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Original Research

Comparison of Clinical Characteristics of COVID-19-Related and Unrelated Acute Stroke Patients During the COVID-19 Pandemic in Turkey

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Abstract

Objectives: Data on the co-occurrence of stroke and coronavirus disease 2019 (COVID-19) infection are limited and need to be improved. In our study, we aimed to evaluate the clinical and laboratory characteristics of COVID-19-related patients admitted to our center with acute stroke and compare them with acute stroke patients without COVID-19 infection during the same period.

Methods: One hundred and eighty-four patients admitted with acute stroke from March 11, 2020, to May 11, 2020, were included in the study. Demographic and clinical characteristics, work-up studies, and clinical scales including National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS) scores were examined retrospectively. All patients diagnosed with acute stroke who were also evaluated for COVID-19 before hospitalization were divided into two groups: COVID-19-related and unrelated cases.

Results: COVID-19-related and unrelated acute stroke patients had similar characteristics in terms of age, gender, and stroke risk factors. The admission NIHSS (mean NIHSS: 9.8 vs. 5.9) scores and the discharge mRS values (mean mRS: 3.9 vs. 2.4) were significantly higher in the COVID-19-related stroke group (p=0.002 and p=0.001, respectively). The prognosis of the COVID-19-related stroke group was significantly worse (69.6% vs. 39.8%) and the mortality rate (39.1% vs. 6.2%) was significantly higher than the COVID-19-unrelated stroke group (p=0.007 vs. p=0.000, respectively). The proportion of patients with large infarcts in the COVID-19-related acute ischemic stroke group was significantly higher than the one in the COVID-19-unrelated acute ischemic stroke group (57.9% vs. 21.9%, p=0.003).

Conclusion: This is the first comparative study to evaluate the clinical presentation and outcome of COVID-19-related acute ischemic and hemorrhagic stroke patients in Turkey. Our results suggest that COVID-19-related acute stroke is associated with more severe clinical presentation and worse outcome. This seems to be linked to the coagulation abnormalities induced by COVID-19 infection.

Keywords: Acute stroke, Coronavirus, COVID-19

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, and it was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, the date of the first case in our country. In the COVID-19 pandemic, the increased frequency of neurological involvement draws attention in addition to respiratory distress in patients. Even in some patients, neurological symptoms can be seen without signs of infection. [1] Numerous neurological manifestations associated with

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COVID-19 have been reported. Acute cerebrovascular diseases (CVDs), impaired consciousness, and neuromuscular involvement seem to be more common, especially in patients with severe infection.[1,2]

Current observational studies suggest an association between COVID-19 and acute stroke. However, studies revealing the characteristics of COVID-19-related acute stroke patients are limited in the literature, and there is no study on this issue in our country yet. We aimed to compare the clinical and laboratory characteristics of COVID-19-related and unrelated acute stroke patients who were admitted in the same period to our pandemic hospital including Stroke Center.

Methods

We performed a retrospective review of acute stroke patients who were admitted to our center from March 11, 2020, to May 11, 2020, during the height of the pandemic in Turkey. The demographic characteristics, stroke risk factors, diagnostic and etiological workup for acute stroke as well as COVID-19 were obtained from the patients' medical records.

Stroke Evaluation

Cranial computed tomography (CT)/magnetic resonance imaging (MRI), transthoracic echocardiography were evaluated for diagnostic and etiological workup. Hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atrial fibrillation (AF), ischemic heart disease (IHD), congestive heart failure (CHF), peripheral artery disease, a history of CVD, smoking and alcohol use were recorded as stroke risk factors. Pre-stroke prophylactic drug (antiaggregants, anticoagulants) use was also noted. Ischemic stroke etiology was determined according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. Stroke severity was measured by National Institutes of Health Stroke Scale (NIHSS) score. Stroke prognosis was assessed by using discharge modified Rankin scale (mRS) score (0-2 good prognosis; 3-6 poor prognosis). The infarct size was considered to be small if the longest diameter was ≤15 mm, large if more than one-third of the territory of the anterior, middle and posterior cerebral arteries or cerebellum, and the rest were considered to be medium in size.

