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Association between acute stroke and COVID-19 infection among patients with acute stroke

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS COV 2) infection is associated with multiple neurological complications. Cerebrovascular accidents are considered as one of the common neurological complications associated with corona virus (COVID-19). It may represent the first presentation of the patients of COVID-19 or may occur anytime during the course of the disease.

Results This study included 381 patients after the diagnosis of cerebrovascular accident. The mean age of the participants was 57.1 ± 15 years. 53.5% of the participants were males and 46.5% were females. The participants had COVID-19 infection in past 3 months with mean duration was 35.5 ± 18 days. The mean NIHSS among the participants was 10.5 ± 6.2. Small artery stroke was higher among PCR negative patients and controls, while large artery stroke was higher among PCR positive patients. 26% of patients with stroke and confirmed COVID-19 infection developed stroke immediately after COVID-19 infection (within 1 week). Within 1 month from getting infection with COVID-19, 41.7% of patients developed stroke and 32.3% had developed stroke after 1 month of infection with COVID-19. Female gender, older age of the patients and presence of vascular risk factors were associated with increased severity of infection as evidenced by higher NIHSS and more ICU admission among COVID-19 positive patients.

Conclusions COVID-19 infection has been associated with both venous and arterial stroke, especially in elderly patients. COVID-19 infection was associated with increased stroke severity as evidenced by higher NIHSS and more ICU admission. Small vessel disease was higher among COVID-19 negative patients, while large artery stroke was higher among positive COVID-19 patients.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared as a global pandemic in December 2019. It is caused by a mutant form of coronavirus (COVID-19). Although the main target of the coronavirus was the respiratory system resulting in symptoms varying from mild upper respiratory tract symptoms to life threatening pneumonia and respiratory failure, multiple organ system affection was related to infection with this virulent mutant form. The nervous system was affected both the peripheral nervous system and CNS [1].

Multiple pathophysiological mechanisms were described for the CNS pathology associated with COVID-19 including the direct virus infection of the CNS either through retrograde neuronal diffusion or via the blood–brain barrier or through the cribriform plate of the ethmoid bone [2], the virus-induced hyper inflammatory and hypercoagulability states resulting in arterial and\or venous thromboembolic events, and post-infectious immune-mediated processes [3]. Basic clinical characteristics was shown in Table 1.

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Table 1 Basic clinical characteristics of the studied participants

Variable		*n* = 381
Special habits	No special habits of medical importance, n (%)	230 (60.4)
	Smoker, *n* (%)	112 (29.4)
	Addict, *n* (%)	39 (10.2)
	Alcohol, *n* (%)	5 (1.3)
	Hashish/ marijuana, *n* (%)	34 (8.9)
Hypertension	No, *n* (%)	234 (61.4)
	Yes, *n* (%)	147 (38.6)
Cardiac	No, *n* (%)	259 (68)
	Yes, *n* (%)	122 (32)
	AF, *n* (%)	38 (10)
	IHD, *n* (%)	66 (17.3)
	CMP, *n* (%)	18 (4.7)
Diabetes	No, *n* (%)	260 (68.2)
	Yes, *n* (%)	121 (31.8)
Hypercholesteremia	No, *n* (%)	268 (70.3)
	Yes, *n* (%)	113 (29.7)
Obesity	No, *n* (%)	285 (74.8)
	Yes, *n* (%)	96 (25.2)
Renal/hepatic	No, *n* (%)	345 (90.6)
	Yes, *n* (%)	36 (9.4)
Hyperthyroidism	No, *n* (%)	363 (95.3)
	Yes, *n* (%)	18 (4.7)
Past history of vascular CNS disease	No, *n* (%)	288 (75.6)
	Hemorrhagic, *n* (%)	29 (7.6)
	Ischemic, *n* (%)	61 (16.0)
	Venous, *n* (%)	3 (0.8)

Laboratory data was shown in Table 2.

Cerebrovascular thromboembolic events affect about 3% of COVID-19 patients [3]. Multiple factors were incriminated to cause cerebrovascular stroke in COVID-19 patients including ACE receptor dysfunction, the cytokine storm caused by uncontrolled activation of the immune system, prothrombotic state as evidenced by elevated D Dimer, myocarditis complicated with vascular embolism, severe hypoxia resulting in neuronal ischemia and apoptosis, thrombocytopenia and coagulopathy [4].

