

Review Article

Ischemic Stroke in COVID-19 Patients: A Narrative Review

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Abstract

Coronavirus disease 2019 (COVID-19) is primarily known as a respiratory illness; however, a wide variety of symptoms and complications can also occur. It is

associated with a small but clinically significant risk of stroke attributed to a hypercoagulable state. There is a need to summarize clinical characteristics, stroke mechanisms, and recommendations to prevent stroke in

this population. The literature search was performed using PubMed, and after applying the inclusion and exclusion criteria, 6 published papers were found. The overall incidence of stroke in COVID patients can range from 1 to 2%, with high variability. COVID patients who developed stroke were mostly men, with a mean age above 60, and had a severe COVID-19 infection. In most cases, it was a large artery stroke. Acute Ischemic Stroke (AIS) in the setting of COVID-19 is associated with worse outcomes. It is very important to practice social distancing to prevent people from getting the infection. Prophylactic treatment should be given in patients with symptomatic COVID-19 infections, while asymptomatic carriers can prevent their chance of COVID-19 stroke by lifestyle changes and dietary modifications.

Keywords: COVID-19; Ischemic Stroke

1. Introduction

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in China and took the world by storm. Its burden on societies has been hefty and catastrophic, affecting millions, and more than 2.6 million people have died till now [1]. It is still a poorly understood disease [2]. COVID-19 has diverse symptomatology, ranging from mild upper respiratory tract infection to pneumonia and even thrombo-embolic events. These thrombo-embolic events can be in the form of stroke, Myocardial Infarction, and Pulmonary embolism [3]. Studies have demonstrated that up to 4.6 % of COVID patients can develop stroke [2]. Ischemic stroke secondary to COVID-19 infection can prove to be fatal. COVID-related stroke can be severe with a high mortality rate. While the reasons for ischemic stroke in COVID-19 are unclear, hypotheses of an inflammatory cytokine storm triggered hypercoagulable state, endothelial damage, and arrhythmias have been postulated [4]. This review aims to discuss different

observational studies highlighting stroke in COVID-19 patients and provide a general overview regarding its incidence. Furthermore, we summarize pathophysiology, possible risk assessment of mortality in in-patient settings, and how the risk of mortality can be reduced.

2. Method

Literature was searched on PubMed. MeSH Keywords used were "COVID-19", "SARS-CoV-2", and "Ischemic Stroke". Studies were selected after applying the following inclusion/exclusion criteria. The inclusion criteria were: 1) human subjects, 2) paper published in the English language and 3) studies that are observational, cohort, and case-control. The exclusion criteria were: 1) animal studies and 2) non-English literature.

3. Results

After applying the MeSH keywords, a total of 62 articles were obtained. Of these articles, about 36 were removed as they were not specifying the disease of interest. On secondary screening, further 20 articles were removed, which consisted of letters to the editor and duplicates. The remaining articles were used for our review article. The total number of participants in our study was 329. We have included 6 observational studies in our traditional review.

4. Discussion

In this current review, we analyzed data from 329 patients with COVID-19 related stroke to look more closely at the incidence, male to female ratio, types of stroke, and mortality. Furthermore, we have also discussed the possible pathophysiology of acute ischemic stroke in COVID-19 patients, the score to analyze the risk of mortality, and recommendations to prevent stroke in this COVID era. SARS-CoV-2 infection increases the risk of developing ischemic

stroke. Incidence rates as high as 4.6% have been observed [2]. Observational studies included in our review reported stroke incidence of 0.9% [5], 1.1% [6], and 2.0 [7], as shown in Table 1. These rates are similar to a meta-analysis that has demonstrated the pooled average incidence of 1.7% for ischemic cerebrovascular

accidents (CVA), ranging from 1.3% to 2.3% [2]. The mean age of patients in studies was mostly more than 60, except for one, where the mean age was 46.5 [8]. In most of the studies, stroke was more common in the male population as demonstrated in Table 2.

Study/ reference	Country	Publication Time	Subjects with stroke (N)	Percentage of Covid patients developing stroke (%)
Yaghi S [5]	USA	2020 Jul	32	0.9
Grewal P [7]	USA	2020 Aug 20	13	2.0
John S [8]	Abu Dhabi	2020 Dec	20	-
Naval-Baudin P [11]	Europe	2021 Jan	19	-
Ramos-Araque ME [6]	4 countries	2021 Jan 30	156	1.1
Perry RJ [12]	UK	2021 Mar	86	-

Table 1: Stroke incidence in COVID-19 patients.

