Neurology Asia 2023; 28(1) : 19 – 27

Effect of the COVID-19 pandemic on young stroke

Abuzer COSKUN, Burak DEMIRCI

Department of Emergency Medicine, İstanbul Bağcılar Education and Research Hospital, İstanbul, Turkey

Abstract

Background & Objective: Covid-19 infection has diverse effect on human health. We aimed to evaluate the effect of COVID-19 pandemic on the young stroke cases in an emergency services in a tertiary hospital in Istanbul, Turkey. *Method:* A total of 86 patients younger than 50 years confirmed to have stroke seen between January 1, 2019 and December 31, 2020 were included in the study. The year 2019 was defined as the pre-pandemic period and the year 2020 as the pandemic period. The patients' stroke type, localization, mortality, laboratory and imaging data were evaluated. *Results:* Eighty-six patients were included in the study. The mean age was 38.69±5.39 years, 49 (57%) were female. Of the patients, 78 (90.7%) were ischemic and 8 (9.3%) were hemorrhagic stroke. In the pandemic group, ischemic stroke was observed in 55 (96.5%) and hemorrhagic stroke in 2 (3.5%) (p=0.010). While the mean age of the patients in the survival group was 39.24±5.70 years, it was 36.61±3.38 years in the mortality group (p=0.008). While the mortality was 18 (20.9%) overall, it was 16 (18.6%) patients during the pandemic period, and 2 (2.3%) patients in the pre-pandemic period, the difference was statistically significant. (p=0.014).
Conclusion: COVID-19 infection appear to increase the risk of ischemic stroke and worsens the mortality among the young. More comprehensive and prospective studies are needed to confirm this observation.

Keywords: COVID-19 Pandemic, Cerebrovascular Stroke, Mortality, Emergency Department

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the new type of coronavirus that emerged in China in December 2019, continues to be an important global health problem, spreading rapidly from Wuhan Province to other provinces and then to the whole world. Numerous studies are showing that the effects of the disease can occur not only in the lungs or the heart but also in many systems and organs, including the central and peripheral nervous system. The common symptoms of impaired smell and taste in COVID-19 disease is an indicator of neurological involvement. The virus can enter the cell by binding to angiotensin-converting enzyme 2 (ACE2), which acts as a receptor.[1] ACE2 is found in many tissues in the human body, including the nervous system and skeletal muscle.[2-4] While the symptoms of patients infected with COVID-19 are commonly fever, cough, loss of appetite and diarrhea, the most common neurological symptoms are dizziness, headache, and altered consciousness.[5]

Stroke is defined as the sudden loss of brain function as a result of interruption of blood flow. According to this definition, stroke can be divided by pathology in two groups, 80-85% are ischemic and 15-20% hemorrhagic.[6] Patients presenting in an emergency department needs to be diagnosed and treated quickly to improve the morbidity and mortality.[7] Assessment of acute cerebrovascular disease in the emergency department is firstly by anamnesis, examination, application of the various , and non-contrast cranial computed tomographic (CT) imaging. Diffusion weighted magnetic resonance imaging (dMRI) or CT angiography is the advanced imaging modality that may be indicated in a patient in whom hemorrhage has been ruled out.[8,9]

Young adults under the age of 50 years constitute 10-15% of stroke patients.[10] Many have reported that ischemic stroke is the most common among young adults, and etiology differs according to age, geographical region, and other factors.[11,12]

In this study, we aimed to evaluate the laboratory, clinical, radiological, and

Address correspondence to: Abuzer Coskun, Assoc. Prof. SBU Istanbul Bagcilar Training and Research Hospital, Emergency Medicine Clinic, Dr. Sadik Ahmet Street, Istanbul, Turkey. Tel: + 90 (212) 440 40 00, E-mail: dr.acoskun44@hotmail.com

Date of Submission: 21 February 2022; Date of Acceptance: 6 December 2022

https://doi.org/10.54029/2023ffi

mortality differences of young patients with the cerebrovascular disease between pre-pandemic and pandemic periods in a tertiary hospital in Istanbul, Turkey.