Table 2 Laboratory data of the participants

Variable	*n* = 381 Mean ± SD
Hemoglobin (g/dl)	11.5 ± 1.3
WBC (*10^9/L)	5.5 ± 1.4
Lymphocytes (*10^9/L)	1.2 ± 0.1
Neutrophils (*10^9/L)	5.1 ± 1.2
Platelet (*10^9/L)	222 ± 15.8
D-dimer (µg/ml)	0.84 ± 0.9
CRP (mg/dl)	15.6 ± 7.9

WBC white blood cells, *CRP* C reactive protein

This study was aiming at investigating the association between stroke subtypes and COVID-19 infection.

Methods

A single-center prospective analytical cross-sectional study. It included all patients 18–80 years presented with abrupt onset of neurological deficit and diagnosed to suffer from cerebrovascular ischemic stroke from September 2021 to March 2022 (Emergency Room, Isolation Department, Outpatient clinics, Neurology Department and Intensive Care Unit). All patients with unexplained fever or any other symptoms related to COVID-19 were isolated in a separate room and screened for COVID-19.

An informed consent was taken from all the included patients or from the caregivers before taking any data or doing any investigations. The research was approved by the Faculty of Medicine, Health Research Ethics Board (research 4637); it follows The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

This study included 381 patients who suffered from cerebrovascular ischemic accidents. Patients were allocated into one of two groups:

Group1 (cases): It included patients with acute ischemic stroke who had past history of positive COVID-19 infection anytime during the past 3 months or who suffers current COVID-19 infection.

Group 2 (controls): It included patients with acute ischemic stroke who did not catch COVID-19 infection and patients with symptoms of respiratory tract infection but their PCR was negative and their CT chest was not suggestive to diagnose COVID-19 (CO-RAD 1 or 2).

Data were collected in a data sheet that included the demographic characteristics, medical history, symptoms, clinical signs, laboratory findings and chest CT scan findings.

The types of ischemic stroke were classified according to the (TOAST) classification [5]. COVID-19 infection was diagnosed based on clinical history of respiratory symptoms and confirmed by PCR in throat swab and chest CT showing evidence of viral-like pneumonia [6].

The diagnosis of acute cerebrovascular stroke was confirmed by clinical presentation and brain imaging (CT, MRI, MRA, MRV).

Computed tomography was performed using 'Toshiba Activion 16' multi-slice scanner (TSX-031A-2012) machine (Toshiba Medical System, Japan).

Magnetic resonance imaging was done using (Philips achieva R 2.5.3) machine with a superconducting magnet with a main strength of 1.5 Tesla. The brain was

imaged in the axial, coronal and sagittal planes T1W, T2W, FLAIR and diffusion sequences; with 5 mm slice thickness.

Regarding D. dimer results were measured with Getein 1100 D Dimer Kit The cutoff value recommended by the manufacturer was 0.5 mg/L.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 26. The data were tested for normal distribution using the Shapiro–Walk test. The qualitative data were represented as frequencies and relative percentages and the quantitative data were expressed as mean and standard deviation. Chi-square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. ANOVA test was used to calculate difference between quantitative variables in more than two groups. Post hoc test was used. Level of P value < 0.05 indicates significant difference. TOAST classification among participants was shown in Fig. 1.

Results

The current study included 381 participants diagnosed to suffer from cerebrovascular accidents.

The findings of the brain imaging of the included patients are shown in Table 3.

Among the 381 participants, magnetic resonance venography (MRV) was performed only in cases suspected to suffer cerebral venous sinus thrombosis; the imaging findings showed venous sinus thrombosis in 27 patients (7.1%); 22.2% had right transverse, sigmoid, jugular sinus thrombosis, 18.5% had superior sagittal and 14.8% had cavernous sinus thrombosis.

All the patients underwent CT chest and were classified according to Co-Rad classification, as shown in Fig. 2 and Table 4.

The mean duration of COVID-19 infection was 35.5 ± 18 days among the cases and ranging from 1 to 90 days. Upon assessing the relation between the onset of COVID infection and the onset of cerebrovascular stroke, 26% of patients with stroke and confirmed COVID-19 infection developed stroke immediately after COVID-19 infection (within 1 week). 41.7% of patients developed stroke within 1 month from getting infection with COVID-19 and 32.3% had developed stroke after 1 month of infection with COVID-19.