COVID-19 Evaluation

All acute stroke patients underwent COVID-19 evaluation including thorax CT, nasopharyngeal swab polymerase chain reaction (PCR) sampling, hemogram, routine biochemistry, coagulation tests, and PaO2/FiO2 ratio. Compatible with the case definition of WHO, the diagnosis of COVID-19 patients in our study was established according to the presence of one of the following:[3]

1. Patients with positive nasopharyngeal swab PCR sample
2. Patients receiving antiviral therapy for COVID-19 because of implying medical history (respiratory symptoms, recent COVID-19 contact), and specific findings suggesting COVID-19 pneumonia on thorax CT (ground-glass opacities, multifocal irregular consolidation, and/or peripherally distributed interstitial changes).

COVID-19 severity was classified as mild, moderate, severe, and critical disease according to WHO intermediate guideline.[4]

COVID-19 Related Stroke

Patients diagnosed with acute stroke were divided into two groups as COVID-19-related and unrelated acute stroke patients. Patients evaluated as COVID-19-related stroke were determined according to the criteria determined by the WHO.[3] COVID-19 related stroke was defined as acute stroke developing within 1 month after the diagnosis of COVID-19. Patients who presented with acute stroke clinic but whose history, physical examination, and laboratory findings (oropharyngeal swab PCR and thorax CT) were not compatible with COVID-19 were considered as COVID-19-unrelated acute stroke patients.

Approval was obtained from the Ministry of Health and Şişli Hamidiye Etfal Hospital Ethics Committee for the study (Approval number: 2020/2795).

Statistical Analysis

SPSS 26.0 program was used in the analyzes. Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov Smirnov test. Kruskal-Wallis and Mann Whitney U tests were used in the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when the conditions of the chi-square test were not met. For variables, $p<0.05$ was considered statistically significant.

Results

One hundred and eighty-four patients were included in the study. Of these patients, 23 (12.5%) had COVID-19-related acute stroke, whereas 161 (87.5%) had COVID-19-unrelated acute stroke.

The mean age was 66.7±13.4 years in COVID-19-related stroke patients (13 men, 10 women) and was 68.8±13.2 years in COVID-19-unrelated stroke patients (93 men, 68 women). There was no significant difference between COVID-19-related and unrelated stroke patients in terms

of gender and mean age (p>0.05) (Table 1). Risk factors for stroke including HT, HL, DM, IHD, CHF, PAH, a history of CVD, AF, and pre-stroke prophylactic drug use rates were similar in both groups (p>0.05).

Admission NIHSS scores and discharge mRS values were significantly higher in the COVID-19-related stroke group than in the COVID-19-unrelated stroke group (mean NIHSS: 9.8 vs. 5.9, respectively; mean mRS: 3.9 vs. 2.4; p=0.002 and p=0.001; t-test). The prognosis of the COVID-19-related stroke group was significantly worse (69.6% vs. 39.8%) and the mortality rate (39.1% vs. 6.2%) was significantly higher than the COVID-19-unrelated stroke group (p=0.007 vs. p=0.000, respectively, Chi-square test) (Table 1 and Fig. 1).

In 43% (10/23) of patients with COVID-19-related stroke, acute stroke were the main clinical manifestation for admission to the hospital. In the remaining 13 patients (57%), the mean time from COVID-19 infection symptoms to the onset of stroke was 6.2 (1–30) days. Six (26%) of the patients had a critical COVID-19 clinic. During the follow-up, 9 (39.1%) patients died. Of COVID-19-related acute stroke patients, 19 (82.6%) had acute ischemic stroke, whereas 4 (17.4%) had hemorrhagic stroke. No transient ischemic attack (TIA) cases were observed. Of COVID-19-unrelated acute stroke patients, 141 (87.6%) had acute ischemic stroke, 15 (9.3%) had hemorrhagic stroke, and 5 (3.1%) had TIA. There was no statistical difference between the two groups.

Acute Ischemic Stroke (COVID-19-related and Unrelated)

According to TOAST classification, of 19 patients with COVID-19-related acute ischemic stroke, 9 (47.4%) had stroke of undetermined etiology, 5 (26.3%) had cardioembolism, 4 (21.1%) had large-artery atherosclerosis, and 1 (5.3%) had the small-vessel occlusion. Of 146 patients with COVID-19-unrelated acute ischemic stroke/TIA, 66 (45.2%) had stroke of undetermined etiology, 29 (19.9%) had cardioembolism, 27 (18.5%) had small-vessel occlusion and 24 (16.4%) had large-artery atherosclerosis. Although TOAST classification of COVID-19-related and unrelated acute ischemic stroke groups showed similar characteristics, the rates of large vessel disease and cardioembolic subtype were slightly higher in patients with acute ischemic stroke related to COVID-19 (p>0.05) (Table 2).