METHODS

Study design and population

In this study, 86 patients (49 females, 37 males; mean age 38.69±5.39 years, range 20-49 years) aged between 18-50 years who sought treatment in the emergency department due to stroke between January 2019 to 2020, were included. Patients seen in January-December 2019 formed the pre-pandemic group, and those in January-December 2020 formed the pandemic group. We included cases of stroke 18 years to 50 years of age, who had laboratory results and radiological imaging, and had complete data records.

Previous cerebrovascular disease, atrial fibrillation, arrhythmias, chronic and congenital heart diseases, hormone-based diseases, psychiatric drug history, chronic liver diseases, kidney failure and dialysis history, additional infectious pathologies, chronic inflammatory diseases, malignancy history, severe anemia and its treatment, other hematological diseases, collagen tissue diseases, and pregnancy were were excluded from the study. In addition, patients who did not have hemogram, biochemistry, and other laboratory tests, as well as CT and dMRI images, or who had missing data at the emergency service application were excluded from the study.

In the pandemic group, cases who had only COVID-19 disease or had a positive polymerase chain reaction (PCR) test without any additional disease were included. Hemogram, biochemistry, C-reactive protein, albumin, D-Dimer, fibrinogen, and troponin T were studied in all these patients at the time of their admission to the emergency department, and brain CT and dMRI were performed according to the clinic and stroke type.

In the one-year period before the pandemic, the total number of stroke cases in all age groups in one year was 686. The minimum number of cases is 29 in the power analysis performed with an acceptable margin of error of 5% and a confidence interval of 95% under the age of 50. During the pandemic period specified as January-December 2020, the number of COVID positive cases who sought treatment to the hospital was 37,876. In our one-year pandemic period, the number of stroke cases in all age groups who sought treatment to the emergency clinic is 1349.

Patients were divided into two groups according to the mortality/survival results and hemorrhagic/ischemic stroke type. Cerebrovascular lesions were classified into eight groups according to their localization: lacunar infarct, basal ganglion, thalamus, corona radiata, cerebellum, brainstem, nucleus caudatus, multiple localization. Demographic, clinical, laboratory data, and radiological imaging of all patients were searched through the hospital automation system, and their entries were reviewed and recorded. The study was performed following the principles of the Declaration of Helsinki after approval by the local ethics committee.

Statistical analysis

The data obtained from this study were analyzed by SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software package. Shapiro Wilk's was used while investigating the normal distribution of the variables. Descriptive statistics were presented as mean±standard deviation or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. The Mann-Whitney U test was used when examining the differences between the groups since the variables did not come from a normal distribution. Values from $P<0.05$ were considered statistically significant when interpreting the results.

RESULTS

The mean age of 86 patients included in the study was 38.69±5.39 years, 49 (57%) were female. Stroke was observed in 86 (1.57%) of 5478 COVID-19 cases under 50 years of age. The mean age of 29 (33.7%) patients in the pre-pandemic group was 42.21±3.65 years, and the mean age of 57 (66.3%) patients in the pandemic group was 36.89±5.26 years. The age of the pre-pandemic group was higher than the pandemic group ($p=0.001$). As for gender, men predominate in the pre-pandemic group and women in the pandemic group ($p=0.011$). Blood sugar, urea, uric acid, creatinine, liver enzymes, albumin, lactate dehydrogenesis, bilirubin, fibrinogen, D-dimer, C-reactive protein, white blood cell (WBC), and neutrophil were significantly higher in the pandemic group ($p=0.001$); while creatine kinase, creatine kinase-MB, and lymphocyte count were not different between the pre-pandemic and pandemic groups (Table 1).

Table 1: Comparison of baseline characteristics and laboratory findings in the pandemic and pre-pandemic Period