Among our cerebrovascular stroke patients, PCR was done to participants who had COVID-19 symptoms or were diagnosed with COVID-19 anytime during the past 3 months. (50.4%) of our patients had PCR positive results, and 7.9% were negative in spite of presence of respiratory symptoms but their CT chest was not suggestive to diagnose COVID-19 as it was only CO-RAD 1 or 2, 41.7% had no symptoms suggestive for COVID-19 infection and their CT chest was free, so they were considered as control group with no statistically significant difference between age and gender among the three groups, as shown in Table 5. 51 (26.6%) of COVID-19 PCR positive cerebrovascular stroke patients needed ICU admission, while 141 (73.4%) were isolated and treated in the inpatient ward.

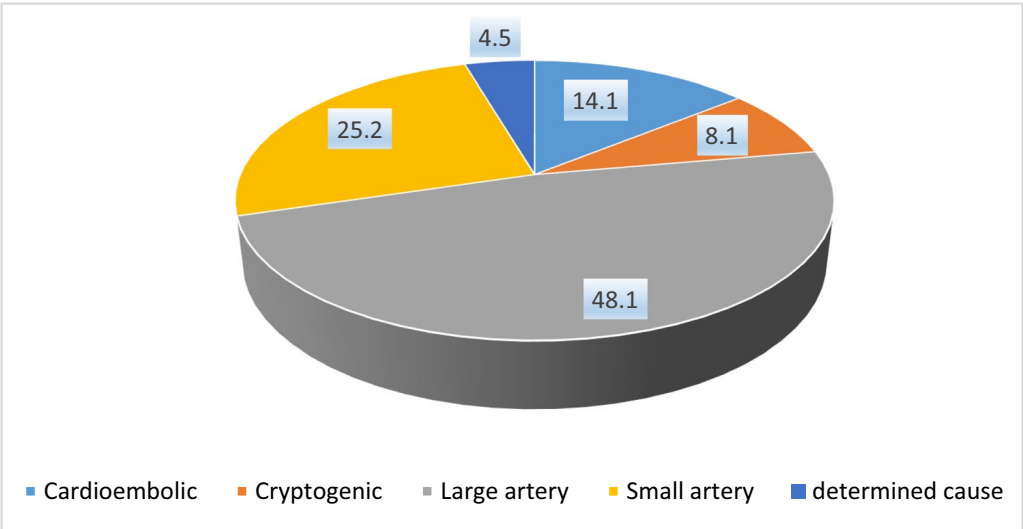

Fig. 1 TOAST classification among the participants

Table 3 Imaging findings of the brain among the participants

Variable	*n* = 381	%
Delta sign	3	0.8
Dense cord sign	5	1.3
Lt ACA inf	17	4.5
Lt br MCA	33	8.7
Lt frontal inf	9	2.4
Lt MCA inf	27	7.1
Lt occipital inf	2	0.5
Lt partial inf	11	2.9
Lt PCA inf	21	5.5
Multilacunar inf	12	3.1
Rt ACA inf	25	6.6
Rt br MCA inf	42	11.0
Rt frontal inf	15	3.9
Rt MCA inf	47	12.3
Rt occipital inf	15	3.9
Rt partial inf	32	8.4
Rt PCA inf	29	7.6
Rt temporal inf	14	3.7
Suspected venous inf	22	5.8

Lt left, *RT* Right, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *Inf.* infarction, *Br.* branch

Table 4 COVID-19 CO-RAD classification Level of suspicion COVID-19

		Ct findings
CO-RADS 1	No	Normal or non- infectious abnormalities
CO-RADS 2	Low	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Intermediate	Unclear whether COVID-19 is present
CO-RADS 4	High	Abnormalities suspicious for COVID-19
CO-RADS 5	Very high	Typical COVID-19
CO-RADS 6	PCR +	

The mean NIHSS (National Institutes of Health Stroke Scale) among the participants who suffered from new vascular symptoms was 10.5 ± 6.2. The highest NIHSS was found among PCR positive COVID patients.

($p < \mathbf{0.001}$*) (Fig. 3).

The type of cerebrovascular accidents that occurred in our patients was classified according to the TOAST classification, as shown in Table 6. Small arteries were higher among PCR negative and controls, while large arteries occlusion was higher among PCR positive than control.

