Turkish Journal of Neurology

Turk J Neurol 2025;31(1):41-45
Doi: 10.55697/tnd.2025.253

ORIGINAL ARTICLE

Characteristics of ischemic stroke during the COVID-19 pandemic

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ABSTRACT

Objectives: The study aimed to evaluate the effects of coronavirus disease 2019 (COVID-19) on stroke frequency and etiological features, as well as course and severity of stroke in patients with ischemic stroke.

Patients and methods: A total of 262 patients with ischemic stroke [59 (36 males, 23 females; mean age: 66.5±12.7 years; range, 33 to 96 years) with COVID-19 infection (COVID-19 group) and 83 (57 males, 26 females; mean age: 67.3±12.9 years; range, 36 to 88 years) without COVID-19 infection (non-COVID-19 group)] during the pandemic and 120 patients (66 males, 54 females; mean age: 65.3±13.8 years; range, 39 to 92 years) with ischemic stroke before the pandemic period (pre-COVID-19 group) were evaluated retrospectively. Patients in the COVID-19 and non-COVID-19 groups were hospitalized between March 2020 and March 2021, whereas patients in the pre-COVID-19 group were hospitalized in 2019. Demographic data, clinical information, and risk factors for ischemic stroke were recorded. Detailed biochemical and cardiac evaluations, as well as cranial and vascular neuroimaging, were performed. The etiological diagnosis of stroke was decided according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification. National Institutes of Health Stroke Scale (NIHSS) scores were calculated according to the neurological examinations at admission and the neurological examinations at discharge from the hospital.

Results: Sex and age did not reveal significant differences between the three groups. The frequency of hypertension and diabetes mellitus did not reveal statistically significant differences between groups (p=0.5 and p=0.27, respectively). The frequency of hyperlipidemia was significantly higher in the COVID-19 group than in the pre-COVID-19 group (p=0.04). When etiology according to the TOAST classification was compared between the three groups, small vessel disease was detected significantly less frequently in the COVID-19 group than in the other two groups (p=0.02). The ratio of cardioembolic stroke in the COVID-19 group was higher than the other two groups. The difference did not achieve but approached statistical significance (p=0.06). The NIHSS scores at admission was compared with the NIHSS scores at discharge, and a statistically significant difference was obtained in all three groups. The NIHSS score at admission was significantly higher in the COVID-19 group than in pre-COVID-19 group (p=0.006). The difference between hospitalization and discharge NIHSS scores revealed a highly significant difference (p<0.001) when the COVID-19 group was compared with the non-COVID-19 group and the pre-COVID-19 group. Furthermore, the NIHSS score at discharge in the COVID-19 group was significantly higher than in the non-COVID-19 and pre-COVID-19 groups (p<0.001).

Conclusion: Findings showed that COVID-19 was mostly caused by cardioembolic and cryptogenic etiology in patients with ischemic stroke. High NIHSS scores in the COVID-19 group suggests that COVID-19 deteriorated neurological findings, in addition to the general medical condition of the patients.

Keywords: COVID-19, ischemic stroke, pandemic.

The coronavirus disease 2019 (COVID-19) pandemic is associated with many neurological symptoms and complications.[1] World Stroke Organization reported that the risk of ischemic stroke during COVID-19 infection is approximately 5%.[2] The clinical course of COVID-19 is more severe in elderly patients, males, and in patients with comorbidities that are also risk factors for stroke, such as hypertension, diabetes mellitus, heart disease, and obesity.[3] Thus, stroke in patients with COVID-19 may occur coincidentally. Another discrepancy during the pandemic was that etiological screening of stroke patients was limited, and patients were frequently classified in

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Received: July 22, 2024 **Accepted:** November 13, 2024 **Published online:** March 05, 2025
Cite this article as: Yalman M, Gökyiğit FM, Gürkan ZM, Yazgu R. Characteristics of ischemic stroke during the COVID-19 pandemic. Turk J Neurol 2025;31(1):41-45. doi: 10.55697/tnd.2025.253.

the cryptogenic group.[4] However, these features also raise the question of whether COVID-19 infection increases the risk of stroke in infected persons who also have conventional risk factors for stroke.