	All patients n:86 mean±SD	Pre-pandemic n:29 mean±SD	Pandemic n:57 mean±SD	P
Baseline characteristics				
Age (Year)	38.69±5.39	42.21±3.65	36.89±5.26	**0.001**
Gender (Female/Male)	49/37	11/18	38/19	**0.011**
Laboratory Findings				
Blood sugar, mg/dL	152.49±53.06	119.59±31.59	169.23±54.09	**0.001**
Urea, mg/dL	37.06±15.34	30.36±10.14	40.48±16.46	**0.001**
Uric Acid, mg/dL	6.67±1.47	5.82±1.56	7.10±1.23	**0.001**
Creatinine, mg/dL	0.90±0.32	0.76±0.25	0.97±0.33	**0.001**
AST, mg/dL	66.25±32.44	36.27±17.22	81.50±27.34	**0.001**
ALT, mg/dL	58.12±29.59	34.93±17.86	69.91±27.38	**0.001**
ALP, mg/dL	101.92±30.79	84.72±39.59	110.67±20.60	**0.001**
LDH, U/L	434.82±145.91	339.17±143.28	483.49±122.08	**0.001**
Albumin, g/dL	3.44±0.56	4.06±0.37	3.12±0.33	**0.001**
CK, U/L	135.34±90.00	117.34±73.26	144.49±100.96	0.127
CK-MB, ng/mL	30.76±24.26	26.96±13.34	32.69±28.16	0.982
Bilirubin, mg/dL	0.90±0.42	0.49±0.32	1.12±0.29	**0.001**
Fibrinogen, mg/dL	486.41±107.38	388.65±72.05	536.14±86.26	**0.001**
Troponin, pg/mL	0.45±0.36	0.13±0.20	0.62±0.31	**0.001**
D-Dimer, ugFEU/mL	645.67±395.83	407.72±180.57	766.74±421.04	**0.001**
CRP, mg/dL	22.60±17.94	9.15±1.98	29.44±18.58	**0.001**
WBC, 10^3/UL	13.92±3.63	11.05±2.09	15.39±3.37	**0.001**
Neutrophil, 10^3/UL	6.92±2.85	4.59±1.45	8.10±2.65	**0.001**
Lymphocyte, 10^3/UL	1.35±0.90	1.64±1.35	1.20±0.52	0.658

PCR: Polymerase chain reaction, SD; Stanndard deviation, AST: Asptartate aminotransferase; ALT: Alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase CK: creatine kinase; CRP: C- Reactive protein WBC: White blood cell

The overall mortality of the 86 patients was 18 (20.9%). Fifteen (17.4%) of the mortality cases were women (p=0.011). While the mean age of the patients in the survival group was 39.24±5.70 years, it was 36.61±3.38 years in the mortality group (p=0.008). The laboratory parameters between the mortal and non-mortal groups is shown in Table 2. As shown, the D-dimer, troponin, bilirubin, fibrinogen, WBC and neutrophil were significantly higher in the mortalily group as compared to the survival group, while no significant association was seen in the other laboratory parameters (Table 2).

Mortality was observed in 16 (18.6%) patients during the pandemic period, and 2 (2.3%) patients in the pre-pandemic period, with a total of 18 (20.9%) patients (p=0.014). In the pre-pandemic group, 23 (79.3%) were diagnosed with ischemic stroke and 6 (20.7%) had hemorrhagic stroke. However, ischemic stroke was observed in 55 (96.5%) and hemorrhagic stroke in 2 (3.5%) patients in the pandemic group (p=0.010). Overall the most common lesion was cerebellum in 23 (26.7%) patients. This was followed by the thalamus and brain stem with 16 (18.6%) patients. However, in the pandemic group, 14 (16.3%) of the lesions were detected in the thalamus, 14

Table 2: Comparison of baseline characteristics and laboratory findings by mortality status

Mortality	No n:68 mean±SD	Yes n:18 mean±SD	P
Baseline characteristics			
Age (year)	39.24±5.70	36.61±3.38	**0.008**
Gender (Female/Male)	34/34	15/3	**0.011**
Laboratory Findings			
Blood sugar, mg/dL	148.87±54.95	166.17±43.87	0.068
Urea, mg/dL	36.02±15.02	41.00±16.33	0.220
Uric Acid, mg/dL	6.59±1.61	6.94±0.74	0.181
Creatinine, mg/dL	0.88±0.26	0.98±0.49	0.438
AST, mg/dL	64.27±34.03	73.72±24.97	0.110
ALT, mg/dL	56.78±31.34	63.17±21.74	0.186
ALP, mg/dL	101.15±30.83	104.83±31.34	0.426
LDH, U/L	428.53±141.22	458.61±161.20	0.570
Albumin, g/dL	3.51±0.58	3.16±0.34	0.068
CK, U/L	135.75±95.66	133.78±84.76	0.640
CK-MB, ng/mL	31.88±25.30	26.50±19.89	0.077
Bilirubin, mg/dL	0.82±0.39	1.21±0.41	**0.001**
Fibrinogen, mg/dL	460.90±86.10	582.78±126.50	**0.001**
Troponin, pg/mL	0.36±0.28	0.82±0.42	**0.001**
D-Dimer, ng/mL	543.63±198.53	1031.17±655.03	**0.001**
CRP, mg/dL	22.11±18.55	24.44±15.77	0.640
WBC, 10^3/UL	13.56±3.79	15.31±2.55	**0.015**
Neutrophil, 10^3/UL	5.94±1.78	10.61±3.13	**0.001**
Lymphocyte, 10^3/UL	1.30±0.92	1.56±0.85	0.137

