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ORIGINAL RESEARCH

Acute ischemic stroke as a major neurologic complication of SARS-CoV-2 infection

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Abstract

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the reason for coronavirus disease 2019 (COVID-19), which was first diagnosed in Wuhan, China. COVID-19 has since led to a worldwide pandemic. SARS-CoV-2 infection increases the risk of thrombotic events, including ischemic strokes. There are limited data on ischemic stroke associated with COVID-19. The aim of our study was to determine the effects of SARS-CoV-2 infection on ischemic stroke. A total of 248 ischemic stroke and transient ischemic attack (TIA) patients hospitalized in our neurology intensive care and stroke units between March 2020 and January 2022 were retrospectively analyzed. Two hundred and five stroke patients were diagnosed with COVID-19-negative strokes. COVID-19-positive patients were first isolated from the relevant units, and neurological follow-up was performed. Forty-three patients who were diagnosed with COVID-19-related ischemic stroke and survived at the end of the isolation period were transferred and followed up in the neurology intensive care and stroke unit. Stroke classifications, vascular risk factors, clinical course, disease severity, laboratory parameters, recanalization treatment results, and mortality rates of ischemic strokes in patients with positive or negative COVID-19 infection were evaluated. COVID-19-positive and COVID-19-negative stroke patients had similar characteristics of age, gender, vascular risk factors and stroke subtype. Cryptogenic stroke was the most common type of stroke in both groups. TIA and small vessel diseases were detected only in the COVID-19-negative group. COVID-19-positive stroke patients had lower lymphocyte counts and higher procalcitonin, troponin and fibrinogen levels. Ischemic strokes had similar clinical characteristics and did not show a different course or prognosis in COVID-19-positive and COVID-19-negative stroke patients.

Keywords

COVID-19; SARS-CoV-2 infection; Acute ischemic stroke

1. Introduction

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the reason for coronavirus disease 2019 (COVID-19), which was first diagnosed in Wuhan, China [1]. COVID-19 disease started and rapidly turned into a worldwide pandemic, as declared by the World Health Organization (WHO) [2]. The disease primarily affects the respiratory system. Although initially described as a respiratory-pulmonary disease, there have been accumulating data showing that COVID-19 causes neurological complications. Headache, dizziness, myalgia, hypogeusia and hyposmia are commonly reported mild symptoms [1, 3, 4]. However, serious neurological or neuropsychiatric manifestations occurs due to COVID-19. Stroke is an important neurological complication of COVID-19 in the central nervous system (CNS) [5–8]. Several mechanisms related to immune-mediated thrombosis, the renin-angiotensin system, and the effect of the virus on the CNS may contribute to the risk of stroke among patients with COVID-19 [9, 10]. In the literature, the incidence of stroke related to COVID-19 disease is approximately 1–3% for hospitalized patients and 6% for patients in the intensive care unit (ICU) [10, 11]. Most cases reported so far are limited to case series. Therefore, minimal data are available regarding the neurophysiological mechanisms of COVID-19.

In the current study, we aimed to determine the neurological consequences in stroke patients with the neurological complications of COVID-19 who were followed up in our neurology intensive care and stroke units.

2. Method

2.1 Study design and patients

A total of 248 adult ischemic stroke and transient ischemic attack (TIA) patients, followed by the authors in neurology intensive care and stroke units, were retrospectively analyzed. Patients under the age of 18 years old were excluded. All stroke patients admitted to the emergency department between March 2020 and January 2022 were evaluated. Patients were divided into two groups, positive and negative, for COVID-19 according to WHO guidance 2020 [12]. Two hundred and five stroke patients were diagnosed with a COVID-19-negative stroke. Patients who were initially admitted to the emergency department with stroke-related complaints and asymptomatic SARS-CoV-2 infection were detected by admission real-time reverse-transcription polymerase chain reaction (RT-PCR) of the nasal–throat swab test. Sixty-seven patients were diagnosed with COVID-19-related ischemic strokes. Patients whose RT-PCR tests became positive later were not included in the study. COVID-19-positive patients were first isolated in the relevant units. Twenty-four patients who died during the isolation period or were transferred to another ICU from the emergency department were excluded due to missing outcome information and laboratory tests. Forty-three patients who were diagnosed with COVID-19-related ischemic stroke and survived at the end of the isolation period were transferred and followed up in the neurology intensive care and stroke unit.

