















Incidence and Features of Acute Ischemic Stroke in Patients Hospitalized with COVID-19: A Multi-center Study in Turkey

Murat Mert ATMACA¹ , Nazlı Gamze BÜLBÜL¹ , Miruna FLORENTINA ATEŞ² , Burcu SELBEST³ , Fettah EREN⁴ , Sibel GÜLER⁵ , Uğur Burak ŞİMŞEK¹ , Mehmet Fatih YETKİN⁶ , Merve AKCAKOYUNLU⁶ , Elif Özge BİÇER⁶ , Soner KILIÇ⁸ , Nur Aleyna YETKİN⁹ , Şazimet TAŞ⁷ , Zeynep KOCAKAYA⁷ , Kevser KARASU⁷ , Ufuk YÜKSEL⁷ , Ayşegül ULU KILIÇ¹⁰ , Zeynep TÜRE YÜCE¹⁰ , Nuri TUTAR¹¹ , Burcu BARAN KETENCİOĞLU¹¹ , Kürşat GÜNDOĞAN⁷ , Şahin TEMEL⁷ , Murad Al HASAN⁶ , Şeyma BENLİ⁶ , Çağla ERÖZ⁶ , Ahmet ÖZTÜRK¹² , Füsun Ferda ERDOĞAN⁶

¹Sultan 2.Abdulhamid Khan Training and Research Hospital Neurology Clinic, Turkey

²Maltepe University, Faculty of Medicine, Department of Neurology, Turkey

³Denizli State Hospital Neurology Clinic, Turkey

⁴Selçuk University, Faculty of Medicine, Department of Neurology, Turkey

⁵Trakya University, Faculty of Medicine, Department of Neurology, Turkey

⁶Erciyes University, Faculty of Medicine, Department of Neurology, Turkey

⁷Erciyes University, Faculty of Medicine, Department of Internal Medicine, Intensive Care Unit, Turkey

⁸Kayseri City Hospital Neurology Clinic, Turkey

⁹Kayseri City Hospital Chest Diseases Clinic, Turkey

¹⁰Erciyes University, Faculty of Medicine, Department of Infectious Diseases, Turkey

¹¹Erciyes University, Faculty of Medicine Department of Chest Diseases, Turkey

¹²Erciyes University, Faculty of Medicine, Department of Biostatistics, Turkey

ABSTRACT

Introduction: Acute ischemic stroke (AIS) is a devastating complication of COVID-19 with high morbidity and mortality. In this study, we reported the frequency, characteristics, and outcome of AIS in patients with COVID-19.

Methods: This multicenter and cross-sectional study was conducted between April 2020 and February 2021. Among the hospitalized patients with COVID-19, the detailed characteristics of those with and without AIS were recorded and compared.

Results: Six hundred ninety-three patients were included in the study. Acute ischemic stroke was detected in 16 (2.31%) patients, the median age was 77 (range, 48–91) years, and 10 (62.5%) were female. The median NIHSS score at admission was 9 (range, 3–17). Total anterior circulation infarction (TACI) was the most common (37.5%) type and cardioembolism was the most common etiology (37.5%). Nine patients

(56.25%) developed AIS within 24 hours of having COVID-19. COVID-19 severity was severe or critical in seven patients (43.75%). Eight patients died, and eight were discharged. Patients with AIS had a higher rate of hypertension, coronary artery disease, heart failure, a history of myocardial infarction, a history of cerebrovascular disease, severe and critical COVID-19, a higher mean age, and a longer ICU stay compared with those without AIS ($p < 0.001$ for each).

Conclusions: AIS can occur in patients with COVID-19 and is associated with mortality. Acute ischemic stroke is encountered at any stage of COVID-19, especially within the first 72 hours of the diagnosis, in older patients with comorbidities and severe COVID-19. There is an increased risk of AIS in patients with COVID-19 with a history of stroke.

Keywords: Acute ischemic stroke, COVID-19, incidence, mortality, outcome, stroke

Cite this article as: Atmaca MM, Bülbül NG, Florentina Ateş M, Selbest B, Eren F, Güler S et al. Incidence and Features of Acute Ischemic Stroke in Patients Hospitalized with COVID-19: A Multi-center Study in Turkey. Arch Neuropsychiatry 2024; 61:241–247.

