

The Impact of COVID-19 Pandemic on the Increased Number of Deaths Due to Heart Attack and Stroke Among Saudis And Egyptians: A Comparative Study

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ABSTRACT

Background: Many articles describing the comorbidities on the gastrointestinal, neurological, and respiratory manifestations of the COVID-19 infection. The cardiovascular system is often affected and caused acute myocardial infarction, venous thromboembolic events, and monitoring with high sensitivity cardiac troponin. Ischemic stroke remains the most common subset of neurological manifestations in COVID- 19 infection.

Aim of research: This comparative cross-sectional retrospective study was carried out to assess and compare the association between COVID -19 infection and the risk of acute ischemic stroke among both Saudi and Egyptian infected patient.

Subjects and Methods: Data was collected through a well-structured questionnaire, distributed among patients who infected with COVID-19 in Saudi Arabia and Egypt. The questionnaire includes patients' Socio-demographic and history of chronic diseases, laboratory investigations, time of getting stroke after COVID-19 infection and symptoms of COVID infection and stroke, as well as stroke outcomes. Then, data was statistically been analyzed using (SPSS, version 25) statistical program.

Results: 635 participants (288 Egyptians and 347 Saudis) were included in this study who were infected with COVID-19 and completed the data of the questionnaire. Most of participants were young (< 46 years old), and females. The total percent of participants who had stroke due to infection with COVID-19 and recovered without side effect was 1% & 1.2%, while 1.7% & 0.9% recovered but having some side effects among Egyptians and Saudis respectively. All these patients with stroke had medical history of cardiovascular diseases, hypertension, diabetes, dyslipidemia with elevated levels of D-dimer, C-reactive protein, white blood cell, neutrophils and low level of lymphocytes.

Conclusion: Our research supports the fact that COVID- 19 infection is associated with a clinical outcome of ischemic stroke that tend to the highest rate of mortality. Also, more research is needed to examine the neurological implications of COVID-19 disease.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [Lai et al., 2019]. Patients with SARS-CoV-2 infection may present symptoms ranging from mild to severe with a large portion of the population being asymptomatic carriers [Ciotti et al., 2020]. The most common reported symptoms include fever, cough, and shortness of breath [Wang 2020]. Although the main target of coronavirus infection is the lung, the wide distribution of Angiotensin Converting Enzyme 2 (ACE2) receptors in organs [Hamming et al., 2004] may lead to damage that has to be closely monitored [Renu et al., 2020]. Thus, the link between SARS-CoV and ACE2 provides

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one theoretical mechanism for cardiac dysfunction in COVID-19: ACE2 downregulation leads to cardiac dysfunction [Oudit et al., 2009]. The cardiovascular system is often affected, with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events, and monitoring with high sensitivity cardiac troponin [Long et al., 2020]. However, it is now well established that this is a multi-system inflammatory process often presenting with acute cardiac events like myocarditis, an acute renal event, and multi-organ failure [Agarwal et al., 2020]. Although a wide range of neurological manifestations have been reported in the literature, ischemic stroke remains the most common subset of neurological manifestations in

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COVID-19 infection [Rahman et al., 2020]. About 5% of patients with COVID-19 developed acute ischemic stroke and 0.5% had intracerebral hemorrhage [Li et al., 2020].

The current study aims to assess the relationship between COVID19, heart attack, stroke, and if it is encountered de novo as part of the clinical course of COVID19 or in those with preexisting cardiac disease. To estimate the privileges of using thrombolytic or anticoagulant drugs in reducing the cardiovascular complications that happen due to COVID-19 infection.

SUBJECTS AND METHODS

This comparative study was conducted by collecting data from people either in Saudi Arabia or Egypt through distribution of questionnaire. We explained the aim of this study, all information related to the research, and their personal information is saved and secured in a file on the computer with secured password and the principal investigator is the person who are responsible for security of this data. Their participation was not obligatory, and they can withdraw from the research at any time without any problem and all their personal information will be secured. Also,

we informed them that filling of this questionnaire is considered as an agreement from them in participation. Collecting data from participants through questionnaires started from 15th December 2021 for 2 months.

