

# Does the Frequency and Etiology of Status Epilepticus Change During the SARS-CoV-2 Pandemic?

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## Abstract

**Objective:** There are limited data regarding the development of status epilepticus (SE) in epilepsy patients during the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) pandemic. In Turkey, no study has investigated the frequency and etiology of SE in patients with epilepsy during the pandemic period. We aimed to evaluate the etiologies, clinical features, treatment, and prognosis of patients who were followed up with a diagnosis of SE in our neurology clinic and intensive care unit during the pandemic period.

**Methods:** In this study, 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%), who were monitored and treated in the Bursa City Hospital Neurology Clinic and Neurology Intensive Care Unit between March 11, 2020 and December 31, 2022, were retrospectively included.

**Results:** When etiologic factors leading to SE were analyzed; it was considered that 16 patients had ischemic stroke (27.1%), 8 had intracranial tumor (13.5%), 4 had intracerebral hemorrhage (6.7%), 4 had medication discontinuation (6.7%), 4 had SARS-CoV-2 infection (6.7%), 3 had other infections (5.0%), 2 had SARS-CoV-2 vaccination (3.3%), 4 had previously diagnosed refractory epilepsy (6.7%), and 8 had NORSE (13.5%). In the present study, 18 patients (30%) received IV levetiracetam, 8 patients (13.5%) received levetiracetam + valproic acid, and 6 patients (10.1%) received levetiracetam + phenytoin infusion for SE. We had 28 patients who needed general anesthesia. Ten patients (16.9%) died.

**Conclusion:** In the etiology of SE in our patients monitored during the pandemic period, it was found that ischemic stroke, cryptogenic causes, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other infections, and irregular drug use were the most common causes.

**Keywords:** SARS-CoV-2, COVID-19, epilepsy, status epilepticus, pandemic, etiology

## INTRODUCTION

Status epilepticus (SE) is defined as a single seizure that lasts longer than 5 min or repetitive seizures in which the patient does not return to the previous state.<sup>1</sup> In cases where seizure activity is still present despite first-line benzodiazepine and second-line intravenous (IV) antiseizure medication, the patient is considered to have developed refractory SE (RSE). RSE is observed in approximately 9-43% of all SE cases, and the mortality rate has been reported to be between 15% and 33%. The mortality rate increases as the duration of SE increases.<sup>2</sup>

In the neurological spectrum of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection; there are many neurological symptoms, including delirium, loss of smell and taste, encephalopathies, stroke, epileptic seizures, and SE.<sup>3</sup> It has been reported that SARS-CoV-2 may cause neurological symptoms due to its neuroinvasive and neurotropic properties and that the inflammatory response (cytokine storm) related to SARS-CoV-2 infection may lead to increased circulating cytokine levels and immune cell hyperactivation, which may cause secondary organ dysfunction and a life-threatening systemic inflammatory syndrome.<sup>4</sup> SARS-CoV-2 may trigger a systemic inflammatory response and result in stroke, epileptic seizures, and SE. Acute symptomatic seizures and SE are the most commonly reported clinical conditions related to SARS-CoV-2 infection, and the mortality rate is high (5-39%).<sup>5</sup> Although vaccines are generally safe for patients with epilepsy, they may lead to seizures, particularly with live vaccines. Although the effects of SARS-CoV-2 vaccines on seizures are still unknown, They have rarely been observed to increase epileptic seizures.<sup>5</sup> It was found that there was a further increase in seizures after vaccination in patients with frequent seizures.<sup>5,6</sup> In a cross-sectional study by Özdemir et al.,<sup>6</sup> it was reported that SARS-CoV-2 vaccines were well tolerated in patients with epilepsy, and more seizures than normal were observed in a small group of patients. In rare cases, SE cases after SARS-CoV-2 vaccination in people without epilepsy have also been reported.<sup>7</sup>

Several studies have evaluated the situation of epilepsy patients during the SARS-CoV-2 pandemic. However, data on SE are limited.<sup>8-10</sup> Furthermore, no study has investigated SE in patients with epilepsy during the pandemic period in Turkey. It was considered that there might be an increase in the frequency of epilepsy seizures and the prevalence of SE in patients with epilepsy during the SARS-CoV-2 pandemic period because of the inability of patients with epilepsy to use their medications on a regular basis, failure to perform neurologic follow-up appropriately, and the possible seizure risk of SARS-CoV-2 infection and vaccines. This retrospective study evaluated the demographic characteristics, etiologies, and whether there was a relationship with SARS-CoV-2 infection in SE patients who were hospitalized in our hospital during the SARS-CoV-2 pandemic.

