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Stroke as a presenting symptom of COVID-19; A study of risk factors, characteristics and outcomes in a sample of Egyptian patients

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ORIGINAL ARTICLE

Stroke as a Presenting Symptom of COVID-19: A Study of Risk Factors, Characteristics, and Outcomes in a Sample of Egyptian Patients

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Abstract

Background: **It is not known whether patients with coronavirus disease 2019 (COVID-19)-associated stroke have worse functional and vital outcomes than those without infection.**

Aim and objectives: **To compare between COVID-19-associated stroke and non-COVID-19-associated stroke cases regarding risk factors, characteristics, and outcome.**

Patients and methods: **In a prospective study, 297 patients diagnosed clinically and radiologically as having stroke and admitted to Emergency Department and stroke unit of Al-Azhar University hospitals were recruited in the period from beginning of December 2021 to the end of May 2022. They were classified into ischemic stroke (IS), cerebral venous thrombosis, subarachnoid hemorrhage, and intracerebral hemorrhage groups. Workup for COVID-19 was done in each group followed by comparison between both groups.**

Results: **We evaluated 297 patients, and 46 (15.4%) had COVID-19 infection. In IS group, age, hypertension, and previous cerebrovascular stroke were significantly lower. Large vessel occlusion, median baseline National Institutes of Health Stroke Scale score, and serum ferritin were significantly higher in COVID-19-associated IS group. Moreover, COVID-19-associated IS had a worse outcome regarding median Modified Rankin scale, hemorrhagic transformation, and mortality rate. According to TOAST classification, cryptogenic subtype was significantly higher in COVID-19-associated IS group. Lymphocyte (%) was significantly lower but D-dimer was significantly higher in COVID-19-infected patients in all stroke groups.**

Conclusion: **Patients with COVID-19-associated IS have more severe strokes, worse functional outcome, and a higher mortality than those without infection.**

Keywords: Cerebral venous thrombosis, Coronavirus disease 2019, Intracerebral hemorrhage, Stroke

1. Introduction

Individuals with coronavirus disease 2019 (COVID-19) typically experience neurological problems, including stroke, which can affect up to 23% of patients.[1] The prevalence of stroke varied from 0.9 to 5% in four retrospective registries of hospitalized COVID-19-infected patients.[2,3] On the contrary, the epidemic has severely affected the use of well-established therapies and the capacity of the health care systems to continue providing care for patients with stroke.[4,5]

Additionally, according to the COVID-19, individuals with vascular risk factors for stroke, such as ageing, diabetes, hypertension (HTN), obesity, and prior cardiac or cerebrovascular illness, are at an elevated risk of death and morbidity.[6,7]

It is not known whether patients with COVID-19-associated stroke have worse functional and vital outcomes than those without infection.[8]

We hypothesized that patients with ischemic stroke (IS) have a worse prognosis than those who do not have COVID-19 infection. We are hoping

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that by contributing toward this topic we may help individuals with concurrent COVID-19 infection and IS receive better care.

In this study, we aimed to compare between COVID-19-associated stroke and non-COVID-19 stroke groups regarding risk factors, characteristics, and outcomes.

2. Patients and methods

The study was approved by the Ethics Committee of the Al-Azhar Faculty of Medicine. We obtained written informed consent from patients or their relatives before enrollment in this study.

In this prospective study, 297 patients diagnosed clinically and radiologically as having stroke and admitted to Emergency Department and stroke unit of Al-Azhar University hospitals were recruited in the period from beginning of January 2022 to the end of June 2022. They were classified into IS, cerebral venous thrombosis, subarachnoid hemorrhage, and intracerebral hemorrhage groups. Workup for COVID-19 was done in each group followed by comparison between both groups.

The following data were collected: detailed medical and neurological history, full general and neurological examination, assessment of stroke severity using the National Institute of Health Stroke Scale (NIHSS) score at admission, assessment of outcome of stroke using modified Rankin scale (MRS) for neurologic disability, neurological imaging: computed tomography (CT) brain and/or MRI brain, chest imaging (CT chest), and laboratory tests (complete blood count, C-reactive protein, D-dimer, serum ferritin, and RT-PCR test for COVID-19).

Infection of COVID-19 was established by positive RT-PCR test of respiratory samples (e.g. nasopharyngeal swab).

2.1. Statistical analysis

SPSS (Statistical Package for the Social Science) program, version 25.0 (IBM Inc., Chicago, Illinois, USA), Microsoft Office Excel 2016 software, was used to calculate the statistical significance. Improvement was measured by mean change.

