypoxia (41.7%, $n = 10$) and hypocalcemia (37.5%, $n = 9$) (Table 5).

Discussion

In this study, seizures were observed in 0.25% ($n = 45$) of 17,806 patients treated for SARS-CoV-2 infection. Most of these patients (93%, $n = 42$) had multiple seizures, 7% ($n = 3$) had a single seizure, and the prevalence of SE was 8.9% ($n = 4$). Only 17.8% ($n = 8$) of the patients had a previous diagnosis of epilepsy, while 82.2% ($n = 37$) had seizures for the first time.

Since the start of the COVID-19 pandemic, different results have been reported regarding the prevalence and outcomes of seizure in SARS-CoV-2. The frequency of seizure was reported by Emami et al. as 0.08% in 6147 patients, by Nalleballe et al. as 0.6% in 40,469 patients in a hospital database, and by Usta as 0.57% in 5430 patients [8, 25, 28]. In our study, we determined the prevalence of seizures to be 0.25% among all patients diagnosed with SARS-CoV-2 infection. Among the 4.9% ($n = 877$) of SARS-CoV-2 patients who had neurological findings during follow-up,

the prevalence of seizure was 5.1% (45/877). The varying rates in the literature appear to be associated with the patient population studied; our observation is that the frequency of seizure development is not low among patients who are diagnosed as having SARS-CoV-2 infection and present neurological findings [23–25, 29].

SARS-CoV-2 infection with concomitant SE has only been reported as cases [19–22], whereas a study including 841 cases had no cases of SE [29]. In our study, the prevalence of SE was 8.9% ($n = 4$) among patients with seizure and 0.0225% among all SARS-CoV-2 cases.

There are insufficient data on age- and gender-related trends in the prevalence of acute symptomatic/de novo seizure associated with SARS-CoV-2 infection. Severe SARS-CoV-2 infection is known to be more common in Blacks and people of Hispanic ethnicity, and cause significantly higher morbidity and mortality in men and adults over 60 years of age [30–33]. However, acute symptomatic/de novo seizure is generally more common in males, in the first year of life, and in older age. Infectious diseases including SARS-CoV-2 are risk factors in the etiology of acute symptomatic seizures, and some publications have indicated that gender and age do not affect this risk in SARS-CoV-2 [8, 28]. However, in our study, we determined that the frequency of seizure was higher in the male gender (57.8%; $n = 26$), in patients aged 18–44 and ≥ 65 years, and in those with multiple comorbidities (48.9%, $n = 22$) (Table 1).

Case fatality rates for SARS-CoV-2 infection are 0.7–4.53%, and as in the rest of the world, in Turkey