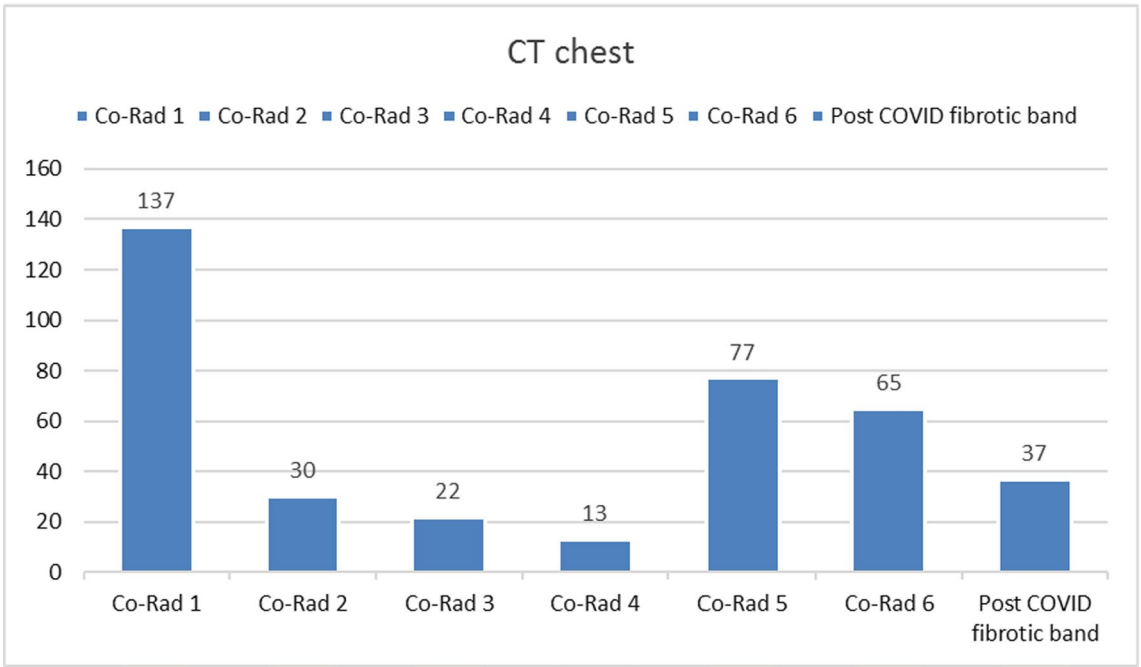

Fig. 2 CT chest findings among the participants

Table 5 Comparison between the studied groups regarding age and gender

Variable		PCR (+ve) *n* = 192	PCR (-ve) *n* = 30	Controls *n* = 159	*P* value
Age (years)	Mean ± SD	59.1 ± 14.6	58.8 ± 13.7	55.5 ± 15.2	0.218[a]
Gender	Male, n (%)	96 (50)	17 (56.7)	91 (57.2)	0.377[b]
	Female, n (%)	96 (50)	13 (43.3)	68 (42.8)	