SD; Stanndard Deviation, AST:Asptartate aminotransferase; ALT: Alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase CK: creatine kinase CRP: C-Reactive Protein WBC: White Blood Cell

(16.3%) in the brainstem, and 9 (10.5%) in the cerebellum (p=0.010, Table 3).

The mortality was 14 (77.8%) cases with infarct and 4 (22.2%) cases with hemorrhage (p=0.034). In addition, lesions were observed in the brainstem in 10 (11.6%) cases, multiple localizations in 4 (4.7%), cerebellum in 3 (3.5%) cases, and thalamus in 1 (1.2%) case in the mortality group. In the survival group, 6 (7%) patients had lesions in the brain stem and 1 (1.2%) had multiple localization lesions (p=0.001, Table 4).

There was ischemic stroke in 78 (90.7%) and hemorrhagic stroke in 8 (9.3%) patients. There was no relationship between stroke type and gender (p=0.740). Infarct lesions were most common in the cerebellum with 22 (25.6%) cases, and hemorrhage was detected in multiple localizations with 4 (4.7%) cases (p=0.001, Table 5).

DISCUSSION

For cerebrovascular effect resulting in young stroke in COVID-19, there has previous studies, but the they generally involve small number of cases. This prompted us to investigate the impact of the COVID-19 disease on stroke among the young adults. We showed in this study that COVID-19 disease is associated with increase in cerebrovascular events with higher mortality among the young adults , this was seen even among patients without pre-existing diseases.

It has been suggested that the neurological effects of COVID-19 occur by different mechanisms. These include invasion of the virus with a neurotropic effect; secondary damage of inflammatory cells; effects on the respiratory and cardiac systems resulting in cerebral hypoxemia, and inflammation triggering coagulation parameters that result in increased

Table 3: Prepandemic and pandemic period comparison of mortality, stroke type and localization

		Pre-pandemic n:29 (%)	Pandemic n:57 (%)	Total (%)	P
Gender	Female	11(12.8)	38(44.2)	49(57)	**0.011**
	Male	18(20.9)	19(21.1)	37(43)	
Mortality	No	27(31.4)	41(47.7)	68(79.1)	**0.014**
	Yes	2(2.3)	16(18.6)	18(20.9)	
Stroke type	Infarct	23(26.7)	55(64)	78(90.7)	**0.010**
	Hemorrhage	6(7)	2(2.3)	8(9.3)	
Lesion localization	Lacunar Infarct	3(3.5)	9(10.5)	12(14)	**0.010**
	Basal Ganglion	4(4.7)	2(2.3)	6(7)	
	Thalamus	2(2.3)	14(16.3)	16(18.6)	
	Corona Radiata	1(1.2)	5(5.8)	6(7)	
	Cerebellum	14(16.3)	9(10.5)	23(26.7)	
	Brainstem	2(2.3)	14(16.3)	16(18.6)	
	Nucleus Caudatus	1(1.2)	1(1.2)	2(2.3)	
	Multiple Localization	2(2.3)	3(3.5)	5(5.8)	
Total		29(33.7)	57(66.3)	86(100)	

PCR: Polymerase chain reactio

cerebrovascular diseases.[13,14] For early neurologic findings most commonly manifest as disturbances in smell and taste, this is likely to be due to the neurotropic effects of the virus as well as gene expression changes.[15,16] There is also increase in the frequency of anxiety and depression, the mechanism of which is uncertain.[17]

