

Review Article

Ischemic stroke in COVID 19: A systematic review

ABSTRACT

Aims: To determine an association between inflammatory and coagulation markers in a COVID-19 patient with ischemic stroke.

Study design: We performed a systematic review of 4 databases using the keywords "ischemic", "stroke", "COVID-19", "Virus"

Place and Duration of Study: (Month) - (Month) 2021

Methodology: Randomised control trials, observational studies, and systematic reviews were evaluated to ascertain the correlation between inflammatory and coagulation markers in COVID-19 patients with Ischemic stroke. Searches were conducted using Cochrane/EMBASE, PubMed/Medline, and PEDro between (2000-2021).

Results: Of the inflammatory markers, white blood cells (WBC) and platelets did not vary considerably outside their normal ranges. All markers of hypercoagulability were elevated, but only Prothrombin Time corresponded with C-reactive protein (CRP).

Conclusion: Inflammatory markers were not useful in forecasting the development of acute ischemic stroke, but CRP levels may be a possible marker to further research. D-dimer is a tried and true lab test that should be part of management guidelines in the ongoing COVID pandemic.

Comment [P1]: Month ? When ?

Keywords: Ischemic stroke, COVID 19 pandemic, C-reactive protein, hypercoagulability

1. INTRODUCTION

It's no understatement to state that COVID-19 has become one of the biggest crises of the modern era. Belonging to the coronavirus genus, it is a highly contagious virus transmitted via droplets in the air [1]. Respiratory involvement is often seen as evidence of the large number of inflammatory cells found in the lung parenchyma [2]. Lab investigations in such patients reveal lymphopenia (as opposed to common viral infections that cause lymphocytosis) and an increase in concentrations of pro-inflammatory cytokines such as interleukin 6 (IL-6) [3]. Recently, the newest variant (OMICRON) has been detected in several areas, and although much of its characteristics are unknown, preliminary data from the WHO has shown increased hospitalization rates. Furthermore, as many as 5 million people have expired due to the virus. Older people and those with chronic illnesses are especially vulnerable [4]. But the modality of death has been different in each case. Some causes of death were respiratory-related (e.g pulmonary embolism, pneumothorax), some heart-related (e.g cardiac arrest, cardiogenic shock), for others septic shock or acute renal failure, and then there were cerebrovascular accidents [5]. This is precisely why patients infected with COVID respond well to low molecular weight heparin (LMWH) because it reduces thrombotic complications such as acute Ischemic stroke [6]. An ischemic stroke should be differentiated from a hemorrhagic stroke which has a different pathophysiology.

Whereas the latter involves rupture of a vessel and consequent bleeding into a closed compartment, the former involves diminished blood supply to the region of interest. This results in a lack of oxygen supply, and ultimately the death of tissue cells secondary to necrosis. One of the common risk factors for ischemic stroke include diabetes mellitus (DM), and according to one study COVID-19 can induce a cytokine storm that leads upto to DM; such patients benefit from use of DPP-4 inhibitors [7]. As described by the Centre for Disease Control (CDC), symptoms can vary depending upon the blood supply compromised, but these include hemiparesis, visual field defects, dysarthria, facial drop, ataxia, aphasia, and sudden drop in consciousness. The cerebral arteries each supply a distinct area of the brain, and it is usually their smaller arterioles that can be blocked or clogged leading to a lacunar stroke [8]. The cause can be thrombus formation, an embolus [9], or hypercoagulable states like DIC. Even a blockage of the internal carotid artery can give rise to stroke-like symptoms, despite anastomosis from the opposite side [10]. The mechanism in which COVID-19 causes ischemic stroke has still yet to be clarified, however, several theories are given: (a) Coagulopathy resulting from endothelial injury, (b) Frequent presence of anti-phospholipid antibodies [11], and (c) Increased incidence of atrial arrhythmias or myocardial infarctions (which can give birth to an embolus) [12]. The purpose of this review is to clarify further how COVID-19 is linked with ischemic stroke. Several systematic reviews have already touched upon the subject concluding the incidence rate of stroke is indeed higher in patients infected with covid, however fell short of exploring pathophysiologic mechanisms related to causality [13]. Our systematic review differs in that our synthesis aims to look at the different inflammatory markers alongside coagulation markers to determine if there is any linkage/patterns.