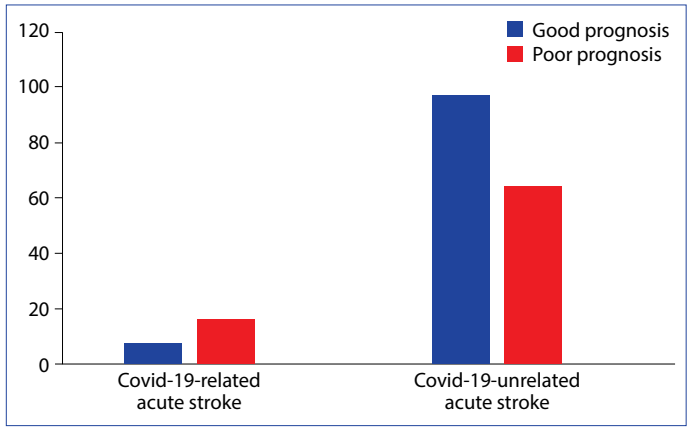

Figure 1. Comparison of COVID-19-related and unrelated strokes in terms of prognosis.

The proportion of patients with large infarct size in the COVID-19-related acute ischemic stroke group was statistically significantly higher than the COVID-19-unrelated acute ischemic stroke group (57.9% vs. 21.9% p=0.003; Chi-square test) (Table 2).

Intravenous tissue plasminogen activator (iv-tPA) was applied to three of 19 cases with COVID-19-related acute

Table 1. Comparison of COVID-19-related and unrelated stroke patients in terms of age, sex, admission NIHSS, discharge mRS, prognosis, and mortality

	COVID-19-related acute stroke n=23 mean±SD/n (%)		COVID-19-unrelated acute stroke n=161 mean±SD/n (%)		p
Age (years)	66.7±13.4		68.8±13.2		0.468
Sex, Male	13	56.5	93	57.8	1.000
Admission NIHSS score	9.8±6.5		5.9±5.2		0.002
Discharge mRS score	3.9±2.2		2.4±2.0		0.001
Prognosis					
Good (mRS 0–2)	7	30.4	97	60.2	0.007
Poor (mRS 3–6)	16	69.6	64	39.8	
Mortality	9	39.1	10	6.2	0.000

SD: Standart deviation; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin score.

Table 2. Comparison of COVID-19-related and unrelated acute ischemic stroke patients by TOAST classification and infarct size

	COVID-19-related acute stroke n=19		COVID-19-unrelated acute stroke n=146		p
	n	%	n	%	
TOAST classification					
Large-artery atherosclerosis	4	21.1	24	16.4	0.512
Cardioembolism	5	26.3	29	19.9	
Small-vessel occlusion	1	5.3	27	18.5	
Other determined etiology	0	0	0	0	
Stroke of undetermined etiology	9	47.4	66	45.2	
Infarct size					
Small	2	10.5	48	32.9	0.003
Medium	6	31.6	66	45.2	
Large	11	57.9	32	21.9	

TOAST: Trial of org 10172 in acute stroke treatment.

ischemic stroke, and mechanical thrombectomy (MT) with iv-tPA was applied to one of them. Of the 146 patients with COVID-19-unrelated acute ischemic stroke, iv-tPA was applied to 18, thrombectomy to 11, and thrombectomy with iv-tPA to 7. There was no statistically significant difference between the groups in terms of acute treatment approaches (Table 3).

Acute Hemorrhagic Stroke (COVID-19-related and Unrelated)

Hemorrhagic stroke was more common in COVID-19-related stroke group (17.4% vs. 9.3%). Of 4 COVID-19-related hemorrhagic stroke patients, three had lobar, and one had putaminal hematoma. Of 15 COVID-19-unrelated hemorrhagic stroke patients, nine had thalamic, four had putaminal, and two had lobar hematoma. This difference between two groups was statistically significant (p=0.031; Chi-square test). Diffusion-apparent diffusion coefficient MRI and thorax CT images of a COVID-19-related acute ischemic stroke patient are presented in Figure 2.