Epidemiological, clinical and experimentally, studies has shown that COVID-19 patients have a higher risk of thromboembolic events, including neurovascular diseases, in the acute phase of infection.[18,19] In a recently published, prospective, multinational study, 123 (0.7%) cases presenting with acute ischemic stroke were reported in a total of 17,799 SARS-CoV-2 infected patients.[20] In another study, it was reported that there were 23 (0.9%) ischemic stroke cases in 3556 COVID-19 patients.[21] A study from Wuhan, China showed

Table 4: Comparison of stroke type and localization by mortality status

Mortality		*No n:68 (%)*	*Yes n:18 (%)*	*Total (%)*	*P*
Gender	Female	34(39.5)	15(17.4)	49(57)	***0.011***
	Male	34(39.5)	3(3.5)	37(43)	
Stroke type	Infarct	64(74.4)	14(16.3)	78(90.7)	***0.034***
	Hemorrhage	4(4.7)	4(4.7)	8(9.3)	
Lesion localization	Lacunar Infarct	12(14)	0(0)	12(14)	***0.001***
	Basal Ganglion	6(7)	0(0)	6(7)	
	Thalamus	15(22.1)	1(1.2)	16(18.6)	
	Corona Radiata	6(7)	0(0)	6(7)	
	Cerebellum	20(23.3)	3(3.5)	23(26.7)	
	Brainstem	6(7)	10(11.6)	16(18.6)	
	Nucleus Caudatus	2(2.3)	0(0)	2(2.3)	
	Multiple Localization	1(1.2)	4(4.7)	5(5.8)	
Total		68(79.1)	18(20.9)	86(100)	

Table 5: Comparison of gender and localization by stroke type

Stroke type		Infarct n:78 (%)	Hemorrhage n:8 (%)	Total (%)	P
Gender	Female	44(51.2)	5(5.8)	49(57)	0.740
	Male	34(39.5)	3(3.5)	37(43)	
Lesion localization	Lacunar infarct	12(14)	0(0)	12(14)	**0.001**
	Basal ganglion	4(4.7)	2(2.3)	6(7)	
	Thalamus	16(18.6)	0(0)	16(18.6)	
	Corona radiata	6(7)	0(0)	6(7)	
	Cerebellum	22(25.6)	1(1.2)	23(26.7)	
	Brainstem	15(17.4)	1(1.2)	16(18.6)	
	Nucleus caudatus	2(2.3)	0(0)	2(2.3)	
	Multiple localization	1(1.2)	4(4.7)	5(5.8)	
Total		78(90.7)	8(9.3)	86(100)	

that acute cerebrovascular disease represents an unfavorable prognostic factor in COVID-19, with 10 (4.6%) ischemic stroke and 1 (0.5%) intracerebral hemorrhage among 219 infected patients.[22] In our study, the rate of stroke was found to be 1.57% in the young adult population without any underlying disease.

Pathologically, ischemic stroke in COVID-19 can usually present with multi-arterial distribution, embolic pattern, and hemorrhagic transformation.[23,24] Large cerebral vascular occlusions with a high thrombus load and a tendency to clot fragmentation have been reported.[25,26] Characteristically, stroke due to large vessel occlusion may affect younger patients without known risk factors, as well as associated with higher in-hospital mortality.[27,28] Hypercoagulation state, cardioembolism, or embolism due to COVID-19 may be potential causes of stroke. In addition, rare localizations of stroke, such as the corpus callosum or frequent involvement of the posterior circulation, have been associated with COVID-19.[29,30] An increased incidence of hemorrhagic transformation of ischemic infarctions has also been observed in COVID-19 stroke patients.[31] It has not been established whether disturbances of hemostasis and increased use of anticoagulants are associated with the possibility of hemorrhagic transformation.

In most studies, the male gender was found to be more common in both young and advanced age ischemic strokes[32-34], while no difference was found between the male and female gender in some studies.[35] In this study, there were 57 young adult patients with COVID-19 who had stroke during the pandemic period. Thirty-eight (67%) of the patients were women with a mean age of 36.89±5.26 years. Compared to the pre-pandemic period, the number of young stroke patients had increased. We think that the increase in the number of young stroke cases is due to the inflammation response and the hemostasis disorder in COVID-19 mentioned in the above section. We are uncertain the explanation for the higher prevalence of stroke patients in women during the pandemic period.