a; Student t test

b; Chi-square test

* p is significant at < 0.05

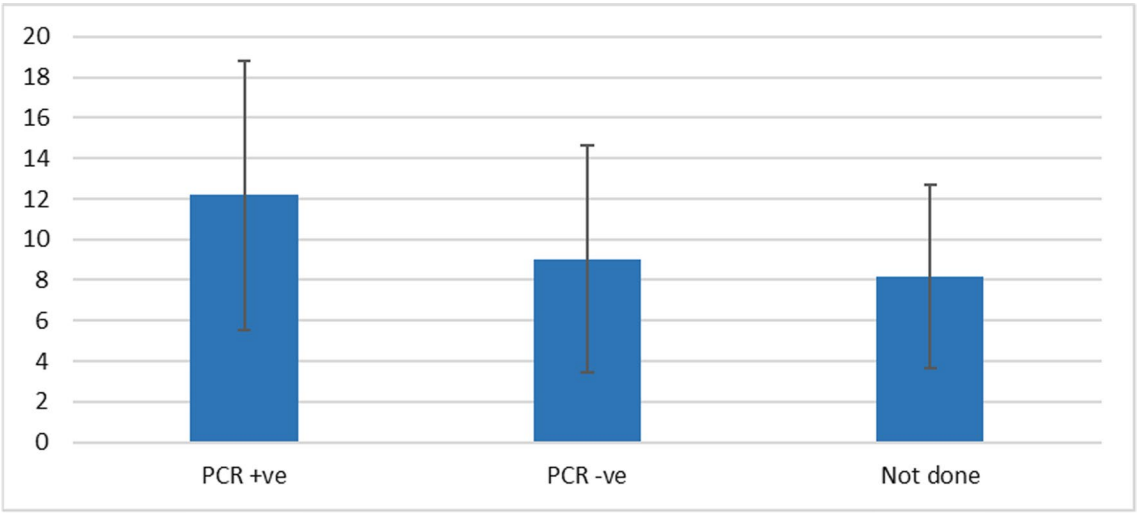

Fig. 3 NIHSS among the participants in all the studied groups

Table 6 Association between TOAST and COVID-19

Variable		PCR (+ve) *n* = 192	PCR (-ve) *n* = 30	Controls *n* = 159	*P* value
TOAST	Cardioembolic	36 (18.7)	1 (3.3)	17 (10.6)	< 0.001*
	Cryptogenic	10 (5.2)	2 (6.6)	19 (11.9)	
	Large artery	105 (54.7)	18 (60)	60 (37.7)	
	Small artery	34 (17.7)	6 (20)	56 (35.2)	
	Determined cause	7(3.6)	3 (10)	7 (4.4)	

Fisher Exact test

* p is significant at < 0.05

The total positive PCR COVID-19 patients were 192. Among them, 51 (26.6%) needed ICU admission, 23 of them were due to chest condition (most probably hypoxia) and 28 were due to deterioration of their neurological condition, 42 of them died, while only 9 improved and discharged to inward department (all of them discharged due to improvement of chest condition only), while 141 (73.4%) did not need ICU admission.

Upon assessment of disease severity, 38% patients suffered mild COVID-19, 34.9% had moderate COVID-19 infection, while 27.1% had severe COVID-19 infection.

Severity of infection was assessed by severity scoring system.

Upon studying the severity of infection in relation to different variables, we found that females had severe infection than males with a statistically significant

difference, older age was associated with more severe infection. The presence of vascular risk factors as hypertension, diabetes, cardiac diseases and chronic vascular diseases and elevated level of D-dimer in serum was associated with more increased severity of COVID infection. There was statistically significant association between the ICU admission and severity of COVID-19 infection.

There was statistically significant association between D-dimer and severity of COVID-19 infection. While there was no statistically significant association between Hemoglobin, WBCs, lymphocytes, neutrophils, platelets, CRP and severity of COVID-19 infection.

Association between TOAST and COVID-19 was shown in Table 6.

ICU admission among COVID-19 patients was shown in Table 7.

Severity of infection among COVID-19 patients was shown in Table 8.

Disease severity classification criteria of COVID-19 pneumonia was shown in Table 9.

Association between severity of infection and laboratory data was shown in Table 10.

Association between severity of infection in different variables was shown in Table 11.

Association between severity of infection and NIHSS and TOAST was shown in Table 12.

Table 7 ICU admission among COVID-19 patients (n = 192)

Variable		n = 192	%
ICU admission	Yes	51	26.6
	No	141	73.4

ICU Intensive Care Unit

Table 8 Severity of infection among COVID-19 patients (n = 192)

Variable		*n* = 192	%
Severity	Mild	73	38
	Moderate	67	34.9
	Severe	52	27.1

Discussion

This analytical cross-sectional study aimed to investigate the association between the stroke subtypes and the COVID-19 infection. This study was conducted among a total number of 381 participants with abrupt onset of neurological deficit patients diagnosed to suffer from ischemic cerebrovascular accidents.

The prevalence of COVID-19 according to PCR results of this study patients was 50.4% without statistically significant differences in age or gender as compared with

Table 9 Disease severity classification criteria of COVID-19 pneumonia

Mild	The clinical symptoms were mild and no signs of pneumonia were found in lung imaging
Moderate	The patient had symptoms of fever and respiratory infection, and the lung imaging showed pneumonia
Severe	Adults meet any of the following criteria: 1. Shortness of breath, RR 30 times/min; 2. In resting state, oxygen saturation 93%; 3. PaO2/FiO2 300 mmHg (lmmHg O.133 kPa) PaO2/FiO2 should be corrected according to the following formula: PaO2/FiO2 (atmospheric pressure