Data Collection & statistical analysis

635 Participants (288 Egyptians and 347 Saudis) completed the questionnaire from Saudi Arabia and Egypt. Data was collected through well-structured Questionnaire, about Scio-demographic data, symptoms, and complications of COVID -19 infection, time of getting strokes, medical history of patients and laboratory tests. Statistical analysis of the results using version 25 SPSS Inc, Chicago, IL, USA.

Inclusion Criteria

Persons who infected with COVID -19 between the age of 18 years old and above from both genders.

Exclusion Criteria

People who didn't infect with COVID-19 or children below 18 years old.

Table 1: Demographic Characteristics of the Egyptian and Saudi Participants who infected with COVID-19. [Total n=635 Participants, n=288 (Egyptians), n= 347 (Saudis)]

Question	Answer	Egypt n (%)	Saudi Arabia n (%)
Total number of Participants		288 (45.4)	347 (54.6)
Gender	Male	94 (32.6)	48 (13.8)
	Female	194 (67.4)	263 (86.2)
Age Groups (years)	18-25	148 (51.4)	177 (51)
	26-35	47 (16.3)	61 (17.6)
	36- 45	42 (14.6)	47 (13.5)
	46- 55	29 (10.1)	21 (6.1)
	56-65	12 (4.2)	8 (2.3)
	>65	10 (3.5)	16 (4.6)
PCR Check for COVID-19 infection.	YES	101 (35.1)	115 (33.1)
	NO	187 (64.9)	232 (66.9)
Severity of symptoms of COVID -19 infection.	5-9 Days, Simple symptoms	186 (64.6)	216 (62.2)
	10-15 Days, Moderate symptoms	86 (29.9)	109 (31.4)
	>15 Days, Critical case (hospital admission)	16 (5.6)	22 (6.3)
Medications received for COVID -19 infection.	Antipyretic and analgesics, vitamins, antivertigo	281 (97.6)	341 (98.3)
	Antibiotics	279 (96.9)	340 (98)
	Anticoagulants or antiplatelet	226 (78.5)	299 (86.2)
	Anti-cough and phlegm	199 (69.1)	211 (60.8)
	Anti-emetic & anti-diarrheal	166 (57.6)	231 (66.6)
	Bronchodilators and Oxygen devices	99 (34.4)	110 (31.7)
	Treatment of heart diseases	95 (32.9)	87 (25.1)

RESULTS

Table 1 shows that 635 COVID-19 infected individuals, 347 (13.8% males) of Saudi patients and 288 (32.6% males) of Egyptian patients. Most of participants are young (< 46 years old), only one third who perform PCR test for COVID-19 infection. Nearly the same percentage of patient either in Egypt or KSA (64.6% & 62.2%) with simple symptoms (5-9 Days), also, about 30% with moderate symptoms (10-15 days), while low percentages with critical cases and need hospitalization (5.6% & 6.3%) respectively (Figure 1). Majority of patients received antibiotics, antipyretic and analgesics, vitamins, anti-cough and mucolytic to treat the symptoms of COVID-19 infection. 78.5% & 86.2% of Egyptian and Saudis received anticoagulants or antiplatelet, respectively, that is very important to prevent stroke.

Table 2. illustrates that about 13.2% & 8.4% of patients with heart diseases such as arrhythmia, heart failure, blood clots

and clogged arteries (either 2 diseases or more) besides, 22.9% & 12.9% knew other patients who died with stroke due to COVID-19 among Egyptians and Saudis respectively. These patients suffered from different symptoms such as shortness of breath, chest pain or arms that may spread to the neck, jaw, or back, cold sweats & extreme fatigue, dizziness. The age of those patients who died with stroke after infection with the COVID-19 ranged from 15-45 (9% & 4%) and more than 45 (13.9% & 8.9%) among Egyptians and Saudis respectively (Figure 2).