Discussion

First case of COVID-19 was reported in Turkey on March 11, 2020. In our study evaluating the first 2 months after the first case which was the height of the pandemic in Turkey, the main finding is larger infarct size, higher admission NIHHS values, higher mortality rates, and worse prognosis in COVID-19-related acute stroke patients. There is limited number of studies in the literature on COVID-19-related acute stroke, and they are mostly presented as case series. Similar to our study, the main feature of these studies is that the prognosis of acute strokes related to COVID-19 is worse.[5-11]

In a study conducted in New York, when COVID-19 positive and negative acute stroke patients were compared, it was reported that positive cases had higher admission NIHSS score (median [IQR] NIHSS score: 19 [23] vs. 8 [12], p=0.007) and a high patient mortality rate (63.6% vs. 9.3%, p<0.001).[6] In a hospital in Wuhan, 5 of 13 acute stroke with COVID-19 cases were reported to be mortal.[11] In a case series consist-

Table 3. Comparison of COVID-19-related and unrelated strokes in terms of acute treatment approaches

	COVID-related acute stroke		COVID-unrelated acute stroke		Total	
	n	%	n	%	n	%
iv-tPA	3	13.0	18	11.2	21	11.4
MT	0	0.0	11	6.8	11	6.0
iv-tPA+MT	1	4,3	7	4.3	8	4.3
None	19	82.6	125	77.6	144	78.2
Total	23	100.0	161	100.0	184	100.0

iv-tPA: Intravenous tissue plasminogen activator; MT: Mechanical thrombectomy.

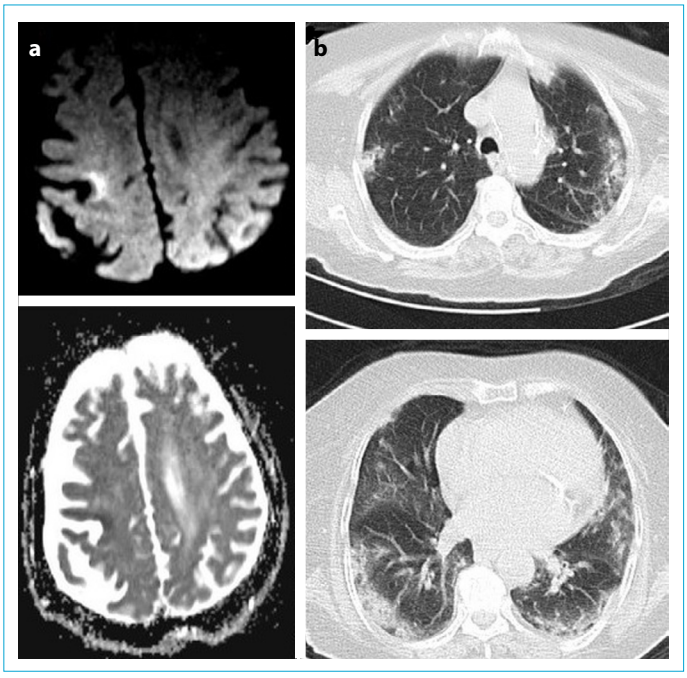

Figure 2. (a, b) Diffusion-apparent diffusion coefficient (ADC) magnetic resonance imaging (MRI) and thorax computed tomography (CT) imaging of a patient who was admitted to the emergency department with sudden onset dysarthria and left hemiparesis and diagnosed with COVID-19-related acute stroke. **(a)** Cortically located acute ischemia in the right middle cerebral artery territory area in diffusion-ADC MRI, **(b)** Multilobar, peripheral, patchy ground-glass infiltration areas in both lungs on thoracic CT imaging.

ing of 6 patients (4 with ischemic stroke and 2 with hemorrhagic stroke), it was reported that 4 (67%) of the patients were dead, 1 was followed in coma and the remaining one patient had an mRS score of 4.[10] In our study, similar to these studies, admission NIHSS scores, poor prognosis, and mortality was found with higher rates in COVID-19-related acute strokes. However, our rates (admission NIHSS score 9,8%, poor prognosis 69,6%, mortality 39,1%) were lower. This result may be due to the fact that we used acute treatment approaches (such as iv-tPA, MT) at the same rates in both groups in our center. This indicates that we should fully implement the acute stroke treatment requirements in COVID-19-related acute stroke patients. The fact that patients are infected with COVID-19 should not require neurologists to hesitate to use these treatments. In our study, the worse prognosis of COVID-19-related acute strokes and their presentation with a more severe stroke clinic can be explained by the role of infections in the pathophysiology of thrombosis.