We used Kolmogorov–Smirnov test to validate normal distribution of data. Descriptive statistics were done for all studied parameters in the studied groups. Percentages and numbers represented qualitative data. Mean ± SD represented quantitative parametric data. Difference between qualitative variables was calculated using χ^2 test, whereas Fisher exact test was used when expected cell count was less than 5. Comparison of numerical variables was done using independent t test when data were normally distributed and Mann–Whitney U test when not normally distributed. The obtained findings were evaluated at 5% significance level.

3. Results

We evaluated 297 patients with stroke. Among 37 COVID-19-associated IS cases evaluated, three (8%) patients presented only with stroke features without fever or other COVID-19 manifestation.

In the IS group, median age, HTN rate, and previous cerebrovascular stroke were significantly lower, but large vessel occlusion (LVO) and median baseline NIHSS score were significantly higher in COVID-19-associated IS group.

Moreover, COVID-19-associated IS had a worse outcome regarding median MRS, hemorrhagic transformation, and mortality rate. According to TOAST classification, cryptogenic subtype was significantly higher in COVID-19-associated IS group (Tables 1–5).

3. Discussion

It is unknown whether patients with stroke with COVID-19 infection have worse functional and vital outcomes than people without COVID-19 infection.

In this study, we aimed to compare between COVID-19-associated stroke and non-COVID-19-associated stroke groups regarding risk factors, characteristics, and outcomes.

In our study, among 37 COVID-19-associated ischemic stroke cases evaluated, three (8%) patients presented only with stroke features without fever or other COVID-19 manifestation.

This is supported by the work of Shah et al.[9] who revealed that only stroke symptoms were observed in 29.2% of the patients, who had no previous COVID-19 symptoms.

In our study, the median age was significantly lower in COVID-19-associated IS group. This is supported by the work of Shah et al.[9] who revealed that patients with COVID-19 made up 58.3% of those under 55 years. In addition, Demirelli et al.[10] found that non-COVID-19 group patients' ages were greater than those of COVID-19-infected patients.

In contrast to our results, Li et al.[3] revealed that older patients with COVID-19 should receive additional care because they are possibly more likely to develop cardiovascular disease.

In addition, Ramos-Araque et al.[11] revealed that the average age of COVID-19-infected patients was between 60 and 79 years.

Table 1. Demographic characteristics of patients with stroke with and without coronavirus disease infection.

Variables	Groups				Test	*P* value
	COVID +ve		COVID −ve			
Age (years)						
Ischemic stroke ($N = 252$)	58.3 ± 11.1		62.96 ± 9.17		t value = 2.77	0.006 significance
N (median, minimum−maximum)	37 (59, 24−82)		215 (62, 33−87)			
Cerebral venous thrombosis ($N = 11$)	54.67 ± 12.86		48.63 ± 12.24		t value = 0.721	0.489 NS
N (median, minimum−maximum)	3 (60, 40−64)		8 (45.5, 33−73)			
Subarachnoid hemorrhage ($N = 5$)	49		43.75 ± 10.90		−	−
N (median, minimum−maximum)	1 (0)		4 (42.5, 32−58)			
Intracerebral hemorrhage ($N = 29$)	67.00 ± 8.31		68.17 ± 9.59		t value = 0.252	0.803
N (median, minimum−maximum)	5 (66, 55−78)		24 (70, 50−88)			NS
Sex [n (%)]						
Ischemic stroke ($N = 252$)						
Male	23	62.2	119	55.3	$\chi^2 = 0.596$	0.440 NS
Female	14	37.8	96	44.7		
Cerebral venous thrombosis ($N = 11$)						
Male	1	33.3	2	25.0	FET	1.00 NS
Female	2	66.7	6	75.0		
Subarachnoid hemorrhage ($N = 5$)						
Male	1	100	2	50.0	−	−
Female	0		2	50.0		
Intracerebral hemorrhage ($N = 29$)						
Male	2	40.0	12	50.0	FET	1.00 NS
Female	3	60.0	12	50.0		

COVID, coronavirus disease; FET, Fisher's exact test; t test, independent t test; χ^2, χ^2 test.

Table 2. Hypertension and previous CVS among the studied groups.