Table 3. shows the results of Egyptian patients. Patients who had stroke after infection with COVID 19 were 5 females (62.5%) + 3 Males (37.5%), three of them >65, 3 (56-65) and 2 (46-55) years old. Four of them have symptoms of stroke 2 - 4 weeks after having COVID 19 and the other four patients diagnosed with COVID 19 after 2-4 months. Compared to Saudi Patients,

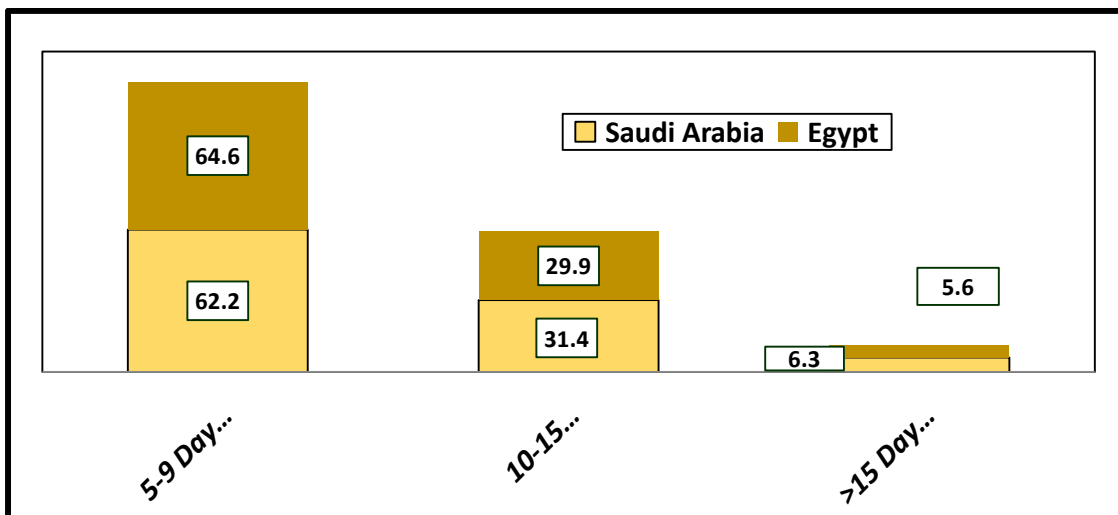


Fig. 1: Severity of symptoms of COVID -19 infection (%)

Table 2: Knowledge about the signs and symptoms among studying groups after infection with COVID-19 and having stroke after covid. [Total n=635 Participants, n=288 (Egyptians), n= 347 (Saudis)]

Question	Answer	Egypt n (%)	Saudi Arabia n (%)
Cardiovascular disease before infection with the COVID-19.	No	250 (86.8)	318 (91.6)
	Heart Failure	10 (3.5)	7 (2)
	Arrhythmia	12 (4.2)	8 (2.3)
	Blood clotting	8 (2.8)	6 (2.4)
	Clogged arteries	8 (2.8)	8 (2.3)
Patients who died with stroke due to COVID-19.	YES	66 (22.9)	45 (12.9)
	NO	222 (77.1)	302 (87.1)
Symptoms of Patients with COVID -19.	Nausea, Heartburn, stomach pain	66 (22.9)	84 (24.2)
	Shortness of breath, Chest pain or arms that may spread to the neck, jaw, or back, cold sweats & extreme fatigue, dizziness.	42 (14.6)	33 (9.6)
	I don't know	220 (76.4)	302 (87)
Age of the Patients who died with stroke after infection with the COVID-19 (years).	18-25	4 (1.4)	5 (1.4)
	26-35	12 (4.2)	5 (1.4)
	36-45	12 (4.2)	4 (1.2)
	46-55	10 (3.5)	11 (3.2)
	56-65	10 (3.5)	10 (2.9)
	>65	20 (6.9)	10 (2.9)
	I do not know	220 (76.4)	302 (87)

