



## Investigating the Frequency of Stroke in SARS-CoV-2 Cases in Sakarya City, Turkey

### Sakarya İli SARS-CoV-2 Olgularında İnme Sıklığının Araştırılması


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#### ABSTRACT

**Aim:** The aim of this study is to identify the frequency of stroke among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases in Sakarya city, to find out the clinical characteristics of patients diagnosed with stroke and to contribute to the national database.

**Material and Methods:** This retrospective study was carried out with 783 cases diagnosed with SARS-CoV-2 between April-June 2020 at the pandemic hospital in Sakarya city. Patients were compared in terms of age, National Institute of Health Stroke Scale (NIHSS), risk factors, radiological findings, inpatient treatment, intubation, and mortality rates.

**Results:** Out of 26 cases of ischemic stroke, 11 (42.3%) were male and 15 (57.7%) were female. In terms of infarction localization, the cause was medial cerebral artery (MCA) in 4 (15.4%) patients, top of the basilar in 2 (7.7%) patients, basilar artery in 1 (3.8%) patient, lacunar in 9 (34.6%) patients and anterior system in 10 (38.5%) patients. There was no significant difference in terms of D-dimer and C-reactive protein (CRP) levels according to disease severity (both  $p=0.262$ ). Three (0.38%) patients presented with stroke findings and were diagnosed with SARS-CoV-2. Cryptogenic stroke was detected in 8 (30.8%) of the SARS-CoV-2 cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.

**Conclusion:** This is the first study to identify the frequency of stroke among SARS-CoV-2 patients in Sakarya city and Turkey. Our study is important as it shows that preventing or treating ischemic stroke in SARS-CoV-2 cases contributes greatly to the reduction of mortality.

**Keywords:** Sakarya city; SARS-CoV-2; stroke; frequency.

#### ÖZ

**Amaç:** Bu çalışmanın amacı Sakarya ilindeki şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) olgularında inme sıklığını tespit etmek, inme tanısı almış olan hastaların klinik özelliklerini ortaya koyabilmek ve ulusal veri tabanına katkıda bulunmaktır.

**Gereç ve Yöntemler:** Bu çalışma, Sakarya ilindeki pandemi hastanesinde Nisan-Haziran 2020 tarihleri arasında SARS-CoV-2 tanısı alan 783 olgu ile geriye dönük olarak yürütüldü. Hastalar, yaş, Ulusal Sağlık Enstitüleri İnme Skalası (National Institute of Health Stroke Scale, NIHSS), risk faktörleri, radyolojik bulgular, yatarak tedavi, entübe olma durumları ve mortalite oranları bakımından karşılaştırıldı.

**Bulgular:** Yirmi altı iskemik inmeli olgunun 11 (%42,3)'i erkek ve 15 (%57,7)'i kadın idi. Enfarkt lokalizasyonu bakımından 26 hastanın 4 (%15,4)'ü orta serebral arter (medial cerebral artery, MCA), 2 (%7,7)'si baziller tepe, 1 (%3,8)'i baziller arter, 9 (%34,6)'u laküner, 10 (%38,5)'u arka sistemden kaynaklanmaktaydı. D-Dimer ve C-reaktif protein (C-reactive protein, CRP) düzeyleri bakımından hastalık şiddetine göre anlamlı bir farklılık yoktu (her iki  $p=0,262$ ). Üç (%0,38) hasta inme bulgusuyla gelip SARS-CoV-2 tanısı almıştı. SARS-CoV-2 olgularının 8 (%30,8)'inde kriptojenik inme tespit edildi. Sakarya ilinde SARS-CoV-2 olgularında inme sıklığı %3,3 olarak hesaplandı.

**Sonuç:** Bu çalışma SARS-CoV-2 hastalarında inme sıklığını tespit etmeye yönelik Sakarya ilinde ve Türkiye'de yapılmış ilk çalışmadır. Çalışmamız, SARS-CoV-2 olgularında iskemik inmenin önlenmesi ve tedavi edilebilmesinin mortalitenin azalmasına belirgin katkı sunduğunu göstermesi bakımından önemlidir.