Severity classification Criterion

Table 10 Association between severity of infection and laboratory data

Variable	COVID-19 infection				*P* value
	No Mean ± SD	Mild Mean ± SD	Moderate Mean ± SD	Severe Mean ± SD	
Hb (g/dl)	11.5 ± 1.7	11.3 ± 2.1	10.9 ± 3.3	11.1 ± 1.9	0.211
WBC (*10^9/L)	5.2 ± 1.5	5.4 ± 0.9	5.3 ± 1.2	5.6 ± 1.4	0.530
Lymphocytes (*10^9/L)	1.1 ± 0.1	1.2 ± 0.09	1.2 ± 0.2	1.2 ± 0.1	0.661
Neutrophils (*10^9/L)	4.9 ± 1.2	4.8 ± 1.1	5.1 ± 1.1	5.2 ± 1.0	0.310
Platelet (*10^9/L)	217 ± 14.6	226 ± 16.1	223 ± 15.6	221 ± 14.9	0.505
D-dimer (µg/ml)	0.8 ± 0.4	1.1 ± 0.6	1.2 ± 0.7	1.5 ± 0.8	0.001*
CRP (mg/dl)	0.20 ± 0.3	10.6 ± 3.4	21.7 ± 9.5	34.4 ± 13.2	0.700

ANOVA

* p is significant at < 0.05 there was statistically significant association between D.dimer and severity of infection

Table 11 Association between severity of infection different variables

Variable		COVID-19 infection				*P* value
		No	Mild	Moderate	Severe	
Age	Mean ± SD	52.7 ± 15.2	55.6 ± 12.9	62.2 ± 12.1	69.1 ± 12.3	< 0.001*
Gender	Male, *n* (%)	114 (60.3)	44 (60.3)	26 (38.8)	20 (38.5)	0.001*
	Female, *n* (%)	75 (39.7)	29 (39.7)	41 (61.2)	32 (61.5)	
HTN	Yes, *n* (%)	53 (28)	35 (47.9)	28 (41.8)	31 (59.6)	< 0.001*
	No, *n* (%)	136 (72)	38 (52.1)	39 (58.2)	21 (40.4)	
DM	Yes, *n* (%)	48 (25.4)	20 (27.4)	23 (34.3)	30 (57.7)	< 0.001*
	No, *n* (%)	141 (74.6)	53 (72.6)	44 (65.7)	22 (42.3)	
Hyperthyroidism	Yes, *n* (%)	6 (3.2)	5 (6.8)	4 (6.0)	3 (5.8)	0.552
	No, *n* (%)	183 (96.8)	68 (93.2)	63 (94.0)	49 (94.2)	
Cardiac	Yes, *n* (%)	36 (19)	23 (31.5)	29 (43.3)	34 (65.4)	< 0.001*
	No, *n* (%)	153 (81)	50 (68.5)	38 (56.7)	18 (34.6)	
	AF, *n* (%)	9 (2.4)	11 (2.9)	8 (2.1)	10 (2.6)	
	IHD, *n* (%)	16 (4.2)	14 (3.7)	17 (4.5)	19 (4.9)	
	CMP, *n* (%)	3 (0.8)	4 (1.0)	6 (1.6)	5 (1.3)	
Renal/hepatic	Yes, *n* (%)	16 (8.5)	4 (5.5)	7 (10.4)	9 (17.3)	0.145
	No, *n* (%)	173 (91.5)	69 (94.5)	60 (89.6)	43 (82.7)	
Hypercholesteremia	Yes, *n* (%)	49 (25.9)	21 (28.8)	25 (37.3)	18 (34.6)	0.286
	No, *n* (%)	140 (74.1)	52 (71.2)	42 (62.7)	34 (65.4)	
Obesity	Yes, *n* (%)	56 (29.6)	13 (82.2)	17 (25.4)	10 (19.2)	0.167
	No, *n* (%)	133 (70.4)	60 (82.2)	50 (74.6)	42 (80.8)	
Chronic vascular CNS problems Hemorrhagic, *n* (%) 29 (7.6) Ischemic, *n* (%) 61 (16.0) Venous, *n* (%) 3 (0.8)	Yes, *n* (%)	34 (18.0)	15 (20.5)	21 (31.3)	23 (44.2)	0.001*
	No, *n* (%)	155 (82.0)	58 (79.5)	46 (68.7)	29 (55.8)	
D-dimer (µg/ml)		0.8 ± 0.4	1.1 ± 0.6	1.2 ± 0.7	1.5 ± 0.8	0.001*
ICU admission	Yes, *n* (%)		0 (0)	0 (0)	51 (98.1)	0.001*
	No, *n* (%)		73 (100)	67 (100)	1 (1.9)	