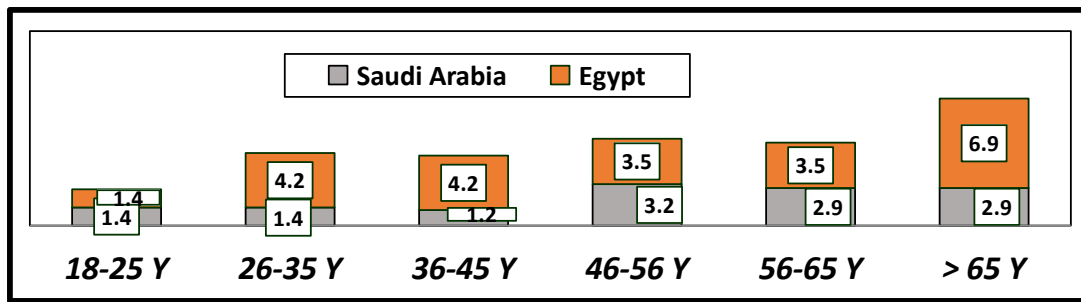


Fig 2: Age of the Patients who died with stroke after infection with the COVID-19 (years)(%)

Table 3: Clinical Characteristics and Laboratory findings of patients with COVID-19 with or without new-onset Stroke

Question	Total Egyptians	Egypt [n (%)]		Total Saudis	Saudi Arabia [n (%)]	
		COVID-19 with Stroke	COVID-19 without Stroke		COVID-19 with Stroke	COVID-19 without Stroke
Total Number	288	8 (2.8%)	280 (97.2%)	347	7 (2%)	340 (98%)
Age (Years)						
<46	237	0	237 (100)	302	0	302 (100)
46-55	29	2 (6.9)	27 (93.1)	21	1 (4.8)	20 (95.2)
56-65	12	3 (25)	9 (75)	16	3 (18.7)	13 (81.3)
> 65	10	3 (30)	7 (70)	8	3 (37.5)	5 (62.5)
The time of having stroke after infection with COVID-19.						
2 - 4 weeks	8	1 (0.3)	---	7	1 (0.3)	---
2 - 4 months		6 (2.1)			3 (0.9)	
>4 months		1 (0.3)			3 (0.9)	
Recovering from stroke.						
Stroke, no side effects	8	3 (1.0)		7	4 (1.2)	
Stroke, with side effects		5 (1.7)			3 (0.9)	
Medical History						
Cardiovascular Diseases	68 (23.6)	8 (11.8)	60 (88.2)	89 (25.6)	7 (24.1)	82 (75.9)
Hypertension	152 (52.8)	8 (5.3)	144 (94.7)	188 (54.1)	7 (3.7)	131 (96.3)
Diabetes	106 (36.8)	8 (7.5)	98 (92.5)	157 (45.2)	7 (4.5)	150 (95.5)
Tobacco Smoking	71 (24.7)	3 (4.2)	68 (95.8)	42 (12.1)	2 (4.8)	40 (95.2)
Dyslipidemia	120 (41.7)	8 (6.7)	112 (93.3)	151 (43.5)	7 (4.6)	144 (95.4)
None	47 (16.3)	0	47 (100)	43 (12.4)	0	43 (100)
D-Dimer (mg/L)						
Normal level	200	0	200 (100)	320	0	320 (100)
Slightly High level	88	0	88 (100)	104	0	104 (100)
Very High Level	10	8 (80)	2 (20)	13	7 (53.8)	6 (46.2)
C reactive protein (mg/L)						
Normal level	217	0	217 (100)	318	0	318 (100)
Slightly High level	61	0	61 (100)	99	0	99 (100)
Very High Level	10	8 (80)	2 (20)	10	7 (70)	3 (30)
White blood cell count, ×10 ⁹ /L						
Normal level	200	0	200 (100)	286	0	286 (100)
Slightly High level	73	0	73 (100)	97	0	97 (100)
Very High Level	15	8 (53.3)	7 (46.7)	14	7 (50)	7 (50)
Neutrophil, ×10 ⁹ /L						
Normal level	202	0	202 (100)	300	0	300 (100)
Slightly High level	75	0	75 (100)	88	0	88 (100)
Very High Level	11	8 (72.7)	3 (27.3)	16	7 (43.7)	9 (56.3)
Lymphocyte count, ×10 ⁹ /L						
Normal level	201	0	201 (100)	326	0	326 (100)
Slightly low level	64	0	64 (100)	80	0	80 (100)
Very Low Level	13	8 (61.5)	5 (38.5)	11	7 (63.6)	4 (36.4)