Variables	COVID + ve [n (%)]		COVID −ve [n (%)]		χ^2 test	*P* value
Hypertension						
Ischemic stroke						
Yes	21	56.7	158	73.5	4.29	0.03 significance*
No	16	43.3	57	26.5		
Cerebral venous thrombosis						
Yes	1	33.3	2	25.0	0.076	0.782 NS
No	2	66.7	6	75.0		
Subarachnoid hemorrhage						
Yes	1	100.0				
No			4	100.0		
Intracerebral hemorrhage						
Yes	4	80.0	17	70.8	0.174	0.677 NS
No	1	20.0	7	29.2		
Previous CVS						
Ischemic stroke						
Yes	5	13.5	63	29.3	0.99	0.046 significance*
No	32	86.5	152	70.7		
Cerebral venous thrombosis						
Yes	1	33.3			= 2.93	0.087 NS
No	2	66.7	8	100.0		
Subarachnoid hemorrhage						
Yes	0					
No	1	100	4	100		
Intracerebral hemorrhage						
Yes	0		5	20.8	1.259	0.262 NS
No	5	100	19	79.2		

COVID, coronavirus disease; CVS, cerebrovascular stroke.
*: $P < 0.05$ = Significant.

Table 3. Large vessel occlusion rate, National Institutes of Health Stroke Scale score in patients with ischemic stroke with and without coronavirus disease infection.

LVO	COVID +ve [*n* (%)]		COVID −ve [*n* (%)]		χ^2 test	*P* value
Ischemic stroke						
Yes	22	59.5	84	39.1	5.385	0.02 significance
No	15	40.5	131	60.9		
NIHSS	COVID +ve		COVID −ve		MW test	*P* value
Ischemic stroke	13.1 ± 6.49		8.29 ± 4.69		2187	<0.001 significance***
N (median, minimum−maximum)	37 (13, 4–26)		215 (7, 3–23)			

COVID, coronavirus disease; LVO, large vessel occlusion; MW-U, Mann−Whitney *U* test; NIHSS, National Institutes of Health Stroke Scale.
*: $P < 0.05$ = Significant. ***: $P < 0.001$ = Highly significant.

Table 4. Average modified Rankin scale and outcome/complications in patients with stroke with and without coronavirus disease infection.

Variables	COVID +ve	COVID −ve	Test	*P* value
MRS				
Ischemic stroke	3.83 ± 1.61	2.87 ± 1.30	MW-U = 2629	<0.001
N (median, minimum−maximum)	37 (4, 1–6)	215 (3, 1–6)		Significance***
Cerebral venous thrombosis	3.33 ± 2.52	1.63 ± 0.52	MW-U = 6.5	0.227 NS
N (median, minimum−maximum)	3 (3, 1–6)	8 (2, 1–2)		
Subarachnoid hemorrhage	2	3.25 ± 1.89		
N (median, minimum−maximum)	1 (0)	4 (2.5, 2–6)		
Intracerebral hemorrhage	3.0 ± 1.87	2.83 ± 1.49	MW-U = 58	0.933 NS
N (median, minimum−maximum)	5 (3, 1–6)	24 (3, 1–6)		
Outcome/complications [*n* (%)]				
Ischemic stroke				
Discharge on treatment	21 (56.8)	190 (88.4)		
Hemorrhagic transformation	6 (16.2)	9 (4.2)	$\chi^2 = 0.791$	<0.001
Death	10 (27.0)	16 (7.4)		Significance***
Cerebral venous thrombosis				
Discharge on treatment	2 (66.7)	8 (100)		
Hemorrhagic transformation	–	–	–	–
Death	1 (33.3)	–		
Subarachnoid hemorrhage				
Discharge on treatment	1 (100)	3 (75)		
Death	–	1 (25)		
Intracerebral hemorrhage				
Discharge on treatment	4 (80.0)	20 (83.3)	$\chi^2 = 8.31$	0.85
Death	1 (20.0)	4 (16.7)		

COVID, coronavirus disease; MRS, modified Rankin scale; MW-U, Mann−Whitney *U* test.
***: $P < 0.001$ = Highly significant.

Table 5. TOAST classification in patients with ischemic stroke with and without coronavirus disease infection.

Variables	COVID +ve	COVID −ve	Test	*P* value
Cerebrovascular disorder/subtype				
Ischemic stroke	*n* (%)	*n* (%)		
Cardioembolic	10 (27.0)	61 (28.4)		
Cryptogenic	12 (32.4)	57 (26.5)	$\chi^2 = 14.58$	0.012 Significance*
Large artery atherosclerosis	9 (24.3)	42 (19.5)		
Small vessel disease	5 (13.5)	53 (24.7)		
Other determined	1 (2.7)	2 (0.9)		

COVID, coronavirus disease.
*: $P < 0.05$ = Significant.

In our study, the HTN rate was considerably lower in the IS group associated with COVID-19.

This is supported by the work of Srivastava et al.[12] who revealed that compared with the COVID-19 group, HTN was considerably greater in patients without COVID-19.

In our study, previous cerebrovascular stroke was significantly lower in COVID-19-associated IS group.