2. METHODOLOGY

From 2010 to 2021, we carried out a systematic review by identifying articles from the Cochrane/EMBASE, PubMed/Medline, and PEDro databases relevant to our study. Using the Boolean operations "AND", and "OR" the following keywords: "ischemic", "stroke", "COVID-19", and "Virus" were used in combination or separately. Only the most recent articles were reviewed to include the latest advances in the field of medicine, particularly with regards to infectious diseases and neurology. Additional relevant research was conducted by hand-searching the reference list of the included papers. The initial screening resulted in 700 records. Duplicates were removed from the titles and abstracts [reviewed for relevant studies by two independent assessors (*author names to be included here*)]. Studies involving animal and pediatric populations were also excluded. Next, these records were scanned and the records that were unavailable as full text or were abstract only were discarded. It resulted in the removal of (639) records. Then, (61) records were screened by title, and (49) records were excluded. Finally, the full texts of (12) records were then retrieved and independently evaluated for eligibility via Mendeley reference manager, resulting in the elimination of (5), and ultimately only 7 were reviewed (Fig. 1). Conflicts were resolved by a third independent assessor (*author name/s to be included here*).

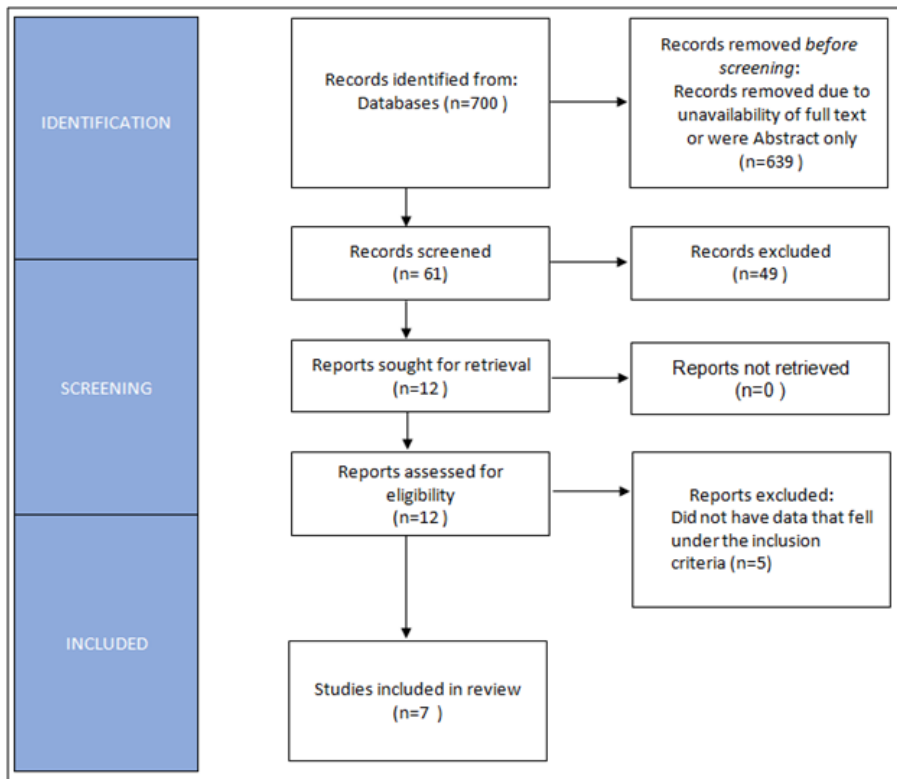


Fig. 1. PRISMA diagram showing screening process of studies

2.1 Eligibility Criteria

The inclusion criteria for the studies were as follows:

1. Studies that contained data regarding inflammatory markers such as white blood cells, platelets, CRP, etc.
2. Studies that contained data regarding coagulation markers such as D-dimers, fibrinogen, PT, APTT, etc.
3. Studies that were conducted on human participants (regardless of age, sex, or race) affected by COVID-19 and had subsequently developed ischemic stroke.
4. Any article type (randomized controlled trials, cohort studies, observational studies, systematic reviews, and meta-analyses - for review of citations and extraction of singular studies, conference proceedings).

The exclusion criteria were as follows:

- a. Studies published in any language other than English.
- b. Studies for which the full text was not available.
- c. Technical papers.

2.2 Data Collection

Data extracted from the compiled studies and results generated in this systematic review provided an ample summary of the present literature regarding the association between COVID-19 and ischemic stroke with regards to laboratory investigations.