5 females (71.4%) + 2 Males (28.6%) had stroke, three of them >65, 3 (56-65) and one with 46-55 years old. Four of them have symptoms of stroke 2 - 4 weeks after having COVID 19 and the other three patients diagnosed with COVID 19 after 2-4 months (Figure 3). The total percent of participants who had stroke due to infection with COVID-19 and recovered without side effects was 1% & 1.2%, while 1.7% & 0.9% recovered but having some side effects among Egyptians and Saudis respectively. All these patients with stroke had medical history of cardiovascular diseases, hypertension, diabetes, dyslipidemia (Figure 4 & 5).

For both Saudis and Egyptians, most of their symptoms were pain in the chest or arms that may spread to the neck, jaw, or back. All of them received treatment protocol for COVID 19 including anticoagulants, also they have history of cardiovascular diseases, hypertension, hyperlipidemia and diabetes Mellitus, and males are smokers.

Regarding the laboratory findings of patients with COVID-19 with new-onset Stroke, D-Dimer (mg/L), C reactive protein (mg/L), white blood cell count, $\times 10^9 /L$ and neutrophil, $\times 10^9 /L$ were significantly higher than normal values, while Lymphocyte count, $\times 10^9 /L$ was low than normal values.

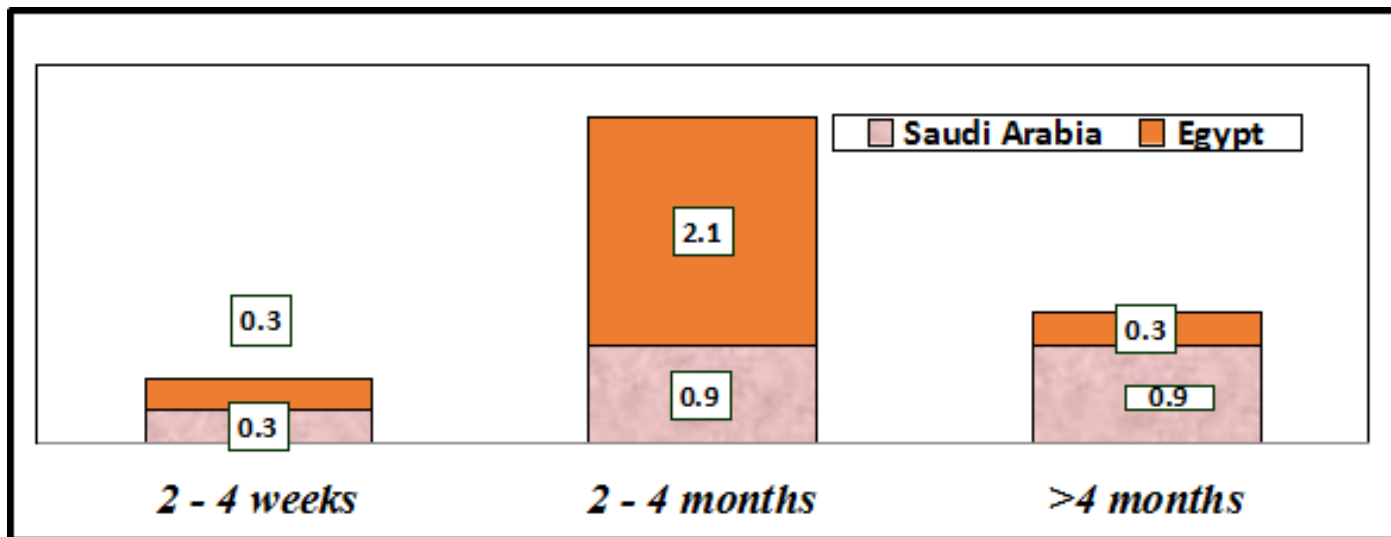


Fig. 3: The time of having stroke after infection with COVID-19 (%)