INTRODUCTION

Corona virus disease 2019 (COVID-19) has affected millions of people worldwide. Although it predominantly affects the respiratory system, it has been understood that COVID-19 is a multisystem inflammatory disease with effects on the neurological system (1). Ischemic stroke is an uncommon complication of COVID-19 that may cause serious morbidity and mortality. It has been shown that stroke survivors among patients with COVID-19 have greater disease severity, older age, and more vascular comorbidities compared with patients without stroke (2). In addition, it has also been observed that patients with ischemic stroke who are positive for COVID-19 are younger, have less vascular

risk factors, higher rates of large vessel occlusion, more multi-territory infarcts, and more cryptogenic stroke etiology compared with patients with COVID-19 without ischemic stroke, and that the risk of thrombotic events, including stroke, is 7.6 times higher in COVID-19 than in influenza (3). This suggests that at least in a proportion of patients, COVID-19 is a risk factor or trigger for stroke (2).

In this multicenter study, we planned to examine the frequency of acute ischemic stroke (AIS), the characteristics and outcome of AIS in patients with COVID-19 followed in wards and intensive care units (ICUs), and compare patients with COVID-19 with and without AIS.

Correspondence Address: Murat Mert Atmaca, Selimiye Mahallesi, Tıbbiye Caddesi, 34668, Üsküdar, İstanbul, Türkiye • E-mail: drmuratmertatmaca@hotmail.com

Received: 09.05.2023, **Accepted:** 03.07.2023, **Available Online Date:** 24.07.2024

©Copyright 2023 by Turkish Association of Neuropsychiatry - Available online at www.noropsikiyatriarsivi.com

Highlights

- The incidence of acute ischemic stroke (AIS) in patients with COVID-19 was 2.31%.
- In 69% of patients, AIS was diagnosed within the first 72 hours of COVID-19 diagnosis.
- There was an increased risk of AIS in patients with COVID-19 with a history of stroke.
- AIS rate was high in older patients with severe COVID-19 and comorbidities.
- The prognosis was mortal in 50% of patients with COVID-19 and AIS.

METHODS

The research was designed as a multicenter, cross-sectional study. Erciyes University Clinical Research Ethics Committee approval (Date: 20.05.2020, decision number: 2020/229) was obtained for the study, which was conducted with the participation of seven centers from various regions of Türkiye. During the first and second waves of the pandemic, between April 2020 and February 2021, patients aged 18 years and over, diagnosed with COVID-19 with positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) in nasopharyngeal swab and/or the presence of typical thoracic computed tomography (CT) findings, and admitted to the ward or ICU, were included.

This multicenter study was prospectively designed to record pathologies in patients with a diagnosis of COVID-19 who were followed on wards and in ICUs. A data form including the parameters of sociodemographic data, systemic comorbidities, and laboratory results related to COVID-19, headache, dizziness, cranial nerve involvement (such as hearing loss, loss of smell and taste), muscle-joint pain, neuropathic pain, psychosocial impairment, epileptic seizures, and acute ischemic stroke was completed for all patients. All centers participating in the study served as pandemic hospitals during the study. In other words, only patients with COVID-19 were hospitalized and followed up in all wards and ICUs in the participating hospitals. Infectious disease specialists, chest disease specialists, and intensive care specialists decided on the hospitalization of patients admitted to the emergency department in a ward or the ICU. Neurology consultation was requested when symptoms suggestive of stroke developed in inpatients. In six of the seven centers participating in the study, neurologists made data entries in the COVID-19 ICUs and wards where they worked. In one center, in addition to neurologists, chest diseases, infectious diseases, and internal medicine intensive care specialists made data entries in the COVID-19 ICUs and wards, under the supervision of neurologists. Acute ischemic stroke (AIS) data in the database created for this study were used. First, all patients diagnosed as having AIS were checked by one of the authors (MMA), neurologists at the centers reporting the patients were interviewed to confirm whether the patients were correctly diagnosed as having AIS (two patients initially diagnosed as having AIS were found not to have AIS and they were excluded), missing data were completed, and data that were not in the data form at baseline (mRS score at discharge and time elapsed between the diagnoses of AIS and COVID-19) were completed by interviewing the neurologists in the centers.