Study/ reference	Mean age (years)	Male (%)	The severity of covid infection	Type of strokes	Outcome/ mortality	Cryptogenic (%)
Yaghi S [5]	62.5	71.9	81.3% had severe illness	-	higher mortality	65.6
Grewal P [7]	61.6	-	A severe form of disease	cortical (84.6%)	Worse outcome	
John S [8]	46.5	93	-	Large-vessel occlusions (75%)		-
Naval-Baudin P [11]	70.2	63	Severe illness		higher in-hospital mortality	-
Ramos-Araque ME [6]	61.5% were between 60 and 79 years of age	60.6	-		high mortality rate	42.6
Perry RJ [12]	-	-	-	multiple large vessel occlusions (17.9% vs 8.1%, p<0.03)	inpatient death (19.8% vs 6.9%, p<0.0001).	-

Table 2: Classification and Outcomes of COVID-19 related strokes.

Several studies have highlighted that mortality tends to be higher in patients with COVID-19 stroke. The observational studies in our review have shown similar results, as illustrated in Table 2. A meta-analysis has demonstrated that stroke-related mortality rates range from 15% to 50% [2]. Grewal P, who studied AIS in a diverse patient population, mentions that AIS in the setting of COVID-19 is associated with worse outcomes, especially among African-American and Latino populations [7]. Two studies from our data-set have demonstrated a higher than expected proportion of patients with cryptogenic stroke. Cryptogenic stroke is defined as a stroke of undetermined etiology after excluding cardiac sources of embolism, large artery atherosclerotic stenosis, and small vessel disease. Ramos-Araque ME mentions that admission white blood cell count, c-reactive protein, and D-dimer levels were significantly higher for patients diagnosed with cryptogenic stroke. This finding suggests that hypercoagulability could be the cause of cryptogenic strokes. The high incidence of intracranial occlusion (46%) and cortical (74.4%) strokes also suggests a disproportionate number of patients with embolic strokes who suffer from COVID-19 [6]. Similar findings were observed in work published from a New York hospital system, where there were three groups, and the incidence of cryptogenic stroke was analyzed. Cryptogenic stroke was more common in patients with COVID-19 (65.6%) as compared to contemporary controls (30.4%, $P=0.003$) and historical controls (25.0%, $P<0.001$). Compared with contemporary controls, COVID-19 positive patients had higher admission National Institutes of Health Stroke Scale score and higher peak D-dimer levels [5]. These studies have also illustrated that patients with cryptogenic stroke and COVID-19 are at a significantly greater risk of early mortality, maybe due to the severe inflammatory or prothrombotic state that is attributed to COVID-19. Large vessel disease was seen in studies

indicating coagulopathy and endothelial dysfunction as a potential etiology of COVID-related strokes.

4.1 Pathophysiology

The association between the thrombo-embolic phenomenon and SARS-COV-2 is strong. There are many hypotheses explaining the possible reason for it. Fore and foremost is that this virus has the tendency to attach to ACE receptors, which are abundant on vascular endothelium. Virus particles bind to these cells resulting in endothelial dysfunction [3]. An autopsy series of 3 COVID-19 patients indicated systemic viral infection of the endothelium with inflammatory cells associated with virally infected cells [9]. Hence, vascular dysfunction plays an integral role in coagulation abnormalities seen in COVID-19 patients. Furthermore, the complement was also co-localized with SARS-CoV-2 S-protein in these patients, indicating complement targeting of virally-infected endothelium. Activation of the complement system has the potential to increase the risk of thrombus formation, both through C3a stimulation of platelets and insertion of terminal complement components into membranes [3].

The inflammatory and immune system further compound endothelial dysfunction in the creation of a pro-coagulant state in COVID-19 patients. Immune cell infiltration of virally-infected tissue occurs, which is evident from previous studies [3]. Immunity and coagulation systems are closely linked, and activation of the immune system during infection will invariably result in a lower threshold for thrombi formation [3]. Also, in an acute inflammatory state, many cytokines are released, leading to platelet activation, further deteriorating the state. Antibody responses may also play a role in COVID-19-related coagulation. Downregulation of ACE2 by SARS-CoV-2 infection may result in an imbalance of interactions between

ACE2 and the RAS axis, leading to a predisposition to thromboembolic events [3].