**Anahtar kelimeler:** Sakarya ili; SARS-CoV-2; inme; sıklık.

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## INTRODUCTION

Even though respiratory symptoms are usually focused on in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases, we predicted that there may be accompanying neurological symptoms due to our familiarity with the coronavirus family. Stroke in SARS-CoV-2 cases is caused by changes in the body due to infection and or the presence of risk factors (1). The study that reported the first cases of stroke in Wuhan also noted that there were risk factors present in these cases. On the other hand, stroke was also reported in young cases without any risk factors. This appears to be evidence suggesting that both ways are possible (1-3). Some studies on SARS-CoV-2 reported that stroke was much more frequent in severe cases with pulmonary involvement (4-6). In cases of SARS-CoV-2, the most commonly reported condition in the literature has been ischemic stroke. Less often, hemorrhagic stroke and sinus vein thrombosis have been reported. In SARS-CoV-2 cases, young cases with stroke along with cases presented with only stroke reveal that stroke can also occur at the onset of the disease (6-8). The fact that thrombotic complications were identified in 31% of the cases despite systematic thrombosis prophylaxis shows the importance of evaluating patients in intensive care in terms of thromboembolism prophylaxis. One of the most important markers of this progression is thought to be the D-dimer level (9-11). Antithrombotic treatment such as low molecular weight heparin and aspirin has been recommended for SARS-CoV-2 patients with low D-dimer level (11,12). Starting from March 11, 2020, the day when the first positive case was detected in Turkey, antithrombotic treatment has been a part of the routine procedure as per the treatment guidelines of the Ministry of Health (13). We think that the reason behind the low mortality rates in Turkey could be this prophylactic treatment. The objective of our study is to identify the frequency of stroke among SARS-CoV-2 cases in Sakarya city and to contribute to the national database and literature.

## MATERIAL AND METHODS

In this study, 783 cases diagnosed with SARS-CoV-2 at the emergency department, wards and intensive care units between April 1 and June 15, 2020 at Sakarya Training and Research Hospital, which was declared a pandemic hospital in March, were retrospectively reviewed. The diagnosis was made by evaluating nasopharyngeal swabs with polymerase chain reaction (PCR) and thorax computed tomography (CT), which presented atypical viral pneumonia. The study was approved by the Ethics Committee of the Sakarya University Faculty of Medicine (27.07.2020, 437) and the General Directorate of Health Services of the Ministry of Health. SARS-CoV-2 cases over the age of 18, who required neuroimaging due to stroke pre-diagnosis, were screened from the hospital registration system. Hemorrhagic stroke cases, cases with previous stroke history, and cases with missing data were excluded from the study. Demographic data, medical history, neurological examination result, electrocardiogram (ECG), brain CT, diffusion-weighted magnetic resonance imaging (MRI), PA chest radiograph, blood biochemistry, hemogram test, C-reactive protein (CRP), D-dimer and

fibrinogen values of the cases, ischemic stroke diagnosis of which was confirmed by clinical and radiological sources, were recorded. Known or newly-identified accompanying chronic diseases such as cardiac failure, arrhythmia, myocardial infarction, diabetes, hypertension, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary embolism, and chronic renal failure were recorded. Stroke localization was performed by evaluating ischemic territories in the brain based on brain CT and diffusion-weighted MRI findings. Infarction areas were divided into three groups, namely anterior cerebral artery (ACA), posterior cerebral artery (PCA) and medial cerebral artery (MCA), taking into account arterial watershed areas. The National Institute of Health Stroke Scale (NIHSS) levels, which determine the severity of the disease based on neurological examination of patients, were recorded. Those with a NIHSS score of 1 to 8 were classified as mild, 9 to 15 as moderate, higher than 16 as severe.

## Statistical Analysis

Statistical analysis was performed by using statistical package SPSS v.25.0. Continuous data are described by mean±standard deviation (SD) or median interquartile range (IQR) and (minimum-maximum), categorical data are presented as numbers and percentages. Shapiro-Wilk test was used to evaluate the normality assumption for numerical variables. In the evaluation of the data, a Student's t-test was used for the data with normal distribution in order to compare numerical variables, a Mann-Whitney U test was used for the data that were not normally distributed, and a Pearson Chi-square or Fisher's exact test was used in the analysis of categorical variables. Statistical significance was considered as 0.05.

## RESULTS

SARS-CoV-2 patients were showing clinical stroke findings and were diagnosed with ischemic stroke with neuroimaging. Out of 26 cases of ischemic stroke, 11 (42.3%) were male and 15 (57.7%) were female. The mean age of the patients was 71.7±12.3, the mean age of the male patients was 72.0±10.8 and the mean age of the female patients was 71.5±12.7 years. Only 2 (7.7%) of the patients were 45 years of age and under. Seventeen (65.4%) of the patients had a medical history of hypertension, 9 (34.6%) patients had diabetes and 3 (11.5%) patients had cardiac disease. Nine (34.6%) of the patients were smokers and 1 (3.8%) patient consumed alcohol. There was no significant difference in terms of advanced age, and comorbidities according to the disease severity. Demographic characteristics and risk factors of patients are shown in Table 1.