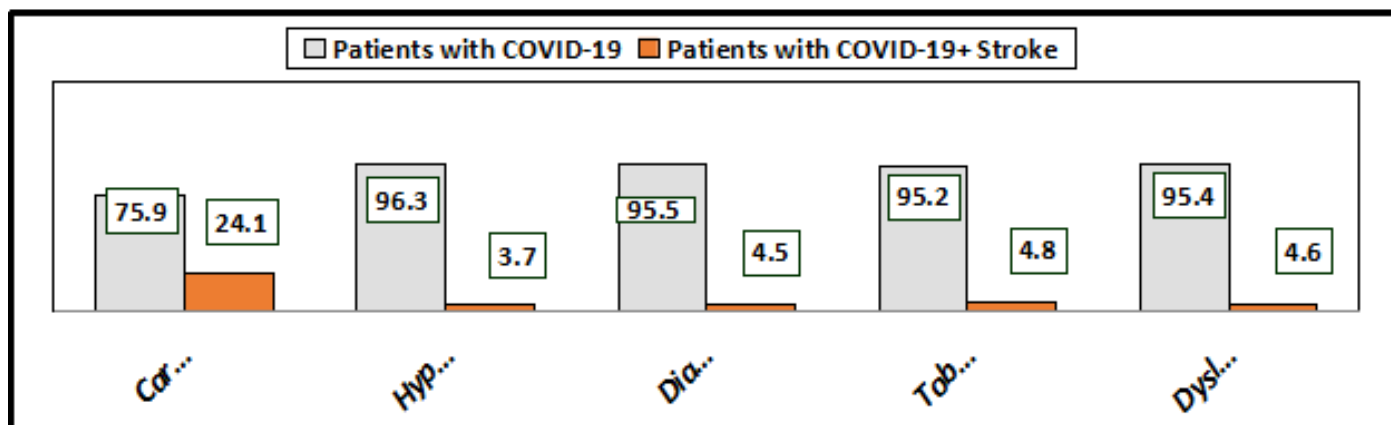


Fig. 4: Medical History of Saudi Arabia patients with COVID-19 compared with COVID-19 + stroke (%)

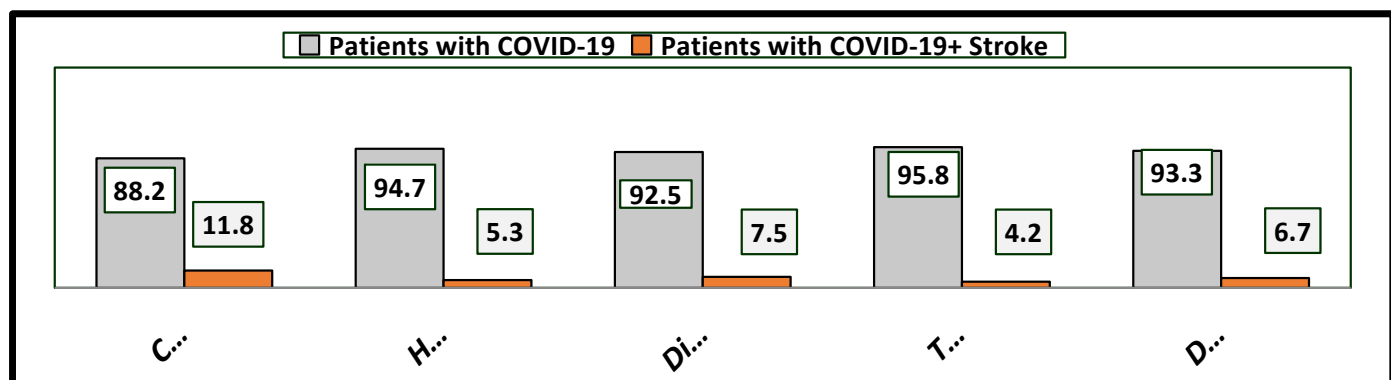


Fig. 5: Medical History of Egyptian patients with COVID-19 compared with COVID-19 + stroke (%)

DISCUSSION

An ample number of reports brings a reasonable concern of SARS-CoV-2 being a new neuropathogenic that is still to be elucidated. [Montalvan et al., 2020] Stroke, predominantly acute ischemic stroke, is a serious complication of COVID-19. [Mendes et al., 2021] Although prior studies have analyzed incidence of cerebrovascular accident during COVID-19 pandemic, further studies are recommended to better understand the risk factors and phenotype.