4.2 Mortality risk assessment

Given the strong association between stroke and early mortality, a mortality risk assessment consisting of criteria of Age, male sex, Diabetes, NIHSS (National Institutes of Health Stroke Scale) score of 10+ and cryptogenic stroke was set up. This assessment would help in the future planning of stroke patients. Patients who met these 5 criteria were at an 80% chance of in-hospital mortality. Although this assessment can help predict the outcome of patients during hospitalization, it does have its downsides. Firstly, the criteria of NIHSS and its scoring can be inaccurate due to the patient being sedated. Secondly, the patients can be falsely labeled as cryptogenic stroke, in case of either incomplete investigations or a premature diagnosis [6].

4.3 Recommendation

Acute ischemic stroke is a dire complication of SARS-COV2. Anti-thrombotic and anti-inflammatory treatment is given to symptomatic SARS-COV2 patients. These treatments can do wonders in preventing acute ischemic stroke. On the other hand, the prevention of stroke in asymptomatic SARS-COV2 patients involves lifestyle changes and dietary modifications. High blood pressure, uncontrolled diabetes, dyslipidemias, and dehydration are all risk factors for acute ischemic stroke. Fortunately, these risk factors can be managed. Regular physical activity and a low salt diet can significantly lower high blood pressure. A higher intake of water to prevent dehydration can also be very effective in preventing stroke. A low-fat diet can decrease the risk of raised LDL. The recommendations for preventing stroke for the general public are also the same as for asymptomatic SARS-COV2 patients. Mitigating factors like raised blood pressure, dyslipidemias, dehydration, and high sugar

levels is the objective of these dietary and lifestyle modifications [10].

5. Conclusion

Stroke in COVID-19 patients is associated with an increased risk of morbidity and mortality. The hyper-coagulable state in COVID is the probable cause of it. It's very important to assess the mortality risk in these patients. Measures should be taken in this COVID-era to reduce the chances of getting infected by maintaining a safe distance. Prophylactic treatment should be given in patients with symptomatic COVID-19 infections, while asymptomatic carriers can prevent their chance of COVID-19 stroke by higher water intake to prevent dehydration, low salt diet, low-fat diet, and controlling diabetes.

References

1. COVID-19 Coronavirus Pandemic updates. Worldometers (2021).
2. Parsay S, Vosoughi A, Khabbaz A, et al. The Incidence and Mortality Ratio of Ischemic Cerebrovascular Accidents in COVID-19 Cases: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis* (2021): 105552.
3. Snell J. SARS-CoV-2 infection and its association with thrombosis and ischemic stroke: a review. *Am J Emerg Med* 40 (2021): 188-192.
4. Spence JD, de Freitas GR, Pettigrew LC, et al. Mechanisms of Stroke in COVID-19. *Cerebrovasc Dis* 49 (2020): 451-458.
5. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke* 51 (2020): 2002-2011.
6. Ramos-Araque ME, Siegler JE, Ribo M, et al. SVIN Multinational Registry and Task Force. Stroke etiologies in patients with COVID-19:

- the SVIN COVID-19 multinational registry. *BMC Neurol* 21 (2021): 43.
7. Grewal P, Pinna P, Hall JP, et al. Acute Ischemic Stroke and COVID-19: Experience From a Comprehensive Stroke Center in Midwest US. *Front Neurol* 11 (2020): 910.
 8. John S, Kesav P, Mifsud VA, et al. Characteristics of Large-Vessel Occlusion Associated with COVID-19 and Ischemic Stroke. *AJNR Am J Neuroradiol* 41 (2020): 2263-2268.
 9. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395 (2020): 1417-1418.
 10. Chen X, Zhao X, Jing H, et al. COVID-19 and ischemic stroke: Mechanisms of hypercoagulability (Review). *Int J Mol Med* 47 (2021): 1.
 11. Naval-Baudin P, Rodriguez Caamaño I, Rubio-Maicas C, et al. COVID-19 and Ischemic Stroke: Clinical and Neuroimaging Findings. *J Neuroimaging* 31 (2021): 62-66.
 12. Perry RJ, Smith CJ, Roffe C, et al. SETICOS collaborators. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry* 92 (2021): 242-248.



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