In terms of the sub groups of infarction localization, the cause was MCA in 4 (15.4%) patients, top of the basilar in 2 (7.7%) patients, basilar artery in 1 (3.8%) patient, lacunar in 9 (34.6%) patients and anterior system in 10 (38.5%) patients. In terms of the anatomical localization of lesions of ischemic stroke patients, 4 (15.4%) patients had partial anterior CI, 13 (50.0%) had posterior CI, 9 (34.6%) had lacunar while no patients had total anterior CI.

Patients were compared in terms of their NIHSS score, which was calculated using the NIHSS during admission to the clinic, risk factors, radiological localization findings,

duration of stay at hospital, duration of intubation, and mortality rates. In terms of risk factors of the patient group, the relationship between age/sex and glucose level at arrival, HbA1C, diabetes, hypertension, heart disease, smoking and alcohol use was not statistically significant. Patients requiring intensive care were grouped under severe cases and those followed-up in wards were grouped under non-severe cases. Sixteen (61.5%) cases were followed-up in intensive care, 10 (38.5%) cases were intubated and 8 (30.8%) cases died. CRP and D-dimer

levels of 26 patients that were included in the study did not show a significant difference between severe and non-severe cases (both  $p=0.262$ ). There only was a significant difference in NIHSS according to the disease severity between severe and non-severe cases ( $p<0.001$ , Table 2). Three (0.38%) patients presented with stroke findings and were diagnosed with SARS-CoV-2. Cryptogenic stroke was detected in 8 (30.8%) of the SARS-CoV-2 cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.

**Table 1.** Clinical characteristics of patients with SARS-CoV-2

	Total (n=26)	Severe (n=16)	Non-severe (n=10)	p
Age (years), mean±SD	71.7±12.3	71.6±14.0	71.4±12.7	0.971
Age, n (%)				
<45	2 (7.7)	1 (6.3)	1 (10.0)	0.730
≥45	24 (92.3)	15 (93.8)	9 (90.0)	
Sex, n (%)				
Male	11 (42.3)	8 (50.0)	3 (30.0)	0.428
Female	15 (57.7)	8 (50.0)	7 (70.0)	
Comorbidities (any), n (%)	8 (28.6)	3 (16.7)	5 (50.0)	0.091
Hypertension, n (%)	17 (65.4)	8 (50.0)	9 (90.0)	0.087
Diabetes mellitus, n (%)	9 (34.6)	4 (25.0)	5 (50.0)	0.234
Cardiac disease, n (%)	3 (11.5)	2 (12.5)	1 (10.0)	0.846
Smoke, n (%)	9 (34.6)	3 (18.8)	6 (60.0)	<b>0.046</b>
Alcohol, n (%)	1 (3.8)	0 (0.0)	1 (10.0)	0.385

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SD: standard deviation

**Table 2.** Laboratory findings of patients with SARS-CoV-2

	Total (n=26)	Severe (n=16)	Non-severe (n=10)	p
C-reactive protein (mg/L)	23.3 (64.2) [1.1-288]	33.2 (59.8) [1.1-288]	7.6 (45.4) [3-231]	0.262
D-dimer (mg/L)	1505 (2247) [331-29400]	1660 (3652) [373-29400]	1450 (1879) [331-3220]	0.262
NIHSS	23 (20) [5-39]	27 (12) [23-39]	9 (6) [5-16]	<b>&lt;0.001</b>
Imaging Pattern, n (%)				
Lacunar	9 (34.6)	4 (25.0)	5 (50.0)	0.234
Other	17 (65.4)	12 (75.0)	5 (50.0)	

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, NIHSS: national institutes of health stroke scale, data were presented as median (interquartile range) [minimum-maximum]

## DISCUSSION

First, from Zhongnan Hospital in Wuhan, China, where the pandemic first emerged, then, from around the world, as of February 7, 2020, neurologists have started to report common neurological symptoms including stroke (6,14-16). It has been reported that blood coagulation tests (prothrombin and D-dimer) of SARS-CoV-2 patients showed abnormal results, which increased the possibility of ischemic stroke. Initial publications reported stroke in 5% of the cases (4,17). Among 388 patients, who applied to a university hospital in Italy, 2.5% had ischemic stroke and the mean age of these patients was 68.4±5.9 years (18). A study involving over 2000 SARS-CoV-2 patients found that the rate of cerebrovascular presentations was higher in severe cases (19). In our study, we investigated 783 SARS-CoV-2 positive patients at a pandemic hospital in Sakarya city and ischemic stroke was detected in 26 of these cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.