Sociodemographic data, comorbid diseases, clinical and laboratory data, and outcomes of the patients were recorded. Age, sex, comorbid diseases, initial National Institutes of Health Stroke Scale (NIHSS) scores, stroke syndromes according to the Oxfordshire Community Stroke Project

(OCSP) classification, etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, outcomes at discharge, duration between stroke and COVID-19 diagnosis, COVID-19 disease severity, and ICU length of stay of the patients with AIS were recorded. Comparisons were made in terms of demographic and clinical characteristics between patients with COVID-19 with and without AIS.

Ischemic stroke was defined as a sudden onset of focal neurologic signs originating in the brain or retina, lasting longer than 24 hours or resulting in death, and was confirmed by neuroimaging showing the infarction in the relevant vascular region and the absence of other obvious cause (4). Stroke severity at admission was graded using the NIHSS (5). The etiology of stroke was classified according to the TOAST criteria (6) and the stroke outcome at discharge was scored using the modified Rankin scale (mRS) (7). Stroke localization was classified according to the OCSP classification as total anterior circulation infarction (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), and lacunar cerebral infarct (LACI)(8).

According to the clinical classification of the World Health Organization, the disease severity of COVID-19 was divided into four groups. In mild disease, symptoms such as fever, cough, sore throat, headache, and weakness are found. In moderate disease, respiratory tract infection symptoms (dyspnea, tachypnea, chest pain) are present but SpO₂ is in the range of 90–94%. In severe disease, the respiratory rate is higher than 30/minute, SpO₂ <90%, PaO₂/FiO₂ <300 mm Hg, or consolidation areas cover more than 50% of the lungs. Acute respiratory distress syndrome (ARDS), septic shock, and/or multi-organ failure are seen in critical illness (9).

Statistical Analysis

The distribution of the data in the study was evaluated using the Shapiro-Wilk test, histograms, and q-q plots. When comparisons between two groups did not provide parametric assumptions for quantitative variables, the Mann-Whitney U test was used. Relationships between categorical variables were evaluated using Chi-square analysis. The statistical significance level was accepted as p<0.05. Statistical analyses were performed using the TURCOSA (Turcosa Analytics Ltd Co, Türkiye, www.turcosa.com.tr) statistical software.

RESULTS

A total of 693 patients who were hospitalized for COVID-19 between April 2020 and February 2021 in 7 centers in Türkiye were included in the study. Acute ischemic stroke was detected in 16 (2.3%) patients. The median age of patients with AIS was 77 (range, 48–91) years. Ten patients (62.5%) were female. Except for two patients, the patients had at least one comorbid disease. The median NIHSS score at admission was 9 (range, 3–17) (one patient's NIHSS score at admission could not be found). According to the OCSP classification, LACI was detected in four (25%) patients, POCI in three (18.75%) patients, PACI in three (18.75%) patients, and TACI in six (37.5%) patients. According to the TOAST classification, cardioembolism was found in six (37.5%) patients, stroke of undetermined etiology in four (25%) patients, small vessel occlusion in four (25%) patients, and large artery atherosclerosis in two (12.5%) patients. Nine (56.25%) patients developed AIS within 24 hours of having COVID-19, and one patient was diagnosed as having COVID-19 three days after the diagnosis of AIS.

COVID-19 severity was moderate in eight (50%) patients and severe or critical in seven (43.75%) patients. The median ICU length of stay of patients with AIS was 8.5 (range, 0–31) days. Eight patients (50%) died, and eight patients were discharged. The median discharge mRS score of the discharged patients was 1 (0–5). The characteristics of the patients with AIS are given in Table 1.