Considering the different results, the relationship between COVID-19 and stroke may be explained through three conditions: hypercoagulopathy, vasculitis, and cardiomyopathy.[4-6] There is a condition similar to sepsis-associated coagulation disorder in COVID-19-related hypercoagulopathy, and this may be a condition that facilitates stroke. In addition, it has been shown that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) itself binds to angiotensin-converting enzyme 2 (ACE2) found in the endothelial and smooth muscle cells of the brain. Angiotensin-converting enzyme 2 is an important part of the renin-angiotensin system. Depletion of ACE2 by SARS-CoV-2 may disrupt the balance in the renin-angiotensin system, shifting it in favor of the ACE1/angiotensin II axis. This situation also worsens the endothelial function in organs such as the heart and brain, and the resulting endothelial damage paves the way for ischemic stroke.[7] In addition to endothelial dysfunction, the vasculitis mechanism listed in the literature as the etiology of stroke is thought to cause a condition similar to antiphospholipid syndrome, complement activation, direct viral spread with systemic endothelial infection, and viral RNAemia with immunothrombosis.[8] In addition, COVID-19 causes acute coronary syndrome, coronary vasculitis, myocarditis, left ventricular systemic dysfunction, stress cardiomyopathy, and cardiac arrest by stimulating the sympathetic nervous system. It was stated that COVID-19 could cause arrhythmia.[9] This shows that COVID-19 increases the prevalence of ischemic stroke through cardiomyopathy. This study aimed to investigate the effects of COVID-19 on stroke frequency and etiological features, as well as course and severity of stroke, in ischemic stroke patients during the pandemic.

PATIENTS AND METHODS

This study was conducted at the Health Sciences University, Gaziosmanpaşa Training and Research Hospital, Department of Neurology. A total of 262 patients with ischemic stroke [59 (36 males, 23 females; mean age: 66.5±12.7 years; range, 33 to 96 years) with COVID-19 infection (COVID-19 group) and 83 (57 males, 26 females; mean age: 67.3±12.9 years; range, 36 to 88 years) without COVID-19 infection (non-COVID-19 group)] during the pandemic and 120 patients (66 males, 54 females; mean age: 65.3±13.8 years; range, 38 to 92 years) with ischemic stroke before the pandemic period (pre-COVID-19 group) were evaluated retrospectively. Patients in the COVID-19 and non-COVID-19 groups were hospitalized between March 2020 and March 2021. Patients in the pre-COVID-19 group were hospitalized in 2019. Demographic data, clinical information, and risk factors for ischemic stroke were recorded. Detailed biochemical and cardiac evaluations, as well as cranial and vascular neuroimaging, were performed. The etiological diagnosis of stroke was made based on the TOAST (Trial of ORG 10172 in Acute Stroke Treatment)[10] classification. National Institutes of Health Stroke Scale Score (NIHSS)[11] was calculated upon arrival and at discharge. NIHSS is a neurological examination scale that evaluates the severity of stroke in patients with stroke and consists of 15 items. Scores between 0 and 42 can be obtained. A higher score indicates a more severe stroke. In all patients, modifiable and non-modifiable risk factors for ischemic stroke, NIHSS scores, and etiological diagnosis of stroke were compared between the three patient groups. The study protocol was approved by the Taksim Training and Research Hospital Clinical Research Ethics Committee (date 23.06.2020, no: 106). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed with the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). In addition to descriptive statistics, depending on the distribution, the chi-square test or Fisher exact tests were used for cross-tabulations. One-way analysis of variance was used for comparisons between multiple groups. A p-value <0.05 was considered statistically significant.