2.3 Data Item

White blood cells ($\times 10^3 \text{ mm}^3$)
Platelets ($\times 10^3 \text{ mm}^3$)
CRP (mg/dl)
D-dimer (ng/ml)
Fibrinogen (mg/dl)
PT (secs)
APTT (secs)
Ferritin (ug/L)

2.4 Information Sources

Cochrane/EMBASE (2000-2021)
PubMed/MEDLINE (2000-2021)
PEDro (2000-2021)

2.5 Search Strategies

Following PRISMA guidelines [14], eligible articles were searched via PubMed and other search engines using the PICO framework on the 15th of December, 2021.

Patient = COVID-19 infected patients with ischemic stroke

Intervention= Laboratory investigations

Comparison= Normal lab values

Outcome= Changes between inflammatory markers and coagulation markers

The list below shows the keywords used in different combinations:

1. COVID-19 Virus Ischemic stroke
- 2.COVID-19 stroke
- 3.COVID-19 Ischemia
4. Cerebral infarction COVID-19
5. CoronaVirus Ischemic stroke
6. Neurology COVID-19
7. Thrombotic COVID-19 Brain
8. Brain Infarction COVID-19
9. Coagulopathy COVID-19

2.6 Risk of Bias

There was a collective low risk of bias of all the reviews and this was assessed using a revised Cochrane's risk of bias method, by identifying any of the following domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Few studies showed

ambiguities in one of the aforementioned domains (Fig. 2), but the overall bias was mostly 'low risk' (Fig.3).

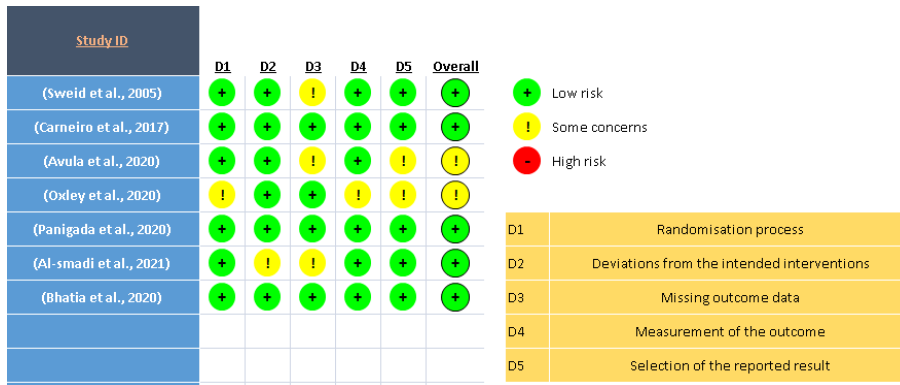


Fig. 2. Risk of bias of the individual studies reviewed

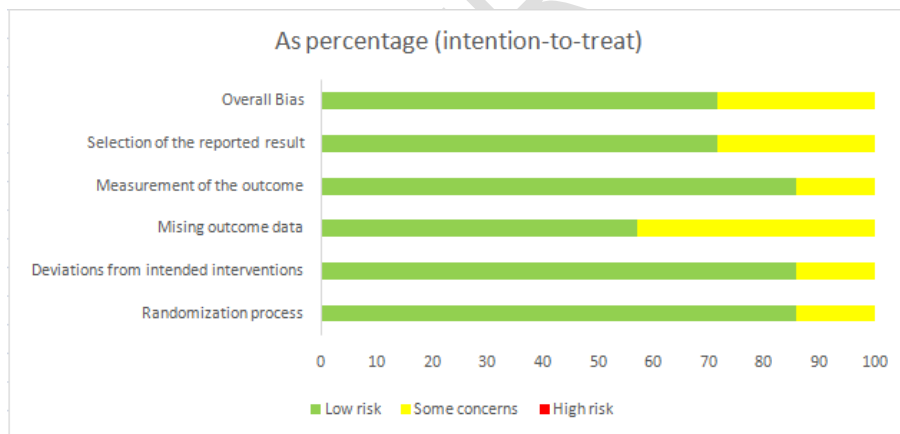


Fig. 3. Summary of Risk of bias according to the 5 domains

3. RESULTS AND DISCUSSION

CRP was always slightly higher than the normal limit (<10mg/dl). A pattern was observed between CRP and prothrombin time but not APTT. As the prothrombin time increased even slightly, CRP levels correspondingly increased as well. In some cases, serum ferritin was also significantly elevated. White blood cells did not rise beyond the normal range (4.5-

11x103mm³), and neither did platelets (150-450x103mm³) (Table2). Otherwise, all COVID-19 patients with ischemic stroke had raised d-dimers, fibrinogen, and prolonged prothrombin time (Table1).