Chi-square test

* *p* is significant at < 0.05

Table 12 Association between severity of infection and NIHSS and TOAST

Variable		COVID-19 infection				*P* value
		No	Mild	Moderate	Severe	
NIHSS	Mean ± SD	8.2 ± 5.0	9.3 ± 4.9	12.3 ± 5.3	18.5 ± 5.4	< 0.001*
TOAST	Cardioembolic, *n* (%)	15 (7.9)	12 (16.4)	18 (26.9)	12 (23.1)	< 0.001*
	Cryptogenic, *n* (%)	26 (13.8)	6 (8.2)	1 (1.5)	1 (1.9)	
	Large artery, *n* (%)	74 (39.2)	39 (53.4)	39 (58.2)	37 (71.2)	
	Small artery, *n* (%)	74 (39.2)	16 (21.9)	9 (13.4)	2 (3.8)	

ANOVA; Exact Fisher test

* *p* is significant at < 0.05 severity of infection was significantly related to elevated NIHSS score, large artery disease occurred more with patients with severe COVID-19 infection

PCR negative results patients and CT chest not conclusive to diagnose COVID-19 infection (CO-RAD 1 or 2). This is consistent with the findings reported by Belani and colleagues [7]. and Martí-Fàbregas and colleagues [8]. Studies in which the prevalence of COVID-19 among acute stroke patients were (46.3% and 41.7%, respectively).

The stroke severity was higher among COVID-positive cases as evidenced by higher NIHSS and higher rate of ICU admission. Our results were in the same line with

a systematic review that included 61 papers about acute stroke among COVID-19 patients. They concluded that the median NIHSS score in patients with acute stroke was 15 (13–18). Stroke severity was higher in patients with stroke and COVID-19 [9].

Our results were also supported by Strambo and colleagues [2] and Martí-Fàbregas and colleagues [8] who found the NIHSS was higher among COVID-19 patients compared with the non-COVID-19 group upon admission. This can be explained by the fact that COVID-19 may induce a prothrombotic state, coagulopathy, hyper inflammation, increase the risk for occurrence of sepsis, leading to severe tissue injury, multiple organ system dysfunction, and promotion of thrombogenesis [10].

In addition, patients hospitalized or admitted to ICU for stroke with COVID-19 suffered from more severe symptoms than patients hospitalized for stroke without COVID-19 as shown by Gabet and colleagues [11].

In the current study, we found that small artery disease was higher among PCR negative patients and controls, while large arteries occlusion was higher among PCR positive cases with a statistically significant difference. These findings go along with the results of the study conducted by Kihira who conducted the first study that showed an association between COVID-19 and large vessel strokes. They reported that 62% of the large vessel strokes involved occlusion of the M1–M2 segments of the middle cerebral artery [12]. Another study by Martí-Fàbregas and colleagues [8] found that 42.9% of the studied patients who catched COVID-19 suffered from a large vessel occlusion.

In agreement with our results, a systematic review by Nannoni, [13] found that acute stroke due to large vessel occlusion was more common in COVID-19 cases.

Results of prior research suggested that the pathologic mechanisms involved in the occurrence of large artery strokes in COVID-19 patients include direct binding to ACE-2 receptors, which are expressed throughout the endothelial cells of the vasculature, which leads to vascular thrombosis within the vessels through a cytokine storm [14]. In other studies, high levels of D-dimer or other signs of hypercoagulability state were documented resulting in the occurrence of arterial cerebrovascular strokes, pulmonary embolism and venous thrombosis [15], thus explaining the occurrence of stroke among young people without vascular risk factors.

In contrast to our results, another studies found that the most common stroke mechanism in acute stroke with COVID-19 was cryptogenic [2]. This may be linked to other still undiscovered mechanisms responsible for the occurrence of ischemic stroke in patients who suffered COVID-19. In addition, the frequency of acute strokes due to small vessel disease was much lower than the approximately 20% mentioned in most stroke databanks [16]. The cause of this phenomenon, however, was not clearly known.

In this study, we found that severity of COVID-19 infection was associated with older age, female gender, presence of vascular disease risk factors as hypertension, diabetes, cardiac diseases and chronic vascular diseases.

Our results goes along with other studies who reported that diabetes, hypertension and other cardiovascular diseases (CVD) are strongly related to a higher risk of mortality or disease's severity among COVID-19 patients. They reported that older age is a major predictor of mortality and it is thus considered a key factor in the proposed clinical severity risk scores [17–21]. This may partly explain the higher proportion of vascular risk factors among the studied patients. Our results were also supported by Gabet and colleagues [11] who reported that female gender is associated with higher risk for stroke among COVID-19 patients.