2.2 Diagnosis of COVID-19

The diagnosis of COVID-19 was made when the RT-PCR test and/or chest computed tomography (CT) was consistent with typical COVID-19 pneumonia (multiple ground-glass opacities in the lungs). Patients with clinical signs of infection but negative RT-PCR tests were excluded from the study, even if their radiological findings were positive.

2.3 Diagnosis of neurological disorders

At least two neurologists performed a detailed evaluation and recorded all responses in a database at baseline and follow-up. The evaluation consisted of neurological history, demographic factors, comorbidities and neurological examinations.

Radiologic assessments, including cranial magnetic resonance imaging (MRI), cranial CT, CT angiography, laboratory tests (whole blood cell, biochemistry, coagulation, liver and renal function tests), and C-reactive protein (CRP) were performed. Admission blood count parameters with normal ranges were studied in all patients as follows: platelet (150–450 $\times$ 10^3/mL), leukocyte (4–10 $\times$ 10^3/mL), neutrophil (1.6–6 $\times$ 10^3/mL), lymphocyte (1.2–3.6 $\times$ 10^3/mL), CRP (0–5 mg/dL), procalcitonin (0–0.5 μg/L), D-dimer (0–243 μg/L), fibrinogen (200–400 mg/dL), troponin (0–0.6 ng/mL), and glucose (70–125 mg/dL). All interventions, including intubation or tracheostomy during hospitalization, were recorded. The severity of COVID-19 was defined according to the COVID-19 treatment guidelines [13]. Stroke patients with positive or negative SARS-CoV-2 were presented.

The diagnosis of ischemic stroke was made on the basis of clinical findings and radiological assessments (cranial CT, MRI and CT angiography). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used for the types of ischemic stroke [14]. The clinical severity of stroke was assessed with the National Institute of Health Stroke Scale (NIHSS) at admission and within 24 hours [15]. If necessary, intravenous recombinant tissue plasminogen activator (IV rtPA), mechanical thrombectomy (MT), or combination (bridging) therapies were applied according to the American Heart Association and American Stroke Association guidelines [16]. Intracerebral hemorrhages after recanalization treatments were classified according to the European Cooperative Acute Stroke Study [17]. We quantified the premorbid and discharge functional statuses of our cases using the modified Rankin scale (mRS) [18]. mRS <3 was defined as "good prognosis", and mRS >3 as "poor prognosis".

2.4 Statistical analyses

All calculations were performed using IBM SPSS statics 22.0 (IBM Corp., Armonk, NY, USA) for Windows. Data are expressed either as frequencies and median (interquartile range (IQR)). The normal distribution suitability of numerical variables was tested with the Shapiro-Wilk test. A two-sided Mann-Whitney U test was applied to compare the differences between groups for continuous variables. A two-sided Pearson chi-square exact test for categorical variables. Binary logistic regression analysis was used to determine the predictive factors related to COVID-19. Propensity scores were calculated to reveal the effect of many covariates in predicting stroke risk and to increase the level of evidence. A statistically significant difference was accepted at $p < 0.05$.

3. Results

We had 205 ischemic stroke patients with negative COVID-19 and 43 ischemic stroke patients with positive COVID-19. The mean age, standard deviation (SD), and median (IQR) of COVID-19-positive acute ischemic stroke patients were 68.8 $\pm$ 15.1 and 72 (29.0). The mean age, SD and median (IQR) of COVID-19-negative acute ischemic stroke patients were 70.04 $\pm$ 13.7 and 72 (18.0) ($p = 0.772$). There were 25 (58%) COVID-19-positive men and 18 (42%) COVID-19-positive female stroke patients.

Vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation and congestive heart failure among acute ischemic stroke patients were similar between the two groups. Chronic obstructive pulmonary disease/asthma and smoking ratios were significantly lower in COVID-19-positive patients ($p = 0.009$ and 0.44, respectively). The demographic and clinical features of the COVID-19-positive and COVID-19-negative patients are summarized in Table 1.

Our results indicated no difference between COVID-19-positive and COVID-19-negative patients according to the TOAST classification. The most detected etiology was cryptogenic stroke in both groups. Large vessel disease was more common in COVID-19-positive ischemic stroke patients under the age of 50. However, cryptogenic stroke was found to be statistically significantly higher in the advanced age group ($p = 0.041$).