In a review of the incidence of stroke in young adults between 1980 and 2009, Marini *et al*., who analyzed 29 studies involving 3,589 first stroke patients under 45 years of age, reported ischemic strokes between 21.0% and 77.9%, intracerebral hemorrhages between 3.7% and 38.5% and showed subarachnoid hemorrhages between 9.6% and 55.4%.[36] In our study, 90.7% of all patients had ischemic stroke. During the pandemic period, ischemic accounted for 96% (55/57). This is consistent with the increased coagulative tendency mentioned above.

Many studies have been conducted on the laboratory values in stroke cases. It has been shown that C-reactive protein significantly increases in patients in correlation with the severity of ischemic stroke.[37] McAlpine *et al*. found that the mean value of C-reactive protein increased and was 17.5 mg/L in stroke patients with COVID-19 infection.[38] In our study, mean C-reactive protein value was 29.44±18.58 mg/L in stroke cases in the pandemic period, and it was found to be significantly higher in stroke cases compared to the pre-pandemic period. We think

that the primary cause of this is infection. In this context, some studies have shown the relationship between ischemic stroke plasma D-dimer level and its consequences.[39-41] Nam *et al*.[39] and Nezu *et al*.[40] reported that plasma D-dimer levels have a predictive effect in cryptogenic stroke. Kim *et al*. showed that plasma D-dimer level has a prognostic effect in non-cardioembolic stroke patients.[41] In our study, D-dimer level was higher in stroke patients during the pandemic period and significantly higher in the mortality group than in the survival group. We conclude that D-dimer elevation may be an unfavorable prognosis criterion in stroke cases of COVID-19 disease.

In some previous studies, it was reported that posterior system infarcts were seen at a higher rate in patients younger than 45 years of age compared to the older age patients, whereas in some studies, anterior system infarcts were found to be higher in the stroke group aged 19-45 years.[42] In our study, while cerebellum involvement was high in young patients in the pre-pandemic period, brain stem and thalamus pathologies were observed more frequently in stroke patients during the pandemic period. In addition, according to the localization of the lesions, thalamus and cerebellum lesions were common in the survival group, while brainstem lesions were found in 10 (55.6%) of 18 (20.9%) patients in the mortality group. This call for larger studies on the relationship between COVID-19, infarct location and mortality.

The prognosis for stroke in younger patients is generally better than in the elderly population. In a study in which stroke patients aged 18-50 were followed for an average of 11 years, the mortality rate was reported as 20%.[43] As for mortality rates in cases of stroke with COVID-19, Benussi *et al*.[44], Ntaios *et al*.[45], Kwernland *et al*.[46] reported 34.9%, 27.6%, and 84.6%, respectively. Thus, the reported mortality rates are variable and high. In our study, mortality was seen in 2 (2.3%) patients in the pre-pandemic period; however, it was 16 (18.6%) patients during the pandemic period. This may be attributed to the other complications of COVID-19 infection. However, compared to similar studies, the mortality of stroke patients with COVID-19 was lower in our study, which may be due to the well-coordinated emergency and neurology clinics of our hospital, which is a tertiary center. It is also noteworthy that hemorrhagic strokes were higher in the mortality group than in the survival group. Our number of hemorrhagic strokes was low.

This study had some limitations; in addition to being single-centered and retrospective, there was also difficulties in accessing the medical records and the various problems associated with the pandemic period on hospital admissions.

In conclusion, COVID-19 infection appear to increase the risk of ischemic stroke and worsens the mortality among the young. More comprehensive and prospective studies are needed to confirm this observation.

DISCLOSURE

Financial support: None

Conflict of interest: None

Ethical approval: The study was approved by the institutional review board (Date:26/10/2021, Decision No:1063).

Availability of data and materials: All data is available on request without restriction.