This is supported by the work of Shah et al.[9] and Srivastava et al.[12] who revealed that previous cerebrovascular stroke was considerably lower in COVID-19-associated IS group compared with non-COVID-19 group.

In our study, LVO was significantly higher in COVID-19-associated IS group.

This is supported by the work of Dogra et al.[13] In this study, LVO was present in 31.7% of patients with COVID-19 versus 15.3% of patients without COVID-19. According to the authors, COVID-19 is linked to LVO strokes.

In addition, Yao et al.[14] found that COVID-19-associated IS patients were more likely to suffer LVO and multi-territory infarcts; rapid patient evaluation is essential for successful reperfusion treatment.

In our study, median baseline NIHSS score was significantly higher in COVID-19-associated IS group.

A recent retrospective study[2] discovered that patients with COVID-19 infection had higher baseline NIHSS scores than patients without COVID-19 infection (median NIHSS score: 19 vs. 8). In contrast, the degree of the stroke in our study was less severe (median NIHSS score: 13 vs. 7).

In addition, Li et al.[3] and Yao et al.[14] reported that severe infection may be linked to cardiovascular disease, particularly acute ischemic stroke.

In our study, COVID-19-associated IS had a worse outcome regarding median MRS.

This is supported by the work of Strambo et al.[15] who stated that in COVID + IS patients, the functional outcome assessed by the MRS at 3 months was considerably worse. Moreover, Grewal et al.[16] revealed that IS in the COVID-19 setting is linked to less favorable results.

In our study, COVID-19-associated IS had a worse outcome regarding hemorrhagic transformation.

This comes in agreement with Dogra et al.[13] who stated that, along with thrombosis, intracranial hemorrhage, either as primary intracranial hemorrhage or hemorrhagic transformation, was also observed in COVID-19-infected patients.

In our study, COVID-19-associated IS had a worse outcome regarding mortality rate. This is supported by the work of Parsay et al.[24] who stated that patients with COVID-19 had a significant death rate of 29.2%, and Yao et al.[14] who revealed that patients with COVID-19 plus acute ischemic stroke (AIS) exhibited a nearly four-fold higher chance of dying than those without COVID-19 infection.

Other recently published studies[2,18] also reported that a greater case-fatality rate was linked to COVID-19 infection in patients with stroke. The respiratory distress and multiorgan failure seen in certain patients, as well as other COVID-19 infection-related factors may help to explain our observation. Aging may also be a factor in the life-threatening evolution, in addition to the cardiovascular risk.[19]

According to this study, a significant number (32.4%) of strokes among COVID-19-infected patients were related to a cryptogenic cause.

This is supported by the work of Ntaios et al.[19] and Yaghi and colleagues,[2,20,21] who reported that cryptogenic stroke prevalence is higher in COVID-19 infection.

In addition, Fuentes and colleagues, Shahjouei and colleagues, Siegler and colleagues, and Yao and colleagues[14,22,23] revealed a higher proportion of cryptogenic stroke ranged from 22 to 35% in COVID + IS patients.

In contrast, Strambo et al.[15] reported that lower proportion of cryptogenic stroke (15%) was observed in COVID + IS patients.

No difference was observed between COVID-19-positive and COVID-19-negative patients in terms of sex, ischemic heart disease, atrial fibrillation, smoking, alcohol intake, and white blood cell count.

Our study has notable strengths. They include prospective design and large sample size of patients with stroke with COVID-19 infection. Moreover, the multicenter design including Al-Azhar University hospitals (Al-Hussien and Bab El-Shaeria) demonstrates the applicability of our findings in general.

Our research has some drawbacks. Patients were chosen from the emergency room, preventing the inclusion of those whose stroke was first identified after spending days or weeks in the ICU and who were frequently intubated or under the influence of sedative drugs. These patients' strokes may have various pathophysiologies and be more severe.

Additionally, because this research was conducted in a hospital, it is possible that the frequency and severity of strokes linked to COVID-19 infections are skewed toward more severe cases, assuming that the milder cases may not have sought medical treatment or gone to the hospital.

Finally, we were unaware of the precise treatments given to individuals who were not hospitalized to the stroke unit. This was likely variable between participating centers and may have contributed to poor results at some locations because of inadequate stroke care.

3.1. Conclusion

With a focus on its prognosis and a determination of its relative frequency at a specific historical

period, we highlighted the characteristics of COVID-19-associated ischemic stroke in our study.

Future studies will help us determine if patients need receive particular care, whether this subtype of stroke has a different physiopathology from stroke without infection, and how the healthcare system should change in response to threats like the one we have seen.

Conflict of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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