Mortality rates were similar between COVID-19-positive

TABLE 1. Demographic characteristics and comorbidities of COVID-19 positive and negative acute ischemic stroke patients.

Demographic and clinical characteristics	COVID-19 negative ischemic stroke	COVID-19 positive ischemic stroke	*p*
Number of patients	205	43	
Age			
Mean ± SD	70.04 ± 13.743	69.63 ± 15.918	0.772
Median (IQR)	72.00 (18)	72.00 (29)	
Age			
19–50	20 (9.8%)	6 (14.0%)	0.414
>50	185 (90.2%)	37 (86.0%)	
Sex			
Males	119 (58.0%)	25 (58.1%)	0.991
Females	86 (42.0%)	18 (41.9%)	
Hypertension	135 (65.9%)	27 (62.8%)	0.701
Diabetes Mellitus	86 (42.0%)	19 (44.2%)	0.787
Dyslipidemia	111 (54.1%)	24 (55.8%)	0.842
Congestive Heart Failure	56 (27.3%)	11 (25.6%)	0.816
Atrial Fibrillation	69 (33.7%)	12 (27.9%)	0.465
History of Stroke	31 (15.1%)	10 (23.3%)	0.192
Malignancy	14 (6.8%)	2 (4.7%)	0.597
Asthma/COPD	30 (14.6%)	1 (2.3%)	0.009
Smoking	59 (28.8%)	6 (14.0%)	0.044

COVID-19: Coronavirus Disease 2019; COPD: Chronic Obstructive Pulmonary Disease; SD: standard deviation; IQR: interquartile range; $p < 0.05$: Chi-Square Test (χ^2); Summary statistics given as number (percentage) value.

and COVID-19-negative patients ($p = 0.459$). No correlation was found between the etiology of stroke and mortality ($p = 0.572$).

The recanalization treatment of COVID-19-positive patients was as follows: IV rtPA was applied to eight (18.6%) COVID-19-positive patients; two of them also underwent MT (bridging treatment). Only one patient treated with IV rtPA died due to systemic infection on the 30th day of intensive care follow-up. Hemorrhagic infarct (HI-1) was detected in only one patient among those who underwent recanalization and bridging therapy. No hemorrhagic transformation was detected in the other COVID-19-positive patients.

The recanalization treatment of COVID-19-negative patients is as follows: recanalization treatment was applied to 69 (33.7%) of 205 COVID-19-negative patients. IV rtPA was used in 28 (13.7%) patients, MT in 10 (4.9%) patients, and bridging treatment in 31 (15.1%) patients. Endovascular treatment was significantly higher in COVID-19-negative patients ($p = 0.016$).

There was no difference between the COVID-19-positive and COVID-19-negative patients in terms of IV thrombolytic treatment application rates. It was observed that most of the patients who died developed parenchymal hemorrhages (PH-2). The clinical characteristics of the COVID-19-positive and COVID-19-negative stroke patients are summarized in Table 2.

In laboratory evaluation, both groups of patients had similar white blood cell, neutrophil and platelet counts and CRP and D-dimer levels. However, COVID-19-positive patients had lower lymphocyte counts ($p = 0.002$), higher procalcitonin levels ($p < 0.001$), and high fibrinogen values ($p = 0.002$). In addition, elevated troponin levels were detected only in COVID-19-positive patients ($p < 0.001$) (Table 3).

When the variables in predicting the risk of stroke in COVID-19 disease were evaluated by receiver operating characteristic curve analysis, the cut-off values (cut-off point) were found to be below ≤1.21 for lymphocytes, procalcitonin was >0.28 and troponin was >0.0024. The negative predictive value was over 80% for all three parameters (Table 4 and Fig. 1).

Elevated CRP, procalcitonin, D-dimer, neutrophils and glucose were found to be associated with mortality ($p = 0.044$, $p < 0.0001$, $p < 0.0001$, $p = 0.010$ and $p < 0.0001$, respectively). The survival rate was significantly lower according to the lymphocyte levels ($p = 0.004$). Elevated procalcitonin and platelet levels were associated with a 1.981- and 1.005-fold increased risk of COVID-19, respectively (Table 5).