REFERENCES

1. Wrapp D, Wang N, Corbett KS, *et al*. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; 367:1260-3. doi: 10.1126/science.abb2507
2. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203:631-7. doi: 10.1002/path.1570
3. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett* 2002; 532(1-2):107-10. doi: 10.1016/s0014-5793(02)03640-2
4. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: Properties and future directions. *J Neurochem* 2008; 107:1482-94. doi: 10.1111/j.1471-4159.2008.05723.x
5. Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77:683-90. doi: 10.1001/jamaneurol.2020.1127
6. Lewandowski C, Barsan W. Treatment of acute ischemic stroke. *Ann Emerg Med* 2001; 37:202-16. doi: 10.1067/mem.2001.111573
7. Marler JR, Winters-jones P, Emr M, eds. National Institute of Neurological Disorders and Stroke. Procceedings of a national symposium on rapid identification and treatment of acute stroke. Bethesda, MD: National Institute of Health (NIH publication No. 97-4239). 1997:157-8.
8. Teasell R, Salbach NM, Foley N, *et al*. Canadian stroke best practice recommendations: Rehabilitation, recovery, and community participation following stroke. Part One: Rehabilitation and recovery following stroke. 6th Edition Update 2019. *Int J Stroke* 2020; 15:763-88. doi: 10.1177/1747493019897843

9. McDonough R, Ospel J, Goyal M. State of the art stroke imaging: A current perspective. *Can Assoc Radiol J* 2021; 27:8465371211028823. doi: 10.1177/08465371211028823
10. Ferro JM, Massaro AR, Mas JL. Aetiological diagnosis of ischaemic stroke in young adults. *Lancet Neurol* 2010; 9:1085-96. doi: 10.1016/S1474-4422(10)70251-9
11. Virani SS, Alonso A, Benjamin EJ, *et al*. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: A report from the American Heart Association. *Circulation* 2020; 3;141:e139-596. doi: 10.1161/CIR.0000000000000757
12. Ekker MS, Boot EM, Singhal AB, *et al*. Epidemiology, aetiology, and management of ischaemic stroke in young adults. *Lancet Neurol* 2018; 17:790-801. doi: 10.1016/S1474-4422(18)30233-3
13. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020; 11:995-8. doi: 10.1021/acschemneuro.0c00122
14. Shi S, Qin M, Shen B, *et al*. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; 5:802-10. doi: 10.1001/jamacardio.2020.0950
15. Giacomelli A, Pezzati L, Conti F, *et al*. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: A cross-sectional study. *Clin Infect Dis* 2020; 71:889-90. doi: 10.1093/cid/ciaa330
16. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci* 2018; 12:386. doi: 10.3389/fncel.2018.00386
17. Ciler Eren E, Gumus Sanli S. The effect of COVID-19 pandemic on depression, anxiety and stress levels of pregnant women. *Bagcilar Med Bull* 2021; 6:306-13. doi: 10.4274/BMB.galenos.2021.04.050
18. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol* 2004; 251:1227-31. Doi: 10.1007/s00415-004-0519-8
19. Arabi YM, Harthi A, Hussein J, *et al*. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 2015; 43:495-501. doi: 10.1007/s15010-015-0720-y
20. Shahjouei S, Naderi S, Li J, *et al*. Risk of stroke in hospitalized SARS-CoV-2 infected patients: A multinational study. *EBioMedicine* 2020; 59:102939. doi: 10.1016/j.ebiom.2020.102939
21. Yaghi S, Ishida K, Torres J, *et al*. SARS-CoV-2 and stroke in a New York healthcare system. *Stroke* 2020; 51:2002-11. doi: 10.1161/STROKEAHA.120.030335
22. Li Y, Li M, Wang M, *et al*. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020; 5:279-84. doi: 10.1136/svn-2020-000431
23. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. *J Stroke Cerebrovasc Dis* 2020; 29:104953. doi: 10.1016/j.jstrokecerebrovasdis.2020.104953
24. Escalard S, Maïer B, Redjem H, *et al*. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: Experience from Paris. *Stroke* 2020; 51:2540-3. doi: 10.1161/STROKEAHA.120.030574
25. Majidi S, Fifi JT, Ladner TR, *et al*. Emergent large vessel occlusion stroke during New York city's COVID-19 outbreak: Clinical characteristics and paraclinical findings. *Stroke* 2020; 51:2656-63. doi: 10.1161/STROKEAHA.120.030397
26. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg* 2020; 12:648-53. doi: 10.1136/neurintsurg-2020-016220
27. Alkhaibary A, Abbas M, Ahmed ME, Khatri IA, Alkhani A. Common carotid artery occlusion in a young patient: Can large-vessel stroke be the initial clinical manifestation of coronavirus disease 2019? *World Neurosurg* 2020; 144:140-2. doi: 10.1016/j.wneu.2020.08.154
28. Altschul DJ, Esenwa C, Haranhalli N, *et al*. Predictors of mortality for patients with COVID-19 and large vessel occlusion. *Interv Neuroradiol* 2020; 26:623-8. doi: 10.1177/1591019920954603
29. Sparr SA, Bieri PL. Infarction of the splenium of the corpus callosum in the age of COVID-19: A snapshot in time. *Stroke* 2020; 51:e223-6. doi: 10.1161/STROKEAHA.120.030434
30. Bonardel C, Bonnerot M, Ludwig M, *et al*. Bilateral posterior cerebral artery territory infarction in a SARS-Cov-2 infected patient: discussion about an unusual case. *J Stroke Cerebrovasc Dis* 2020; 29:105095. doi: 10.1016/j.jstrokecerebrovasdis.2020.105095
31. Siegler JE, Cardona P, Arenillas JF, *et al*. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry. *Int J Stroke* 2021; 16:437-47. doi: 10.1177/1747493020959216
32. Dash D, Bhashin A, Pandit AK, *et al*. Risk factors and etiologies of ischemic strokes in young patients: a tertiary hospital study in north India. *J Stroke* 2014; 16:173-7. doi: 10.5853/jos.2014.16.3.173
33. Putaala J, Yesilot N, Waje-Andreassen U, *et al*. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. *Stroke* 2012; 43:2624-30. doi: 10.1161/STROKEAHA.112.662866
34. Demirci B, Karakılıç ME, Coşkun A, *et al*. The brain ischemic volume correlation with the ischemic modified albumin level. *Bagcilar Med Bull* 2021; 6:26-31. Doi: 10.4274/BMB.galenos.2020.10.068
35. Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. *JAMA Neurol* 2013; 70:51-7. doi: 10.1001/jamaneurol.2013.575
36. Marini C, Russo T, Felzani G. Incidence of stroke in young adults: a review. *Stroke Res Treat* 2010;2011:535672. doi: 10.4061/2011/535672
37. Eikelboom JW, Hankey GJ, Baker RI, *et al*. C-reactive