Table 5 Demographic and clinical characteristics of non-surviving patients

Age (years)/Gender	Hospital stay (days)	Day of seizure onset	Comorbid diseases	Neurological findings	Antiepileptic drug administered at time of seizure	Cerebral imaging findings on day of seizure onset	Major systemic problems on day of seizure onset
57/M	78	30	HT	Impaired consciousness	Levetiracetam	Normal	Hypoxemia, hypocalcemia, hypomagnesemia, septicemia
70/F	38	4	DM, HT, CKD + AKI, Bladder CA	None	Midazolam	–	Hypoxemia
57/F	33	1	DM, HT, CVD	Left hemiplegia Impaired consciousness	–	Right cerebellar, right thalamus and pons chronic lacunar infarct	Hypoxemia
73/M	21	5	Lung CA	None	Levetiracetam	Chronic periventricular ischemia	Hypoxemia
23/M	42	5	Down syndrome, ALL	Impaired consciousness	Levetiracetam	Normal	Hypocalcemia, hypomagnesemia
66/F	65	1	ASHD	Impaired consciousness	Midazolam, levetiracetam	Normal	Hypoxemia
66/M	8	6	DM, acute pancreatitis, diabetic ketoacidosis	None	Levetiracetam diazepam, valproic acid	Chronic periventricular ischemia	Hypoxia, hyperglycemia, diabetic ketoacidosis
57/M	17	16	HT, AKI	Impaired consciousness	Levetiracetam	Subarachnoid hemorrhage	Hypoxia, septic shock
65/F	19	2	Morbid obesity, DHF, COPD	Impaired consciousness	Diazepam, fentanyl	–	Hypoxia, hyperpotassemia
28/M	21	10	CP sequelae, epilepsy,	Spastic tetraplegia	Levetiracetam, valproic acid	Acute ischemic stroke	Hypocalcemia, hypernatremia
67/F	43	29	DM, HT, ASHD, AKI	Impaired consciousness	Levetiracetam, fentanyl	–	Uremia, hypernatremia, cardiac arrest
71/M	5	1	ASHD	Impaired consciousness	Midazolam, fentanyl	–	NSTEMI and cardiac arrest,
62/F	6	6	DM, HT	Impaired consciousness	Levetiracetam	–	Hyponatremia, hypocalcemia, hypomagnesemia, cardiac arrest
59/M	124	101	HT	Impaired consciousness	Levetiracetam, fentanyl	Leukomalactic area, ICH (seizure after resorption)	Hypomagnesemia
71/M	22	19	DM, Parkinson's, dementia	Right HP	Valproic acid, fentanyl	Left parietal hemorrhage (ICH)	Hypomagnesemia, hypocalcemia,
72/F	7	6	HT	Impaired consciousness, right HP	Levetiracetam	Right MCA, left parietal acute ischemia	Hypocalcemia, ischemic stroke
51/M	43	28	Asthma, suspected TB,	Impaired consciousness	Levetiracetam Valproic acid	Intracranial cyst and edema	Hypocalcemia, hypopotassemia, sepsis, cardiac arrest
62/M	24	17	None	Impaired consciousness	Levetiracetam, valproic acid, diazepam, midazolam, fentanyl, propofol	Normal	Hypernatremia, septicemia, hypoxemia
71/M	57	8	HT AF	Impaired consciousness	Levetiracetam, diazepam, fentanyl	Chronic periventricular ischemia	Respiratory acidosis, hypocalcemia, septicemia

Table 5 (continued)

Age (years)/Gender	Hospital stay (days)	Day of seizure onset	Comorbid diseases	Neurological findings	Antiepileptic drug administered at time of seizure	Cerebral imaging findings on day of seizure onset	Major systemic problems on day of seizure onset
20/M	5	1	CKD, HD, GH deficiency	Impaired consciousness	Valproic acid	Normal	Metabolic acidosis, hypercalcemia, uremia, hyperpotassemia, hypoxia
76/M	5	1	COPD, HT, post-cardiac arrest seizure	Impaired consciousness	Levetiracetam, diazepam	Normal	Hyponatremia, hypocalcemia, hypoxemia, metabolic acidosis
76/M	50	31	HT, DM, CVD	Impaired consciousness	Levetiracetam	Chronic ischemia	Hyponatremia, sepsis
27/M	23	4	TB, HCV, substance use	Impaired consciousness	None	–	Hypocalcemia, fever, sepsis
74/M	12	1	DM, HT, CHF	Impaired consciousness	Levetiracetam, diazepam	Ischemic stroke	Hyponatremia, NCSE during stenting

HT hypertension, *DM* diabetes mellitus, *AF* atrial fibrillation, *CKD* chronic kidney disease, *AKI* acute kidney injury, *CHF* congestive heart failure, *ASHD* atherosclerotic heart disease, *CA* cancer, *ALL* acute lymphocytic leukemia, *CP* cerebral palsy, *CVD* cerebrovascular disease, *COPD* chronic obstructive pulmonary disease, *HD* hemodialysis, *TB* tuberculosis, *HCV* hepatitis C virus, *GH* growth hormone, *MCA* middle cerebral artery, *ICH* intracranial hemorrhage, *NSTEMI* non-ST-elevation myocardial infarction, *NCSE* nonconvulsive status epilepticus