RESULTS

Sex and age did not reveal significant differences between the groups (p=0.15 and p=0.56, respectively). Risk factors of the patients are shown in Table 1. The frequency of hypertension did not show a statistically significant difference

TABLE 1
Demographic data of patients, risk factors, and NIHSS scores

	Pre-COVID stroke			COVID + stroke			COVID – stroke			
	n	%	Mean±SD				n	%	Mean±SD	*p*
Age (year)			65.3±13.8			66.5±12.7			67.3±12.9	0.56*
Sex										0.15**
Female	54	45		23	39		26	31.3		
Hypertension	82	6.3		37	62.7		59	71.1		
Diabetes mellitus	62	51.7		25	42.4		43	51.8		
Hyperlipidemia	71	59.2		25	42.4		46	55.4		
Admission NIHSS			3.00±2.876			4.61±3.587			3.86±2.951	
Discharge NIHSS			1.61±2.254			3.92±4.556			3.14±2.939	
Difference between the NIHSS at admission and discharge			1.44±0.515			2.8±1.551			1.61±0.621	<0.001*

NIHSS: National Institutes of Health Stroke Scale; COVID: Coronavirus disease; SD: Standard deviation.

between three groups (p=0.5). The frequency of diabetes mellitus was found not statistically different but higher in the COVID-19 group than in the pre-COVID-19 group (p=0.27). The frequency of hyperlipidemia was significantly higher in the COVID-19 group than in the pre-COVID-19 group (p=0.04; Table 1).

When etiology according to the TOAST classification was compared between the three groups, small vessel disease was detected significantly less in the COVID-19 group than in the other two groups (p=0.02; Figure 1). The frequency of cardioembolic stroke in the COVID-19 group did not reach but approached a statistically higher value compared to the other two groups (p=0.06; Figure 1).

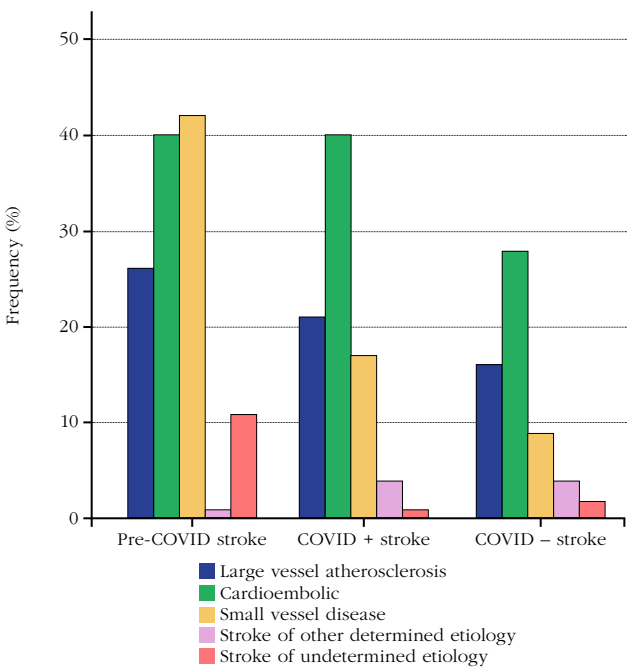

Figure 1. Comparison of groups according to the TOAST classification.

COVID: Coronavirus disease; TOAST: Trial of ORG 10172 in acute stroke treatment.

When the NIHSS scores of the patients at admission to the hospital were compared with the NIHSS scores at discharge, there was a statistically significant difference between the NIHSS scores at admission and discharge in all three groups. Hospital admission NIHSS scores were significantly higher in the COVID-19 group than in the pre-COVID-19 group (p=0.006). The difference between hospitalization and discharge NIHSS scores in the COVID-19 group and the non-COVID-19 and pre-non-COVID-19 groups revealed a highly significant difference (p<0.001). Furthermore, the NIHSS score at discharge in the COVID-19 group was significantly higher than in the non-COVID-19 and pre-COVID-19 groups (p<0.001).