Infections activate an activation cascade leading to cytokine production. The release of proinflammatory cytokines triggers the production and release of new cytokines, causing damage to local or distant organs. It has been shown that "Cytokine storm," which is thought to be the result of excessive or uncontrolled release of proinflammatory cytokines, may occur due to a virus, bacterial and fungal infections.[12,13] Recent studies have shown that severe COVID-19 is associated with increases in interleukin (IL)-6, IL-10, and cytokine storms may be the pathogenesis of severe COVID-19 disease.[14,15] Increased cytokines can stimulate thrombopoietin and fibrinogen production, causing ischemic stroke by promoting hypercoagulability, atherosclerosis, plaque rupture, and thrombosis.[16,17] Acute myocardial injury, which has been shown to develop in the course of COVID-19, may be associated with increasing the risk of cardioembolic stroke.[18] Another factor is the increased susceptibility to deep vein thrombosis due to stasis secondary to immobilization.

In our study, the majority of patients with acute ischemic stroke related to COVID-19 were cryptogenic subtypes with a rate of 47.4% according to the TOAST classification. Similarly, in the New York study, it was reported that the most common subtype was cryptogenic subtype (34.4%) in 32 COVID-19 patients diagnosed with acute stroke.[6] There are many risk factors for ischemic stroke, but strokes due to cryptogenic or uncertain causes, which make up about a third of all strokes, do not have these risk factors.[19] This situation makes the relationship between infections and stroke more important. Acute infection is an important risk factor for cerebral infarction, usually originating from the respiratory tract and especially in the week before stroke, even if the effects of other risk factors are taken into account.[20-22]

The risk of stroke is highest during the 1st week after diagnosis of acute infection and gradually decreases over the following weeks.[21,23] Similarly, in our study, it was observed that patients had an acute stroke on average 6.2 days after the onset of COVID-19 complaints. In the study of Li et al., the average time from COVID-19 infection to the onset of stroke was approximately 12 days, and in the study of Yaghi et al., this period was 10 (5–16.5) days.[6,11]

In our center, among 19 patients with acute ischemic stroke related with COVID-19, acute stroke treatment interventions such as iv-tPA and MT were applied to eligible cases. The principles of treatment for acute ischemic stroke did not differ in patients related to COVID-19, and the team was continued to use full personal protective equipment and comply with contact safety rules.

Knowing the factors associated with stroke and structuring the treatment plan for them is important to reduce the risk of stroke. It is recommended that anti-inflammatory and anticoagulation therapy are used to prevent thrombotic complications in COVID-19 patients.[24,25] Diagnosing in the early stages based on clinical symptoms and labo-

ratory tests and starting anti-inflammatory/anticoagulant therapy as early as possible may be one way to stop the clinical worsening of COVID-19 and reduce the risk of CVD.

Regarding hemorrhagic stroke, the results of our study are also remarkable. Although rates vary in different studies, basal ganglia are the most common localization with hemorrhagic stroke, while lobar hemorrhage is the least common.[26] In our study, in accordance with the literature, 13 basal ganglia and 2 lobar hemorrhagic strokes were detected in the group unrelated to COVID-19, while three of 4 cases in the COVID-19-related hemorrhagic stroke group were lobar; one of them was localized to the basal ganglia. In the case series of Benger et al., it was reported that lobar hemorrhage was found in 4 of 5 COVID-19 patients with hemorrhagic stroke, and the only hemorrhagic stroke detected among COVID-19-related stroke in another case series was located in the lobar.[10,27]

The main limitation of our study is the small sample size. Studies with longer follow-up and larger patient groups are needed for more precise results.

Conclusion

This is the first comparative study to evaluate the clinical presentation and outcome of COVID-19-related acute ischemic and hemorrhagic stroke patients in Turkey. Our study suggests that COVID-19-related acute stroke is associated with more severe clinical presentation and worse outcome. This seems to be linked to the coagulation abnormalities induced by COVID-19 infection. Considering the worse prognosis and higher mortality rates of COVID-19-related acute stroke patients, it is very critical for clinicians to be alert about the coexistence of COVID-19 and stroke, and not to delay the diagnosis.

Disclosures

Ethics Committee Approval: Approval was obtained from the Ministry of Health and Şişli Hamidiye Etfal Hospital Ethics Committee for the study (Approval number: 2020/2795).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.S.D., G.G.; Design – D.S.D., G.G.; Supervision – G.G., S.B.; Materials – D.S.D., C.İ.B.; Data collection &/or processing – D.S.D., C.İ.B.; Analysis and/or interpretation – G.G., S.B.; Literature search – D.S.D.; Writing – D.S.D., G.G.; Critical review –G.G., S.B.

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