Table 1. Characteristics of patients with COVID-19 who had acute ischemic stroke

Patient no.	Sex	Age	Comorbid diseases	NIHSS score at admission	OCSF classification	TOAST classification	Outcome	mRS score at discharge	Time from diagnosis of COVID-19 to stroke	COVID-19 disease severity	Hospitalization in intensive care unit (days)
1	M	76	HT, COPD	6	POCI	Cardioembolism	Exitus	6	Simultaneous	Moderate	3
2	F	90	HT	12	LACI	Small vessel occlusion	Discharged	5	Stroke 3 days before COVID-19 diagnosis	Moderate	16
3	F	74	HF	17	TACI	Cardioembolism	Discharged	4	3 days	Severe	10
4	F	68	HT, CAD		LACI	Small vessel occlusion	Discharged	2		Moderate	3
5	F	83	HT, DM, HF	3	PACI	Cardioembolism	Exitus	6	1 day	Critical	7
6	M	89	HT, DM	3	POCI	Stroke of undetermined etiology	Discharged	0	1 day	Mild	1
7	M	77	HT	12	TACI	Stroke of undetermined etiology	Exitus	6	1 day	Critical	10
8	F	89	HT, CAD	9	TACI	Cardioembolism	Exitus	6	Simultaneous	Moderate	31
9	F	89	CRF	11	TACI	Stroke of undetermined etiology	Exitus	6	Simultaneous	Severe	8
10	F	91	HT, DM	16	TACI	Stroke of undetermined etiology	Exitus	6	2 days	Moderate	12
11	M	77	CAD, HF	12	PACI	Cardioembolism	Exitus	6	Simultaneous	Severe	9
12	M	62	None	8	LACI	Small vessel occlusion	Discharged	1	1 day	Severe	10
13	M	48	None	5	POCI	Large artery atherosclerosis	Discharged	1	10 days	Moderate	0
14	F	54	HT, HF	15	TACI	Large artery atherosclerosis	Exitus	6	Simultaneous	Severe	18
15	F	68	HT	4	LACI	Small vessel occlusion	Discharged	4	8 days	Moderate	0
16	F	83	HT, DM	4	PACI	Cardioembolism	Discharged	1	6 days	Moderate	0

CAD: Coronary artery disease; CRF: Chronic renal failure; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; F: Female; HF: Heart failure; HT: Hypertension; LACI: Lacunar cerebral infarct; M: Male; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OCSF: Oxfordshire Community Stroke Project; PACI: Partial anterior circulation infarct; POCI: Posterior circulation infarct; TACI: Total anterior circulation infarct; TOAST: Trial of Org 10172 in Acute Stroke Treatment

Patients with COVID-19 who had AIS had significantly higher rates of hypertension (HT), coronary artery disease (CAD), heart failure (HF), a history of myocardial infarction (MI), and a history of cerebrovascular disease (CVD) compared with patients without AIS ($p < 0.001$ for all). There was no difference between the two groups in terms of the frequency of peripheral vascular disease and diabetes mellitus (DM). There was no difference between the two groups in terms of sex. The rates of severe and critical COVID-19 and rates of mortality were higher in patients with AIS compared with those without AIS ($p < 0.001$) (Table 2). In addition, patients with AIS had higher mean age, longer ICU stay, lower Glasgow Coma Scale (GCS) scores at follow-up, and a higher comorbidity index ($p < 0.001$ for all) (Table 3).

DISCUSSION

According to the data from this multicenter study, the incidence of AIS was 2.3%. Total anterior circulation infarction was the most common stroke type (37.5%), and cardioembolism (37.5%) was the most common etiology. Of the patients, 56.2% developed AIS within 24 hours of having COVID-19, and 43.7% had severe or critical COVID-19. Half of the patients with AIS died. Compared with the patients without AIS, the rates of HT, CAD, HF, history of MI, and history of CVD were found to be higher in patients with AIS. Patients with AIS were older, had longer ICU stays, higher rates of severe or critical COVID-19 disease, and higher mortality rates than patients without AIS.

Table 2. Comparison of categorical variables of patients diagnosed with COVID-19 with and without acute ischemic stroke

Variables	COVID-19-associated acute cerebrovascular disease		p
	No n (%)	Yes n (%)	
Peripheral vascular disease			
No	672 (99.5)	16 (2.4)	0.789
Yes	3 (0.5)	0 (0.0)	
History of stroke			
No	611 (90.5)	3 (18.75)	<0.001
Yes	64 (9.5)	13 (81.25)	
Congestive heart failure			
No	666 (98.7)	13 (81.25)	<0.001
Yes	9 (1.3)	3 (18.75)	
History of myocardial infarction			
No	648 (96)	10 (62.5)	<0.001
Yes	27 (4)	6 (37.5)	
Hypertension			
No	546 (80.9)	6 (37.5)	<0.001
Yes	129 (19.1)	10 (62.5)	
Coronary artery disease			
No	632 (93.6)	10 (62.5)	<0.001
Yes	43 (6.4)	6 (37.5)	
Diabetes mellitus			
No	581 (96.1)	12 (75)	0.264
Yes	94 (13.9)	4 (25)	
COVID-19 clinical classification			
Mild	326 (48.5)	1 (6.3)	<0.001
Moderate	317 (47.2)	8 (50)	
Severe	24 (3.6)	5 (31.3)	
Critical	5 (0.7)	2 (12.5)	
Outcome			
Discharged	556 (82.4)	8 (50)	<0.001
Exitus	9 (1.3)	8 (50)	
Incomplete*	110 (16.3)	0	
Sex			
Female	265 (39.3)	10 (62.5)	0.061
Male	410 (60.7)	6 (37.5)	