DISCUSSION

In our study, unlike some studies in the literature, large vessel atherosclerosis did not reveal a significant difference between the COVID-19, non-COVID-19, and pre-COVID-19 groups.[4,12] We found that the ratio of cardioembolism was high in the COVID-19 group. The ratio of small vessel disease was significantly lower in the COVID-19 group compared to the other two groups. Since

the etiology of small vessel disease is known to be caused by microatheroma, lipohyalinosis, fibrinoid necrosis, and embolic occlusion and is known to occur with a slowly developing process, this may explain its lower incidence in patients with rapidly developing ischemic stroke caused by COVID-19.[13] In addition, since lacunar infarctions can often be mildly symptomatic or asymptomatic, it may be thought that the reluctance of these patients to come to the hospital during the pandemic may have an impact. In addition, since some studies proved that COVID-19 causes acute coronary syndrome, coronary vasculitis, myocarditis, left ventricular systemic dysfunction, stress cardiomyopathy, and cardiac arrhythmia by stimulating the sympathetic nervous system, it may explain the high ratio of cardioembolic etiology the in COVID-19 group, as in our study.[14] Spence et al.[4] argued that higher NIHSS scores at admission could be attributed to the higher risk of large vessel atherosclerosis in patients with ischemic stroke without COVID-19. In our study, the NIHSS score at hospital admission of the COVID-19 group was higher than the non-COVID-19 group. However, there was no significant difference in large vessel atherosclerosis between the two groups. Based on these findings, we emphasize that a high NIHSS may have aggravated the symptoms of ischemic stroke due to COVID-19 symptoms rather than large vessel atherosclerosis.

In a study, mortality in COVID-19-positive patients with ischemic stroke was found to be higher in all age groups compared to COVID-19-negative patients, even with no risk factors or accompanying conditions, and this was associated with the hypercoagulation mechanisms of COVID-19.[15] Another study found that ischemic stroke findings were more severe in COVID-19-positive patients with ischemic stroke. Regarding the relationship between COVID-19-related ischemic stroke and increased stroke severity, it was emphasized that viral infections could directly cause a vasculopathic effect or strengthen the prothrombotic environment through various mechanisms, such as immune-mediated platelet activation, dehydration, and infection-related cardiac arrhythmias.[16] This showed that COVID-19 had an impact on stroke morbidity, consistent with our study. The significant difference in NIHSS scores at admission and discharge between the COVID-19 and non-COVID-19 groups in our study also supports this opinion.

When the groups were compared in terms of stroke risk factors, there was no difference in the incidence of hypertension. Diabetes mellitus frequency was higher in the COVID-19 group compared to the pre-COVID-19 group, although it was not statistically significant. Hyperlipidemia was found to be statistically significantly higher in the COVID-19 group than in the pre-COVID-19 group. As mentioned in the literature, vascular risk factors were found to be significantly higher in COVID-19-positive patients with ischemic stroke than in the pre-COVID-19 period.[14,17] Furthermore, a study found that 24 patients with no other comorbidities other than diabetes mellitus were at higher risk for the release of enzymes associated with tissue damage, excessive uncontrolled inflammatory responses, and hypercoagulation state associated with dysregulation of glucose metabolism.[18] This appears to indicate that the stroke-causing mechanisms of COVID-19 increase the risk of stroke in infected people with more traditional stroke risk factors.

This study had some limitations, however, given that those with cardiovascular and stroke risk factors are more likely to be hospitalized for COVID-19 than those without these risk factors, our sample may be prone to selection bias. Since most of the patients we included in the study had risk factors for both small vessel and large vessel disease (e.g., DM, HT, and HL), this may limit the ability to determine the specific role of COVID-19 in the stroke mechanism.

In conclusion, this study showed that ischemic stroke in COVID-19-positive patients was mostly caused by cardioembolic and cryptogenic etiology. High NIHSS scores in the COVID-19 group suggests that COVID-19 deteriorates neurological findings, in addition to the general medical condition of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Design, literature review, writing the article: M.Y.; Idea/concept: Z.M.G., F.M.G.; Interpretation: M.Y., F.M.G.; Analysis, control/supervision: F.M.G., Z,M,G.; Data collection: R.Y.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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