TABLE 2. Clinical characteristics of patients with COVID-19 positive and negative stroke patients.

	COVID-19 negative ischemic stroke	COVID-19 positive ischemic stroke	*p*
Number of patients	205	43	
TOAST classification			
Large Vessel Disease	69 (33.7%)	16 (37.2%)	
Cardioembolic	46 (22.4%)	7 (16.3%)	
Cryptogenic	77 (37.6%)	20 (46.5%)	0.239
Stroke of Determined Origin	0 (0.0%)	0 (0.0%)	
Small Vessel Disease	13 (6.3%)	0 (0.0%)	
IV rtPA	58 (28.3%)	8 (18.6%)	0.191
Endovascular treatment	41 (20.0%)	2 (4.7%)	0.016
NIHSS on admission	9.6146 (0–22)	8.0233 (0–22)	0.113
NIHSS At 24 hours	8.5366	8.2558	0.972
Length of Stay	21.39 (1–167)	20.84 (1–133)	0.738
mRS at 24 hours	3.12	3.14	0.721
Intubation	66 (32.2%)	13 (30.2%)	0.802
Tracheostomy	22 (10.7%)	2 (4.7%)	0.220
Decompression	13 (6.3%)	3 (7.0%)	0.877
Mortality	42 (20.5%)	11 (25.6%)	0.459

COVID-19: Coronavirus Disease 2019; IV rtPA: intravenous recombinant tissue plasminogen activator treatment; mRS: modified Rankin scale; NIHSS: National Health Stroke Scale; TOAST classification: Trial of Org 10172 in Acute Stroke Treatment classification.
$p < 0.05$: Chi-Square Test (χ^2); Summary statistics given as number (percentage) value.

TABLE 3. Laboratory results of patients with COVID-19 positive and negative stroke patients.

Laboratory	COVID-19 negative ischemic stroke	COVID-19 positive ischemic stroke	*p*
C-reactive protein. median (IQR)	4.99 (16.82)	8.86 (49.84)	0.133
Procalcitonin. median (IQR)	0.05 (0.10)	0.95 (3.10)	<0.0001
D-dimer. median (IQR)	297 (549)	339 (654)	0.252
Fibrinogen. median (IQR)	323 (203)	427 (211)	0.049
Troponin. median (IQR)	0.003 (0.01)	0.01 (0.05)	0.002
Platelet count. median (IQR)	237,000 (90,000)	264,000 (149,000)	0.050
Leukocyte count. median (IQR)	9000 (3460)	9000 (5200)	0.536
Lymphocyte count. median (IQR)	1.70 (1.07)	1.50 (1.11)	0.025
Neutrophil count. median (IQR)	5.67 (3.70)	5.76 (4.98)	0.396
Propensity Score	0.87 ± 0.11	0.61 ± 0.33	0.246

COVID-19: Coronavirus Disease 2019; $p < 0.05$: Independent-samples Mann-Whitney U test; IQR: interquartile range.

TABLE 4. Laboratory findings which predicting the risk of COVID-19 related stroke.

	Cut-off	AUC	95% CI	*p* value	Sens	Spec	PPV	NPV
Lymphocyte	≤1.21	0.608	0.545 to 0.670	0.029	34.88	87.32	36.6	86.5
Procalcitonin	>0.28	0.772	0.715 to 0.823	<0.001	67.44	84.88	48.3	92.6
Troponin	>0.0024	0.651	0.588 to 0.710	0.001	83.72	37.56	22.0	91.7

Cut-off: laboratory value; AUC: area under the curve; 95% CI: 95% confidence interval; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value.