## METHODS

Patients who were hospitalized, monitored, and treated in the Neurology Clinic and Intensive Care Unit of Bursa City Hospital between March 11, 2020 and December 31, 2022 were scanned. Patients with a diagnosis of SE were extracted from the hospital data processing system and analyzed.

### Study inclusion criteria:

1. Patients must be over 18 years of age,
2. Patients in whom seizures were consistent with the International League Against Epilepsy SE diagnostic criteria (continuous clinical and/or electrographic seizure activity that lasts longer than 5 min or recurrent seizure activity that does not return to baseline).

We excluded patients under 18 years of age and those with a single clinical seizure with a duration of less than 5 min.

If SE developed in the first 3 weeks after SARS-CoV-2 vaccination (patients without any underlying etiologic cause and without a history of epilepsy), it was a possible vaccine-associated SE.

During the pandemic period, 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%), were hospitalized, monitored, and treated in our hospital. Data on age, gender, previous history of epilepsy, comorbidities, SE occurrence, SE etiology, brain computed tomography and magnetic resonance imaging findings, electroencephalography (EEG) findings, laboratory findings, SE treatments, and SE prognosis were evaluated.

For this study, ethics committee approval number: 2023-8/5, date: 10.05.2023 was obtained from the Bursa City Hospital Ethics Committee.

### MAIN POINTS

- Status epilepticus is an important life-threatening neurological condition that may occur during the clinical course of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection.
- In the SARS-CoV-2 pandemic, epilepsy patients could not go for regular controls because of fear of infection and various other reasons.
- Ischemic stroke, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other systemic infections, and medication discontinuation were the common etiological factors of status epilepticus in our patients who were followed up during the SARS-CoV-2 pandemic.

## Statistical Analysis

All statistical analyses were performed using MedCalc® (Mariakerke, Belgium) software. Comparisons between groups were performed using the chi-square test and independent two-sample t-test.  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 59 patients (mean age 51.7±2.7 years), 32 males (54.2%) and 27 females (45.7%) were retrospectively included in the study.

Ischemic stroke was the most common underlying etiologic cause of SE in our study group of 16 patients (27.1%). It was found that there is intracranial tumor in 8 patients (13.5%), intracerebral hemorrhage in 4 patients (6.7%), medication discontinuation in 4 patients (6.7%), SARS-CoV-2 infection in 4 patients (6.7%), other infections in 3 patients (5.1%), possible vaccine-associated in 2 patients (3.3%), drug-resistant epilepsy in 4 patients (6.7%), autoimmune encephalitis in 1 patient (1.6%), neurodegenerative disease in 1 patient (1.6%), and no identified cause in 8 patients (13.5%) (Table 1). The most common factors triggering the onset of SE were epilepsy after stroke, hemorrhage and intracranial tumours, medication discontinuation, epilepsy secondary to Coronavirus disease-2019 (COVID-19) infection, and other systemic infections. The underlying causes of SE in our patients are listed in Table 1.

Considering the drugs used for treating SE; 18 patients (30%) received levetiracetam (LEV), 8 patients (13.5%) received LEV + valproic acid, and 6 patients (10.1%) received LEV + phenytoin infusion. In 27 patients (45.7%), other anti-seizure drug combinations were used. Additionally, there were 28 patients (47%) who needed general anesthetics such as midazolam, ketamine, thiopental, and propofol. Thirty-one patients (53%) did not receive general anesthetics. It was seen that only 15 (25%) of the patients could undergo EEG and the remaining 44 patients could not undergo EEG due to pandemic conditions. Considering the EEG findings; 6 patients had generalized slow wave paroxysms, 1 patient had generalized epileptic abnormality, 2 patients had focal epileptic abnormality, 1 patient had focal epileptic abnormality with secondary generalization, and 5 patients had normal EEG findings. EEG was performed in all patients after the seizures ended (Table 2). When the mortality rates were evaluated, 10 of the 59 patients were lost (16.9%). The mortality period ranged between 5 and 137 days.