* "Continuing hospitalization in the ward or intensive care unit" was noted in the outcome section of the records of 110 patients due to cross-sectional design of the study

Table 3. Comparison of numerical variables of patients with COVID-19 with and without acute ischemic stroke

Variables	COVID-19 associated acute cerebrovascular disease		p
	(No) median (min-max)	(Yes) median (min-max)	
Age	40 (18-90)	77 (48-91)	<0.001
Number of days of hospitalization in the intensive care unit	0 (0-60)	8.5 (0-31)	<0.001
Lowest Glasgow Coma Scale score in the follow-up	15 (3-15)	8 (3-15)	<0.001
Charlson comorbidity index	1 (0-9)	6 (2-10)	<0.001

The incidence of stroke in the normal population varies between 0.6% and 0.8% (10). In large case series including patients with COVID-19, the incidence of stroke has been reported as 1–6% (11) and 1–2% in meta-analyses, and the incidence of ischemic stroke was found to be significantly higher in studies where ischemic and hemorrhagic strokes were reported together (2,12–15). There are also differences between continents in terms of the incidence of AIS in patients with COVID-19.

The incidence of AIS was 3.1% in Asia, 1.2% in Europe, and 1.1% in North America (2). Our incidence rate was between those of Asia and Europe and North America. For the remainder of the discussion, we use the term "stroke" when referring to studies that evaluated ischemic and hemorrhagic stroke together, and the term "AIS" when referring to studies that only mentioned AIS.

Thirteen (81.25%) of our patients were aged over 65 years and the median age was 77 years. In the literature, the median age of patients with COVID-19 and stroke was reported as 65–67 years (2,12,16). In one study, the mean age and standard deviation of the patients with COVID-19 without stroke was 57.8 ± 15.6 , whereas it was reported as 74.2 ± 10.6 years in patients with stroke (17). Our study has one of the oldest stroke groups in the literature. In many case series and meta-analyses, advanced age was found to be a risk factor for the development of acute stroke in patients with COVID-19. (2,12,17,18)

Of the 16 patients with AIS, 13 had a history of neurologic disease, and 10 (62.5%) of these patients had a previous stroke. The rate of previous stroke varied between 10–28% in patients with COVID-19 with stroke in the literature (12,18,19). In a case series, the rate of previous stroke was found as 42.9% in patients with COVID-19 with acute stroke, significantly higher than in those with COVID-19 without acute stroke (16). The stroke group in our study has the highest previous stroke rate in the literature. The results of a study conducted on a large COVID-19 database suggested that patients with a history of stroke had more severe COVID-19 because they were older and had more comorbidities than those without a history of stroke; however, it was shown after propensity matching that a history of stroke was not an independent risk factor for intubation and death (20).

The relationship between sex, COVID-19 severity, vascular comorbidities, and the development of stroke in patients with COVID-19 has been investigated in multicenter studies and meta-analyses. In patients with COVID-19, acute stroke was found to be associated with HT (2,13,14,17), DM (2,13,14), male sex (14,17), advanced age (17,18), severe COVID-19 (2,15,16), CAD (2), and smoking (13). It is concluded that stroke is more common in older patients with COVID-19 who have more vascular comorbidities. In addition, there are studies in which no relationship was found between sex and stroke (2,16,18), and no relationship was found between vascular comorbidities and stroke (16,18). Studies that found male sex to be associated with stroke suggested that a different innate immunity, steroid hormones and factors related to sex chromosomes, which played a role in susceptibility to coronavirus infection, might cause a worse clinical course of COVID-19 in men than in women, as well as cause extrapulmonary complications such as stroke to occur more frequently in men (21). In our study, there was a relationship between previous MI, HF, HT, CAD, COVID-19 severity, and the development of AIS, but no relationship was found between DM and sex and the development of AIS. The patients in our AIS group, except for two patients, had at least one comorbid disease and therefore the comorbidity index was significantly higher than in the group without AIS.