In addition, other studies reported that pre-existing conditions, such as cardiovascular disease, chronic kidney disease, chronic lung diseases, diabetes mellitus, hypertension, immunosuppression, obesity, and sickle cell disease, predispose patients to an unfavorable clinical course and increased risk of intubation and death [22–27].

Consistent findings were reported in a study by Tan and colleagues [28] who found that the severity of COVID-19 was correlated with the health status of the patients and presence of chronic diseases as well as laboratory data as D-dimer and CRP.

In contrast to our results, a systematic review of acute stroke and COVID-19, found that female sex was less frequently affected [150/395 versus 773/1670; OR ¼ 0.71 (95%CI 0.51–0.99)] [28]. This may reflect differences in the population studied. It may also reflect differences in healthcare system organization and intensity of neurologic screening.

In the same line with our results, in a cohort study by Yu and colleagues [29]. patients with severe disease were more likely to exhibit dysregulated coagulation function, and a significantly higher D-dimer level (median 1.8 μg/ml [interquartile range 0.9–4.6] versus 0.5 [0.3–1.1], $p < 0.001$) was found in severe cases than the mild ones.

Similar to our results, Soni and colleagues [1]. and Düz and colleagues [30]. reported that D-dimer level ≥ 2.01 μg/mL was a significant predictor of subsequent deaths among patients with confirmed COVID-19 ($P < 0.01$; HR, 3.165; 95% CI 2.013–4.977). In addition, D-dimer level of > 2.48 μg/mL has worse prognostic value among COVID-19 patients reported by Wagner and colleagues [31].

This was explained as activation of the coagulation pathway with elevated D-dimer and fibrinogen is a common feature of many individuals with severe COVID-19 infection. This coagulopathy, termed "sepsis-induced coagulopathy" (SIC), is related to the infection-induced systemic inflammatory response and may contribute to the increased risk of thrombosis and stroke [32].

Conclusion

COVID-19 infection has been associated with both venous and arterial cerebrovascular stroke, especially in elderly patients. COVID-19 infection is associated with the occurrence of more severe stroke. Small artery stroke was higher among COVID-19 negative patients, while large artery stroke was higher among positive COVID-19 patients.

The severity of COVID-19 was associated with increased risk for ICU admission, higher NIHSS, and elevated D-dimer serum levels. In addition, chronic diseases as hypertension, diabetes, cardiac diseases, chronic vascular diseases are associated with increased severity of COVID-19.

Recommendations

We recommended that larger comprehensive studies are mandatory to completely understand the association between COVID-19 and acute cerebrovascular stroke. In addition, to identify the specific mechanisms of pathogenesis of COVID-19 causing cerebrovascular diseases.

Limitations

This study limitations include the limited number of patients included in this study which limits generalizability of the results. We included only symptomatic COVID-19 patients; all asymptomatic cases were missed.

Abbreviations

SARS-CoV-1	Severe acute respiratory syndrome
COVID-19	Coronavirus disease 2019
MERS-CoV	Middle East respiratory syndrome
ADC	Apparent diffusion coefficient
ICUs	Intensive care units
CRP	C-reactive protein
ACE2	Angiotensin-converting enzyme 2
NIHSS	National institutes of health stroke scale

Author contributions

MMH searched medical literature, databases, conceptualized, conducted the case review. IAY was responsible for revision of methodology and data analysis and reviewing the final manuscript. MAE was responsible for reviewing the final manuscript. AOH was concerned with reviewing the final manuscript. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

Data of patients collected are available whenever requested.

Declarations

Ethics approval and consent to participate

Approval from Research Ethics Committee of faculty of Medicine, Suez Canal University was taken before starting of the data collection on 3/8/2021 with number 4637. An informed written consent was taken from all patients before taking any data or doing any investigations. In case of illiterate patients, a fingerprint and a witness were available. The consent contained: explanation of the study aim in a simple manner to be understood by the common people. No harmful maneuvers were performed or used. All data were considered confidential and will not be used outside this research. All data were discarded after the end of the research. All participants were announced by the result of the study. Participants had the right to withdraw from the study at any time without giving any reason No financial compensation for the patients for time and effort. Administrative consent was taken including the emergency department consent.

Competing interests

The authors declare no conflict of interest in connection with the reported research. Authors declare veracity of information.

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