mortality is known to be higher in patients who are male and those with diabetes, HT, and comorbidities causing impaired lung and kidney function [34]. Some studies have indicated that seizure development during SARS-CoV-2 infection is not associated with prognosis [35, 36]. In our study, the case fatality rate among patients with SARS-CoV-2 and seizure was 0.135% (95% CI 80.86–188.71). However, none of the non-surviving patients had a previous diagnosis of epilepsy. In a study by Sanchez-Larsen et al. including only people with epilepsy, the mortality rate was reported to be 4.61% overall and 2.57% in the Hispanic population [37]. This finding may indicate that SARS-CoV-2 is not associated with more severe disease or poor prognosis in patients with epilepsy [37–40].

Seizures frequently occurred in the first 2 days after admission (mean: day 9) and 75.6% in the first week ($n=34$); in other words, during the acute symptomatic period of COVID-19 (Table 3). Seizures observed in the first 2 days in particular were thought to be associated with the cytokine storm that occurs in severe SARS-CoV-2 infection [41].

Inflammatory and hypercoagulability markers such as neutrophil-to-lymphocyte ratio, D-dimer, CRP, ferritin, and PCT are known to be associated with COVID-19 severity and mortality [41–45]. It has been emphasized that elevation of these parameters is related to both severe COVID-19 and the occurrence of common neurological findings [7, 46, 47]. In people with epilepsy, the presence of intellectual disability, dyslipidemia, advanced age, and long-term residential care were shown to be risk factors for the development of severe SARS-CoV-2 [37].

Although some studies showed that biomarkers and the presence of neurological findings are associated with high mortality, other studies suggested there is no significant relationship [41, 42]. A mortality rate was reported for a series of 465 cases in a study examining biomarker levels and prognosis in complicated medical conditions such as seizure, but the old age of the sample group (mean: 69 years) precluded comparison with normal population data [48]. Sanchez-Larsen et al. emphasized in their study that SARS-CoV-2 infection was associated with higher mortality in patients with epilepsy who were older and had HT, dyslipidemia, and heart disease [37].

Low lymphocyte percentage is known to be associated with disease severity and mortality in COVID-19 patients, but we encountered no study demonstrating its relationship with biomarkers and prognosis related to seizure development during infection [41, 49]. In our study, we found that high levels of blood glucose, BUN, creatinine, ferritin, fibrinogen, CRP, pro-BNP, and PCT at admission were associated with mortality. Similarly, low lymphocyte and calcium levels and high WBC, neutrophil, blood glucose, LDH, AST, BUN, creatinine, ferritin, CRP, pro-BNP, D-dimer, and PCT levels on the day of seizure onset were associated with higher mortality in patients

with seizures, consistent with other studies [41, 49]. PCT is a known marker of mortality in SE, and we also found that PCT was an important risk factor for seizure development and SE [50]. Prognosis was not associated with platelet, magnesium, ALT, or pCO_2 levels in our study.

Limitations

One limitation of this study is its retrospective design. In addition, many patients did not undergo EEG and lumbar puncture test because of mechanical ventilation support and infection control measures. As a result, cases of non-convulsive status epilepticus could not be identified. Furthermore, as our patient group included only hospitalized patients, the results of this study may not represent the biomarkers affecting seizure frequency and mortality in SARS-CoV-2 patients in the community.

Conclusion

Our results suggest that seizures and SE are not uncommon during SARS-CoV-2 infection. Seizures may be associated with elevated WBC, neutrophil, blood glucose, LDH, AST, BUN, creatinine, ferritin, CRP, pro-BNP, D-dimer, and PCT levels and low lymphocyte and calcium levels in patients with severe SARS-CoV-2 patients, and these markers are also associated with high mortality. In patients with multiple comorbidities with previous cerebral insult, long hospital stay and excessive changes in infection parameters increase the likelihood of seizures.

Therefore, close monitoring of these biomarkers is important in terms of seizure and mortality in patients hospitalized with SARS-CoV-2 infection, especially those with multiple comorbidities. We hope this study will serve as a starting point for more comprehensive studies.

Declarations

Conflict of 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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