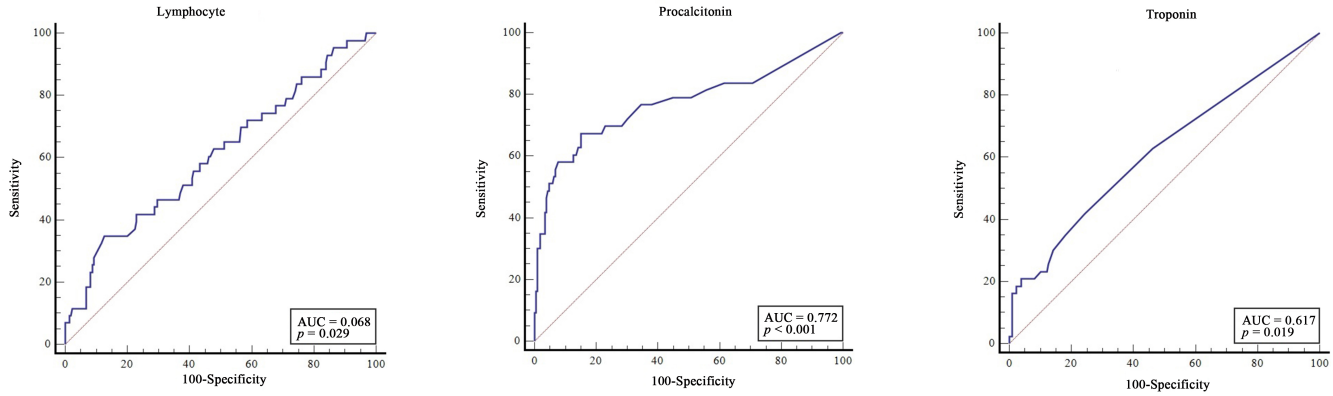

FIGURE 1. Evaluation of the performance of variables which predicting the risk of COVID-19 related stroke with ROC curve analysis. AUC: area under the curve.

TABLE 5. Evaluation of the factors affecting Covid-19 with binary logistic regression analysis. Elevated procalcitonin and platelet levels were associated with a 1.981- and 1.005-fold increased risk of COVID-19, respectively.

	Regression Coefficients						
	β	SD	Wald Statistics	p	Exp (β)	95% CI for *exp* (β)	
						Lower Limit	Upper Limit
Constant	−1.947	0.817	5.674	0.017	0.143		
Procalcitonin	0.684	0.179	14.668	<0.001	1.981	1.396	2.811
Platelet	0.005	0.002	4.380	0.036	1.005	1.000	1.009

Variables included in the model: Age, Gender, Platelet, Lymphocyte, Leukocyte and Neutrophil count, C-reactive protein (CRP), D-dimer, fibrinogen, procalcitoninand troponin levels. Model Statistics: Hosmer and Lemeshov Test $\chi^2 = 6.892$; $p = 0.862$; *Nagelkerke* $R^2 = 0.305$. *Elimination Method: Backward-Wald. 95% CI: 95% confidence interval; SD: standard deviation.*

4. Discussion

COVID-19 is a disease caused by SARS-CoV-2 infection. It is increasingly emphasized that SARS-CoV-2 infection has an effect on both the central and peripheral nervous systems [6]. Symptoms of patients infected with SARS-CoV-2 may range from mild to severe respiratory failure. However, cases presenting with neurological symptoms without respiratory symptoms have also been reported [19]. In our study, 16 (23.9%) of the 67 COVID-19-positive patients had respiratory distress concurrent with neurological findings. Of these 16 patients, 12 (75%) were diagnosed with ischemic stroke.

It has been suggested that neurological complications occur due to hypoxia, cytokine storms, autoimmune responses, hypercoagulation and endotheliopathy [20].

The most commonly reported neurological manifestations related to COVID-19 are cerebrovascular diseases [9, 21, 22]. In the literature, the incidence of stroke related to COVID-19 disease is approximately 1–3% for hospitalized patients and 6% for patients in the ICU [10, 11]. In our study, the incidence of ischemic stroke associated with COVID-19 disease was 12.4%, which is higher than previously reported cases in the literature.

Vascular risk factors were similar between the two groups. Previous reports have stated that important vascular risk factors, especially hypertension and diabetes mellitus, are present in most cases of COVID-19-related ischemic stroke; therefore, infection is a triggering factor rather than an independent cause [11]. However, since the incidence of stroke due to SARS-CoV-2 infection is 7.6 times higher compared to influenza, it is thought that COVID-19 may be the primary cause rather than the triggering factor [11]. Since there were no differences between the two groups in terms of major vascular risk factors in our study, we believe that COVID-19 is an independent risk factor for stroke.

In our study, there were no differences among stroke types between COVID-19-positive and COVID-19-negative patients according to the TOAST classification. The most common stroke type in both groups was cryptogenic stroke. TIA and small vessel disease were detected only in the COVID-19-negative patients.