To the best of our knowledge, this study is among the descriptions of incidence at a broad level, comparing Saudi Arabia and Egypt. We performed this comparative cross-sectional retrospective study to investigate risk factors, comorbidities, and outcomes in patients with ischemic stroke derived from a both Saudi and Egyptian confirmed COVID-19 infected patient. It is not surprising that patients with COVID-19 who developed acute ischemic stroke in our cohort were older, smoker and had a higher frequency of hypertension, diabetes, hyperlipidemia, arrhythmia, heart valve problems and congestive heart failure, which were important predictors of poor COVID-19 outcomes.

According to the American Heart Association/American Stroke Association Stroke Council Leadership, stroke mechanisms in COVID-19 could include different processes, involving the release of proinflammatory cytokines with a direct effect on plaque rupture through local inflammation and activation of coagulation factors or cardiac embolism from virus-related cardiac injury, in addition to the role of the angiotensin-converting enzyme 2. [Benussi et al., 2020] Therefore, a clear association of acute cerebrovascular disease with COVID-19 has been observed. Acute ischemic stroke is the most common manifestation of acute cerebrovascular disease in patients suffering from COVID-19 and is reported as a presenting feature of the young. [Nannoni et al., 2021, Oxley et al., 2020]

The present study identifies several differences between patients infected with COVID-19 who have developed stroke and those who haven't developed stroke. In this cross-sectional analysis of 635 COVID-19 infected individuals, 2.8% of Saudi patients developed stroke, compared to 2% of Egyptian patients. The observed higher rate in Saudi Arabia may be explained in part by the higher availability of testing. Our results concur with other recent reports studying the incidence of ischemic cerebrovascular accident (CVA) in the setting of COVID-19. A recent systematic review and meta-analysis quantitative outcomes have revealed an average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3%, depicting that infection with COVID-19 might be a crucial factor in increasing the incidence of acute ischemic stroke. [Arsay et al., 2021] Other recent studies have reported a prevalence rate of acute stroke in COVID-19 patients of 1.4%. [Nannoni et al., 2021] Others demonstrated 1.48% stroke rate across more than 119,000 COVID-19 hospitalizations and SARS-CoV-2 infection was noted in 3.3% of all stroke admissions. [Nogueira et al., 2021] Higher rate of re-occlusion within 30 days compared with a previous analysis of non-infected patients (4.5% vs 0.4%). Re-occlusions might be promoted by a prothrombotic state, antiphospholipid syndrome, cytokine storm or other coagulopathies-factors that have already been described with COVID-19 and related stroke pathogenesis. [Styczen et al., 2020] Other reported that patients received at least standard

doses thromboprophylaxis, ultrasonography confirmed venous thromboembolism in 27% and arterial thrombotic events in 3.7% and pulmonary embolism was the most frequent thrombotic complication. [Klok et al., 2021]

In the current study, ischemic stroke mostly occurred 2-4 months after COVID-19 symptom onset, suggesting that COVID-19 associated ischemic stroke is usually delayed, as reported in an earlier report. [Beyrouiti et al., 2020] Other revealed that increased risk of acute ischemic stroke in the first 3 days after covid-19 diagnosis specially in patients more than 65 years old. [Yang et al., 2022] The mortality rate in acute COVID-19 infection is more than that corresponding to rates of mortality in non-infected stroke patients. [Styczen et al., 2022]