**Table 1.** Main underlying causes in SE cases

	Number of cases	Percentage (%)
Acute/remote stroke	16	27.1%
Brain metastasis	8	13.5%
Intracranial hemorrhage	4	6.7%
Epilepsy inadequate medication	4	6.7%
COVID-19 pneumonia	4	6.7%
Drug resistant epilepsy	4	6.7%
After vaccination	2	3.3%
Other infections	3	5.0%
Other causes	6	10.2%
Unknown	8	13.5%

SE: Status epilepticus, COVID-19: Coronavirus disease-2019

**Table 2.** Demographic and clinical data of patients

Gender	Male	32	54.2%
	Female	27	45.7%
Age	Arithmetic mean	51.7±2.7	
	Median	54	
History of epilepsy	Yes	33	55.9%
	No	26	44.0%
Comorbidity	Yes	50	84.7%
	No	9	15.3%
Intubated	Yes	27	45.7%
	No	32	54.3%
Relation with vaccination	Yes	2	3.3%
	No	57	96.6%
Exitus	Yes	10	16.9%
	No	49	83.1%
EEG	Yes	15 (25.4%)	Normal 5
			Abnormal 10
	No	44 (74.6%)	

EEG: Electroencephalography

## DISCUSSION

Several studies have been conducted to investigate the situation in epilepsy patients during the SARS-CoV-2 pandemic. In these studies, the effects of the pandemic on epilepsy were evaluated.<sup>11-15</sup> There are limited studies investigating SE in patients with epilepsy during the pandemic period.<sup>13-16</sup> To our knowledge, there is no study on SE during the pandemic period in Turkey. It has been reported that there was an increase in seizure frequency with an increase in fatigue, irritability, and anxiety in patients with epilepsy during the SARS-CoV-2 period.<sup>9</sup> Another study showed that the course of epilepsy was generally stable in pediatric patients during the pandemic period. It has been emphasized that sleep irregularities are also more frequent in patients with worsening seizures.<sup>11</sup>

In a study by Emami et al.<sup>9</sup>, newly developing seizure cases without a history of epilepsy were reported in critically ill patients with SARS-CoV-2. The reasons for this were hypoxia, metabolic disorders, organ failure, and neuroinvasion of the virus. In one survey study, it was observed that approximately 5% of patients with epilepsy decreased the doses of anti-seizure medications or discontinued the medication during the pandemic period due to lack of access to anti-seizure medications and difficulty in communication with their physicians.<sup>12</sup> In this study, 55.9% of our patients had a previous history of epilepsy. In 6.7% of our patients, we thought that SE developed because of inadequate drug intake due to pandemic conditions. SE due to intracranial mass was observed in 13.5% of our patients. In a study by Arik et al.<sup>17</sup>, it was stated that SE due to intracranial tumor was observed in 7% of all SE cases before the pandemic period. The rate of SE due to intracranial tumors was higher in our study. This was thought to be due to patients' SARS-CoV-2 fear of going to the hospital.

Furthermore, an increase in cerebral edema as a result of decreased access to treatment in patients with cerebral masses may be another reason for the development of SE.

Status epilepticus is a neurologic condition that may occur during the clinical course of SARS-CoV-2 infection. The exact mechanism of the relationship between SE and SARS-CoV-2 is not known, but it may be related to the systemic inflammatory response due to cytokine release.<sup>13</sup> SARS-CoV-2 pneumonia was present in 6.7% and other infectious conditions in 5.0% of the patients with SE in our study. It is thought that the systemic inflammatory response secondary to infection may have triggered epileptic attacks.<sup>9,13</sup> New-onset RSE (NORSE) has been reported as a SARS-CoV-2-related condition. It was observed as the most common type of SE in this patient population, and a positive correlation was found between the advanced age of the patients and SE severity score.<sup>13</sup> Kheradmand et al.<sup>14</sup> reported that severe hyponatremia, ischemic stroke, and meningoencephalitis were causes of seizures in 3 of 5 cases of SARS-CoV-2-related SE. No specific cause of epileptic seizures was identified in the two cases. Three of the five patients died because of advanced age and accompanying comorbidities. The cause could not be determined in 13.5% of our patients with SE in our study. Post-stroke SE was found at a rate of 27.1%, which is higher than the prevalence of post-stroke SE found in previous studies during the pandemic period.<sup>18</sup>