In the literature, the mortality and morbidity of patients with COVID-19 with stroke were higher compared to those without stroke. Reported mortality rates ranged from 30% to 84% in critically ill patients (2,12,18). In a meta-analysis, 31.5% of patients died in hospital, 19.1% were discharged home, and 25.7% were discharged to a rehabilitation center (2). It was shown that the mortality rate of patients with COVID-19 with AIS was 2–3 times higher than in patients with COVID-19 without AIS (12,17,18). In our study, the mortality rate in patients with COVID-19 with AIS was 50%, and the median discharge mRS score of the discharged patients was 1 (range, 0–5). The overall mortality rate in our study was 2.45%. Approximately one-sixth of the patients were still hospitalized in the ward or ICU in the presented cohort, at the time of data censoring and this led to a low mortality rate in our study, due to the cross-sectional nature of our study.

It was reported that mortality and morbidity rates were higher in patients with AIS with COVID-19 than in patients with AIS without COVID-19 (2,22–24). In a study, the mortality rate, which was found to be higher

in patients with AIS with COVID-19 than in patients with AIS without COVID-19, lost its significance after propensity score adjustment, and the authors concluded that COVID-19 itself had an impact on mortality (25). It was also shown that the severity of stroke in patients with AIS with COVID-19 was higher than in patients with AIS without COVID-19 (22,24). This result may be caused by hospitals' reluctance to admit patients with mild AIS due to the pandemic or that mild strokes were overlooked in pandemic wards and ICUs. In our study, no comparison was made with a group with AIS without COVID-19, but it was remarkable that the mortality rate was 50% in the group with COVID-19 with AIS. The median NIHSS score at the admission of patients with COVID-19 with AIS was 9 (range, 3–17) in our study, suggesting that patients with COVID-19 with AIS generally had AIS of moderate severity.

In our study, patients with COVID-19 with AIS had a longer ICU stay and a lower GCS score at follow-up compared with those with COVID-19 without AIS. These findings were consistent with the higher mortality rate and greater disease severity in patients with COVID-19 and AIS. In a study, it was shown that COVID-19 was more severe in patients with AIS. This relationship did not change when the severity of COVID-19 was defined by both clinical parameters and ICU needs (15). In another study, the rate of confusion was 36% in patients with stroke; this rate was reported as 2% in patients with non-stroke COVID-19 (17).

The time from onset of COVID-19 symptoms to stroke was reported as 10 ± 8 days, (26) 8 days (12), and 2 weeks (18) in various studies. This time was highly variable. There were reports of patients who developed a stroke within 48 hours of the onset of symptoms of COVID-19 (27), or even patients who presented with stroke without symptoms of COVID-19 and were subsequently diagnosed as having COVID-19 through PCR (2). One to 2 weeks between symptoms of COVID-19 and the development of AIS supports the existence of a prothrombotic phase complicated by arterial and venous thromboembolism following early hyperinflammation caused by cytokine storm in severe COVID-19 infection, (28) but the explanation for concurrent or simultaneous COVID-19 symptoms and stroke symptoms is unclear. Another study showed that the incidence of AIS was ≈ 10 -fold higher for 14 days after the diagnosis of COVID-19, and it remained statistically significantly higher when the risk interval was extended to 21 and 31 days after the diagnosis of COVID-19 (29). In our study, nine (56.25%) patients developed AIS within 24 hours of the diagnosis of COVID-19, and one patient was diagnosed as having COVID-19 3 days after the diagnosis of AIS. Patients with mild COVID-19 symptoms may not go to the hospital and patients with COVID-19 symptoms might go to the hospital when stroke symptoms occur, thus leading to the finding of 24–48 hours between the diagnosis of COVID-19 and stroke in some studies (27), as in our study. We conclude that AIS can occur at any stage of SARS-CoV-2 infections.

In many studies, stroke of undetermined etiology was reported at rates of up to 55% and was higher in patients with AIS with COVID-19 compared with patients with AIS without COVID-19 (22,30). In one study, it was found that cardioembolic stroke due to AF was the most common etiology in patients with AIS with COVID-19. This was explained by the fact that COVID-19 facilitated thromboembolism in patients with AF or might trigger AF in patients without AF (24). In another study, a lower rate of cryptogenic stroke was detected in patients with AIS with COVID-19 than in patients with AIS without COVID-19. The authors explained this situation through the high completion rate of etiologic investigations in their study and the increase in the rate of defined rare stroke mechanisms, including coagulation disorder and vasculitis, which might be caused by COVID-19 (25). In our study, cardioembolism (37.5%) was the most common etiology while the least detected etiology was large artery atherosclerosis (12.5%), and other etiologic subtypes were found at rates similar to each other.