In the literature, the D-dimer value, which is a marker of hypercoagulability, has been found to be high in patients with large vessel occlusion [11]. In our patients, no significant relationship was found between the D-dimer level and stroke etiology. The researchers suggested that high D-dimer levels could predict disease severity, lung complications and thromboembolic events [11]. In our study, although it was not statistically significant, the D-dimer value was high in all patients with severe COVID-19 disease. Moreover, in accordance with the literature [23], procalcitonin and fibrinogen values were found to be significantly higher in the COVID-19-positive group. Additionally, the troponin level was found to be high only in COVID-19-positive stroke patients.

It has been stated that COVID-19-positive patients have lower lymphocyte counts [8, 9, 13]. We also observed signifi-

cant differences between the values of lymphocytes, procalcitonin, and troponin in COVID-19-positive patients.

The mortality rate has been reported to be 36.23–42.24% in ischemic strokes [24]. In our study, the mortality rate in COVID-19-related ischemic strokes was 25.6%. It was observed that mortality in our patients was not related to etiology and age but was correlated with the severity of COVID-19 disease.

In our study, high levels of CRP, procalcitonin, D-dimer and neutrophils were found to be associated with mortality. The survival rate was significantly lower according to the lymphocyte levels. Elevated procalcitonin and platelet levels were associated with a 1.981- and 1.005-fold increased risk of COVID-19, respectively. Limited previous studies have stated that COVID-19-related strokes have a worse prognosis than other strokes [11, 23, 25], and longer hospitalizations cause dysfunctional outcomes [26]. However, in our study, there was no difference in mortality and hospitalization rates between COVID-19-positive or COVID-19-negative ischemic stroke patients. There were similar elevations in D-dimer and CRP values, and high intubation and mortality rates in both groups. It was thought to be caused by concomitant systemic infections in non-COVID-19 stroke patients. The proportion of asthma or chronic obstructive pulmonary disease and smoking patient rates is much higher in COVID-19-negative patients, which may lead to a poor prognosis. Similar mortality rates might also be related to the low number of COVID-19-positive patients with severe diseases.

In our study, the rate of IV thrombolytic therapy was not different between COVID-19-positive and COVID-19-negative patients, while the rate of thrombectomy was higher in the COVID-19-negative group. We believe that patients with respiratory system complaints were first evaluated for SARS-CoV-2 infection. This strict infection control system and limited workforce sources may have caused a delay in MT.

The current study has shown that IV rtPA administration to COVID-19-positive stroke patients is safe. One study suggested that symptomatic hemorrhagic complications due to IV rtPA administration in COVID-19 patients are rare, and the complication rate is lower (between 2% and 3.3%) than in the general population [27]. Although it is thought that the risk of intracranial bleeding secondary to thrombolysis may be high due to high inflammation and hypercoagulation markers in COVID-19 disease, IV rtPA should not be delayed in acute ischemic stroke patients with SARS-CoV-2 infection, and early reperfusion should be targeted. Although our study has a small number of patients, we support this treatment approach.

This study has several limitations. First, COVID-19 patients who were hospitalized in all ICUs could not be evaluated. For this reason, the stroke rate among all COVID-19 patients could not be detected. Only the data of the patients in the neurological intensive care and stroke units were obtained. Second, the number of patients with COVID-19-related ischemic strokes was insufficient. Despite these limitations, the data were considered reliable for evaluating COVID-19-releted strokes because patients with a definite diagnosis of COVID-19 and acute stroke patients were included in the study.

5. Conclusions

Neurological complications, especially ischemic strokes, are common in patients with COVID-19. The most common stroke type in COVID-19-positive patients is cryptogenic stroke. Despite the absence of COVID-19-related TIA and small vessel disease patients, making it difficult to compare the two groups, we think that this is important data for SARS-CoV-2-related strokes. Mortality-related factors of COVID-19-positive stroke patients were lymphocytopenia and high procalcitonin and troponin levels. These parameters can be used as markers of the severity of the disease.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ZT, YB and HST—designed the research study. HST—performed the statistical analyses and drafted the tables. OY and TB—involved in data collection, literature review. All authors contributed to editorial changes, read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Turkish Ministry of Health and The Ethics Committee of İzmir Katip Çelebi University, Atatürk Training and Research Hospital approved the study (Ethics Approval Number: 0040, Date: 22 February 2022). Written informed consent was obtained from the participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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