protein in ischemic stroke and its etiologic subtypes. *J Stroke Cerebrovasc Dis* 2003; 12:74-81. doi: 10.1053/jscd.2003.16
38. McAlpine LS, Zubair AS, Maran I, *et al*. Ischemic stroke, inflammation, and endotheliopathy in COVID-19 patients. *Stroke* 2021; 52:e233-8. doi: 10.1161/STROKEAHA.120.031971
39. Nam KW, Kim CK, Kim TJ, *et al*. D-dimer as a predictor of early neurologic deterioration in cryptogenic stroke with active cancer. *Eur J Neurol* 2017; 24:205-11. doi: 10.1111/ene.13184
40. Nezu T, Kitano T, Kubo S, *et al*. Impact of D-dimer levels for short-term or long-term outcomes in cryptogenic stroke patients. *J Neurol* 2018; 265:628-36. doi: 10.1007/s00415-018-8742-x
41. Kim TW, Song IU, Chung SW. Prognostic value of serum D-Dimer in noncardioembolic ischemic stroke. *Can J Neurol Sci* 2017; 44:404-9. doi: 10.1017/cjn.2016.299
42. Chatzikonstantinou A, Wolf ME, Hennerici MG. Ischemic stroke in young adults: classification and risk factors. *J Neurol* 2012; 259:653-9. doi: 10.1007/s00415-011-6234-3
43. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, *et al*. Long-term mortality after stroke among adults aged 18 to 50 years. *JAMA* 2013; 309:1136-44. doi: 10.1001/jama.2013.842
44. Benussi A, Pilotto A, Premi E, *et al*. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology* 2020; 95:e910-20. doi: 10.1212/WNL.0000000000009848
45. Ntaios G, Michel P, Georgiopoulos G, *et al*. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: The Global COVID-19 Stroke Registry. *Stroke* 2020; 51:e254-8. doi: 10.1161/STROKEAHA.120.031208
46. Kvernland A, Kumar A, Yaghi S, *et al*. Anticoagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a New York healthcare system. *Neurocrit Care* 2021; 34:748-59. doi: 10.1007/s12028-020-01077-0