In the literature, it has been shown that AIS develops in the carotid territory in patients with COVID-19 (22,27). In a study comparing COVID-19-negative and positive patients with AIS, there was no difference in terms of stroke localization (23). By contrast, in another study, infarcts in the temporal, parietal, occipital, and cerebellar regions were found more frequently in patients who were COVID-19 positive (30). Generally, studies showed that large vessel occlusion was more common in patients with AIS with COVID-19 than in patients with AIS without COVID-19 (2). However, a study also found a higher incidence of large vessel occlusion in a COVID-19-negative group, and the authors explained this with a higher rate of distal vessel occlusion in the COVID-19-positive group, possibly due to a microangiopathic involvement (23). In some studies, it was shown that multi-territory infarct was more common in patients with AIS with COVID-19 than in patients with AIS without COVID-19 (2,25). More frequent large vessel occlusion and multi-territory infarction in patients with AIS with COVID-19 suggest that cerebral thrombosis and/or thromboembolism are the main mechanisms leading to stroke (2). In accordance with the literature, in our study, TACI was found to be the most common type (37.5%), suggesting that cardioembolism was common in patients with AIS and COVID-19.

One of the limitations of our study is the cross-sectional design, causing incomplete outcome information for approximately one-sixth of the patients, leading to a low total mortality rate. Another limitation was that the diagnosis of AIS may have been missed by non-neurologists in severely intubated and sedated patients hospitalized in ICUs and in patients with minor symptoms hospitalized in COVID-19 wards, although the data were collected by neurologists in most of the centers. The strengths of the study were that it was a multicenter study, the number of patients was high, and it represented a large population of Türkiye.

In conclusion, although AIS is not common in patients with COVID-19, it can occur and should be treated appropriately because the mortality rates are high. We may encounter AIS at any stage of the disease in older patients with comorbidities and severe COVID-19. Physicians should be vigilant for the development of new strokes in patients with COVID-19, especially in those with a history of stroke.

Ethics Committee Approval: Erciyes University Clinical Research Ethics Committee approval (Date: 20.05.2020, decision number: 2020/229) was obtained for the study.

Informed Consent: Informed consent was obtained from the patients unless they had impaired consciousness or aphasia. In the presence of these conditions, informed consent was obtained from the first-degree relatives of the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- FFE, KG, ŞT, AUK, ZTY, NT; Design- FFE, KG, ŞT, AUK, ZTY, NT, AÖ; Supervision- FFE, KG, ŞT, AUK, ZTY, NT, MMA, NGB, MFA, BS, FE, SG, SK; Resource- FFE, KG, ŞT, AUK, ZTY, NT; Materials- ŞT, ZK, KK, UY, MFA, BS, FE, SG, UBS, MFY, MA, EÖB, SK, BBK, MAH, ŞB, ÇE; Data Collection and/or Processing- ŞT, ZK, KK, UY, MMA, NGB, MFA, BS, FE, SG, UBS, MFY, MA, EÖB, SK, BBK, MAH, ŞB, ÇE; Analysis and/or Interpretation- FFE, KG, ŞT, AUK, ZTY, NT, AÖ, MMA; Literature Search- MMA, FFE; Writing- MMA, FFE; Critical Reviews- FFE, KG, ŞT, AUK, ZTY, NT, AÖ.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: None