Literature reports that in stroke cases, hypertension, diabetes and cardiovascular diseases increase the severity of disease (6,14,17,20). Especially in cases where risk factors for stroke are present such as hypertension, diabetes and smoking, SARS-CoV-2 is much more frequent and severe. In our study, only 8 (30.8%) cases developed stroke without having any risk factor. In cryptogenic cases, transthoracic echocardiogram and Doppler ultrasonography of the carotid vertebral artery could not be performed due to pandemic restrictions, which led to a limitation in determining stroke etiology. The age range of SARS-CoV-2 patients with ischemic stroke has varied in studies. In a most comprehensive study carried out on more than 26 thousand SARS-CoV-2 cases in 99 centers, the mean age of ischemic stroke was 71 (6). In our study, the age range was in line with the literature. Only 2 (7.7%) cases were below the age of 45. Subtyping, which is the next step after a stroke diagnosis, is

of vital importance in predicting prognosis, determining discharge and treatment strategies and preventing recurrence. In literature, large vascular occlusion has been reported in the majority of the cases (6,21). Only 6 (23.1%) of our stroke patients had large vascular occlusion. 3 (11.5%) cases arrived at the hospital presenting with stroke. Out of these, 2 cases actually started having fever and fatigue symptoms a few days back but refrained from going to the hospital because of the pandemic. Another case applied to another hospital presenting with weakness of the left side. Upon suspicion at the ER, this case was tested and was referred to the pandemic hospital after being diagnosed with SARS-CoV-2.

Literature reports that stroke can also occur at the onset of SARS-CoV-2 in cases who only present with stroke manifestations without showing any other symptoms such as fever, cough and loss of appetite (19). Only one case in our study presented with stroke at the onset of SARS-CoV-2.

SARS-CoV-2 can enter the brain via retrograde neuronal or hematogenous propagation (9,17). Due to its direct damage on the nervous system and inflammation, hypoxia, immobilization and disseminated intravascular coagulation it causes, this virus is thought to make people susceptible to venous and arterial thromboembolic events. Due to the known fact that the disease makes people susceptible to thromboembolic events, prophylactic antithrombotic treatment is recommended for patients with high D-Dimer levels (13,22-24). Twenty three (88.5%) of our cases were receiving prophylactic subcutaneous heparin and acetylsalicylic acid treatment at two equal doses before the diagnosis. CRP and D-dimer levels of our stroke cases significantly decreased over time. This significant decrease over time is thought to be due to the antithrombotic and infection treatment patients were receiving. We found a positive correlation between D-dimer and CRP levels of stroke cases in our study and the severity of SARS-CoV-2, and the majority of these cases were followed up under intensive care conditions with respiratory support. We were not able to find a relationship between NIHSS, which is used to identify the severity of stroke, and D-dimer and CRP levels. We predict one reason for this to be the regular and early administration of subcutaneous heparin in all SARS-CoV-2 cases with high D-dimer levels.

In Turkey and all around the world, rigorous and diligent efforts are being exerted to prevent death in SARS-CoV-2 cases. A patient presenting with cerebrovascular event findings during the pandemic should be suspected for SARS-CoV-2, a detailed medical history should be taken and the patient should be tested, if necessary. This is highly important both for diagnosing the disease early and for preventing the spread of the infection in the hospital and in the community. In our study, only 1 case presenting with stroke was tested after suspecting SARS-CoV-2 due to a routine thorax CT, which then resulted in this case to be diagnosed early with SARS-CoV-2.

The most important limitation of our study was that etiological subtyping could not be done in stroke cases. Etiology could not be established in cases due to pandemic-related restrictions. The cases were only compared based on risk factors for stroke. Another limitation was that our results only cover moderate and severe SARS-CoV-2 cases requiring hospitalization.

Another limitation was that the association of medication used for SARS-CoV-2 with stroke cases could not be investigated. As we are facing with a new disease, medications used for treatment should also be investigated for cerebrovascular side effects.

## CONCLUSION

It could be noted that our study is significant as it will contribute to the literature by providing information on cerebrovascular events observed in SARS-CoV-2 positive cases and will further improve experience on this issue.

Our study supports the need for patients suffering from stroke, even if they are cryptogenic, regardless of the etiology of stroke, to be suspected of SARS-CoV-2 during the pandemic and for testing suspected cases.

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (27.07.2020, 437).

**Conflict of Interest:** None declared by the authors.

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