In a multicenter retrospective study conducted by Kohle et al.<sup>19</sup> in Germany, cases with SE before and during the pandemic were compared. It has been suggested that SARS-CoV-2 is not directly related to SE. There are differences in the causes of SE, and it has been reported that cryptogenic and anoxic-induced SE are more common. Likewise, we found that ischemic stroke, brain metastasis, and cryptogenic SE were more frequent in our study. Several hypotheses have been proposed to explain the possible underlying causes of SARS-CoV-2-related SE. One controversial hypothesis is that SARS-CoV-2 is capable of direct invasion into the central nervous system (CNS). Because of its neuroinvasive and neurotropic properties, the virus may lead to SE.<sup>20</sup> In addition, it may enter the nervous system directly through neural pathways or indirectly through the ACE2 receptor. The entry of proinflammatory cytokines into the nervous system or the production of these cytokines by microglia and astrocytes may lead to disruption of the blood-brain barrier, increase in glutamate and aspartate, decrease in GABA levels, and consequently epileptic seizures.<sup>21</sup>

In epidemiologic studies, it was observed that the incidence of SE during the pandemic was consistent with the overall SE incidence recorded in the previous 5 years. Our results were also similar. However, difficulties in the use of EEG and other examinations may have led to a significantly lower recognition of NKSE.<sup>22</sup>

In patients older than 60 years with SARS-CoV-2, new-onset neurological symptoms, seizures, CNS infections, and stroke are frequently reported.<sup>23</sup> There are increasing data on the relationship between ischemic stroke and SARS-CoV-2. The association between SARS-CoV-2 and ischemic stroke is thought to be most prominent in cases involving anterior circulation and male gender. In these cases, cardioembolic strokes were observed more frequently.<sup>24</sup> Ischemic stroke was found in approximately 0.5-1.3% of hospitalized SARS-CoV-2 patients. It was suggested that

there was a 3- to 4-fold relative risk increase in ischemic stroke in hospitalized SARS-CoV-2 patients. Increased D-dimer levels, history of ischemic stroke, presence of diabetes mellitus, and additional vascular risk factors have shown that the likelihood of stroke increases in patients with SARS-CoV-2.<sup>25</sup> there is a risk of epileptic seizures and SE development after stroke.<sup>26</sup> In one study that investigated the etiology of SE, stroke-related SE was found to be 14.5%.<sup>27</sup> We found that 27.1% of patients developed SE after stroke in our study, and this rate was quite high. Although it is thought that the increased risk of stroke during the SARS-CoV-2 period may play a role in this, the data are not sufficient.

Although all vaccines, including the SARS-CoV-2 vaccine, are safe in patients with epilepsy, seizures can sometimes occur after vaccination. Although SARS-CoV-2 vaccines are recommended to patients with epilepsy considering the risk-benefit ratio. In a study, it was found that there may be an increase in seizures after vaccination in patients with frequent seizures.<sup>6</sup> A few cases of SE after SARS-CoV-2 vaccination in people without epilepsy have been reported.<sup>8,17</sup> Encephalopathy and NKSE were reported in two cases after the SARS-CoV-2 vaccine.<sup>17</sup> Post-SARS-CoV-2 vaccine SE was observed in approximately 3.3% (2 cases) of our patients with SE during the pandemic period in our study, and its relation to the vaccine is not clear.

### Study Limitations

The limitations of our study is that EEG recordings could not be performed or performed with a delay during the pandemic period. therefore, we may have missed non-convulsive conditions. In addition, the course of COVID-19-related SE could be better understood using a multicenter status epilepticus study.

### CONCLUSION

As a result, ischemic stroke, cerebral hemorrhage, intracranial tumors, SARS-CoV-2 and other systemic infections and medication discontinuation were found to be at the forefront of the etiology of SE in our patients who were followed up during the pandemic. It has been suggested that the development of SE, seen mainly in post-stroke patients during the pandemic, may be attributed to the multisystemic involvement of SARS-CoV-2 infection.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Ethics Committee of the Bursa City Hospital under the ethical approval number 2023-8/5, date: 10.05.2023.

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: S.G., Ö.K., Concept: S.G., Ö.K., A.Ö., Design: S.G., Ö.K., A.Ö., Data Collection or Processing: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Analysis or Interpretation: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Literature Search: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö., Writing: S.G., Ö.K., C.H., M.A.A., G.M., G.Ö.

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