REFERENCES

- Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg*. 2020;194:105921. [Crossref]
- Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke*. 2021;16(2):137–149. [Crossref]
- Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with coronavirus disease 2019(COVID-19) vs patients with influenza. *JAMA Neurol*. 2020;77(11):1–7. [Crossref]
- Lansky AJ, Messe SR, Brickman AM, Dwyer M, van der Worp HB, Lazar RM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium Initiative. *J Am Coll Cardiol*. 2017;69(6):679–691. [Crossref]
- Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864–870. [Crossref]
- Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35–41. [Crossref]
- Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J*. 1957;2(5):200–215. [Crossref]
- Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337(8756):1521–1526. [Crossref]
- Living guidance for clinical management of COVID-19: living guidance N. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics –2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146–e603. [Crossref]
- Fifi JT, Mocco J. COVID-19 related stroke in young individuals. *Lancet Neurol*. 2020;19(9):713–715. [Crossref]
- Yamakawa M, Kuno T, Mikami T, Takagi H, Gronseth G. Clinical characteristics of stroke with COVID-19: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2020;29(12):105288. [Crossref]
- Cho SM, Premraj L, Fanning J, Huth S, Barnett A, Whitman G, et al. Ischemic and hemorrhagic stroke among critically ill patients with coronavirus disease 2019: an international multicenter coronavirus disease 2019 Critical Care Consortium study. *Crit Care Med*. 2021;49(12):e1223–e1233. [Crossref]
- Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. *J Neurol*. 2022;269(4):1731–1740. [Crossref]
- Lu Y, Zhao JJ, Ye MF, Li HM, Yao FR, Kong Y, et al. The relationship between COVID-19's severity and ischemic stroke: a systematic review and meta-analysis. *Neurol Sci*. 2021;42(7):2645–2651. [Crossref]
- Siepmann T, Sedghi A, Simon E, Winzer S, Barlind J, de With K, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. *Eur J Neurol*. 2021;28(1):238–247. [Crossref]
- Yao X, Liu S, Wang J, Zhao K, Long X, He X, et al. The clinical characteristics and prognosis of COVID-19 patients with cerebral stroke: a retrospective study of 113 cases from one single-centre. *Eur J Neurosci*. 2021;53(4):1350–1361. [Crossref]
- Sluis WM, Linschoten M, Buijs JE, Biesbroek JM, den Hertog HM, Ribbers T, et al. Risk, clinical course, and outcome of ischemic stroke in patients hospitalized with COVID-19: a multicenter cohort study. *Stroke*. 2021;52(12):3978–3986. [Crossref]
- Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute cerebrovascular events in hospitalized COVID-19 patients. *Stroke*. 2020;51(9):e219–e222. [Crossref]
- Nalleballe K, Siddamreddy S, Sheng S, Dandu V, Arulprakash N, Kovvuru S, et al. Coronavirus disease 2019 in patients with prior ischemic stroke. *Cureus*. 2020;12(9):e10231. [Crossref]
- Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents*. 2020;34(2):339–343.
- Mathew T, John SK, Sarma G, Nadig R, Kumar RS, Murgod U, et al. COVID-19-related strokes are associated with increased mortality and morbidity: a multicenter comparative study from Bengaluru, South India. *Int J Stroke*. 2021;16(4):429–436. [Crossref]
- Naval-Baudin P, Rodriguez Caamano I, Rubio-Maicas C, Pons-Escoda A, Fernandez Vinas MM, Nunez A, et al. COVID-19 and ischemic stroke: clinical and neuroimaging findings. *J Neuroimaging*. 2021;31(1):62–66. [Crossref]
- Pezzini A, Grassi M, Silvestrelli G, Locatelli M, Rifino N, Beretta S, et al. SARS-CoV-2 infection and acute ischemic stroke in Lombardy, Italy. *J Neurol*. 2022;269(1):1–11. [Crossref]
- Strambo D, De Marchis GM, Bonati LH, Arnold M, Carrera E, Galletta S, et al. Ischemic stroke in COVID-19 patients: mechanisms, treatment, and outcomes in a consecutive Swiss Stroke Registry analysis. *Eur J Neurol*. 2022;29(3):732–743. [Crossref]

26. Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis*. 2020;50(3):587–595. [\[Crossref\]](#)
27. Sundar U, Karnik ND, Mukhopadhyay A, Darole P, Kolte S, Bansal A, et al. COVID-19 associated stroke-a single centre experience. *J Assoc Physicians India*. 2021;69(6):11–12. [\[Crossref\]](#)
28. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094–1099. [\[Crossref\]](#)
29. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, et al. Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation*. 2020;142(21):2080–2082. [\[Crossref\]](#)
30. Dharmoon MS, Thaler A, Gururangan K, Kohli A, Sisniega D, Wheelwright D, et al. Acute cerebrovascular events with COVID-19 infection. *Stroke*. 2021;52(1):48–56. [\[Crossref\]](#)