Regarding the age and sex as demographic risk factors, our patients suffering from stroke as a complication of COVID-19 are generally male elderly, more than 65 years, who need more attention and precise care. This comes in accordance with various reports showing a mean age of at least 60 years old. [Merkler et al., 2020; Bach et al., 2020]. Other revealed that increased risk of acute ischemic stroke was observed in ≥ 65 years old. [Yang et al., 2022] In contrast, some studies have reported stroke as a complication of COVID-19 in young age. [Khan et al., 2020; Pons-Escoda et al., 2020; Ashrafi et al., 2020] Other study reported that a clear association of acute cerebrovascular disease with COVID-19 has been observed, with overall incidence of 1.4% [Nannoni et al., 2021], and 4% is reported as a presenting feature of the young. [Nannoni et al., 2021, Oxley et al., 2020] Also, other reported that patients with COVID-19 and stroke were significantly younger than patients with stroke without COVID-19. [Oxley et al., 2020; Majidi et al., 2020; Sweid et al., 2020; Srivastava et al., 2021]

Herein, severe illness was defined as patients who required admission to the ICU, or manifesting symptoms lasting more than 15 days. The incidence of stroke among severely ill patients COVID-19 patients was 2.8% & 2%. This observation can be attributed to an elevated D-dimer level and coagulation cascade activation among the critically ill COVID-19 patients, which could be responsible for further thrombotic cerebrovascular events in infected patients. [Tang et al., 2020]

In the current work, patients with COVID-19 who developed acute ischemic stroke (compared with those who didn't develop stroke) have a higher frequency of smoking (4.2%), hypertension (5.3%), diabetes (7.5%), hyperlipidemia (6.7%), and cardiovascular diseases (11.8%), predisposing to large vessel atherosclerosis and small vessel disease. Consistently, the current findings agree with earlier studies, suggesting that even if COVID-19 is a predisposing factor, the risk is mainly seen in those at risk for acute ischemic stroke due to other cardiovascular risk factors. [Benussi et al., 2020, Qin et al., 2020, Morassi et al., 2020, Fatima et al., 2020] However, other reports demonstrated that that occurrence of acute ischemic stroke in COVID-19 infected patients were without preexisting cardiovascular risk factors [Oxley et al., 2020; Yaghi et al., 2020]

It has been well-established that diabetes is one of the comorbidities for COVID-19 progression, critical clinical outcomes and mortality. This has been explained based on the

increase in the serum angiotensin-converting enzyme 2 (ACE2), and an overexpression of ACE2, the known entry receptor for SARS-CoV, as a result of taking of angiotensin-converting enzyme (ACEs) inhibitors and angiotensin II receptor blockers (ARBs).[Elemam et al., 2021]

Various hypotheses have been suggested to explain the apparent link between COVID-19 infection, cardiovascular risk factors, and increased risk of stroke including, but are not limited to shock, hypotension, heart failure, and disseminated intravascular coagulation that can potentially contribute to hypoperfusion, embolic mechanism of stroke, and large vessel occlusion. [Fatima et al., 2020; Montalvan et al., 2020; Avula et al., 2020]

From the present analysis, Egyptian infected patients have developed worse outcomes of stroke as compared to Saudi patients. This can be partly contributed to social distancing and avoiding visiting the hospitals for fear of catching COVID-19 infection, resulting in a decrease in presentation of Transient ischemia attacks, mild, or moderate strokes. [Diegoli et al., 2020]

CONCLUSION

In conclusion, it is mandatory to raise awareness to go to the emergency department due to any acute neurological symptoms regardless of any pandemic. Also, stroke teams should be aware of the fact that COVID-19 patients can present with cerebrovascular accidents and dawn appropriate personal protective equipment in every suspected patient. Indeed, more research is needed to examine the neurological implications of COVID-19 disease.

Informed consent Statement was made to protect their rights and ensure the security of their information. There is a phrase at the top of the questionnaire that states that completing the questionnaire constitutes acceptance to participate in this study

Ethical Approval: Research ethical approval number was (H-2021-228) that was reviewed and approved by the Research Ethical Committee (REC) at the University of Hail dated: 06/12/2021.

Authors' contributions: This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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