Table 1. Laboratory values of coagulation markers

Study No.	Sample Size	D-Dimer (ng/ml)	Fibrinogen (mg/dl)	Prothrombin Time(secs)	APTT(secs)
1	22	3497.40	329.50	n/a	n/a
2	13	4284.60	262.20	13.09	28.95
3	4	4352.00	n/a	15.48	30.18
4	5	884.17	516.80	13.82	31.86
5	30	4877.00	680.00	n/a	n/a
6	2	4810.00	300.00	11.35	24.15
7	115	3442.00	5.50	14.10	35.00

Table 2. Laboratory values of inflammatory markers

Study No.	Sample Size	CRP (mg/dl)	Whit Blood Cell ($\times 10^3$ mm ³)	Platelets ($\times 10^3$ mm ³)	Ferritin (ug/L)
1	22	20.80	n/a	n/a	n/a
2	13	n/a	8.25	250.00	291.56
3	4	13.79	10.92	219.00	256.73
4	5	n/a	7.42	297.6	658.00
5	30	16.10	n/a	348.00	1485.00
6	2	7.40	n/a	n/a	54.25
7	115	10.11	8.70	183.00	655.00

C-reactive protein is normally made in the liver and is released in response to inflammation. Hepatic injury can also result in the seepage of the protein into blood circulation. It has been proven in previous studies that the protein can act as a procoagulant in antibody neutrophil cytoplasmic antibody (ANCA) associated vasculitis by activating platelets [15]. Whether this is the same mechanism inducing acute ischemic stroke has yet to be elucidated.

Ferritin is another protein that stores iron, and studies have suggested it as a predictor of severity in COVID infections, stating that such patients would be more prone to liver injury [16]. Our analysis discovered ferritin levels did not always increase, which may be secondary to other underlying causes beyond the scope of this study. In comparison, D-dimer is more reflective of the course of COVID illness and a better predictor of developing ischemic stroke.

Regarding therapeutic implications of our findings, it should be noted that an elevation of either inflammatory or hypercoagulability markers alone is not an indication to start thrombolytics, as previous studies done on non-infected individuals led to a higher rate of death due to either reperfusion injury or hemorrhage [17]. Also, elevated PT, APTT and INR levels (indicating hepatic dysfunction) are not a dependable index to decide management via thrombolysis [18]. Al Qureshiproposed a workflow that combined lab findings with radiography, particularly CT scan/angiography/perfusion or MRI to diagnose ischemic stroke before initiating treatment [19].

Management of COVID patients with ischemic stroke remains a grey area that requires further guidelines. Escalard noted that of the 37 patients with large vessel occlusion (LVO)

admitted in his institute, 10 of them were infected with COVID[20]. While only 5 were treated with intravenous thrombolysis, ultimately all 10 required mechanical thrombectomy (MT); this was initiated only 6 hours from stroke onset. Despite recanalization of 90% of the patients after a failed first pass (i.e more than one attempt was made), there was no neurological improvement in symptoms and 4 experienced re-occlusion even while on oral anticoagulation therapy. Six patients expired during hospitalization; however, this was not due to intracranial hemorrhage but has been attributed to microvascular thromboinflammation or endotheliitis[21]. This shows a poorer outcome when treating ischemic stroke patients with COVID using current medications.

Four cases in the city of Sakarya, Turkey diagnosed with COVID (via nasopharyngeal swab and CT scan of lungs) and subsequently treated with hydroxyquinoline plus azithromycin were unfit to receive alteplase due to having elevated blood pressures (a contraindication to thrombolysis) or undergo MT. These same patients had to be managed with antithrombotics [22].

In Atlanta, Georgia, of the 396 ischemic stroke patients only 13 were diagnosed with COVID-19; all 13 of them had a common pattern of stroke which was embolic in origin. The embolus was traced to the heart in 4 of those cases. This hinted that there were indirect causes of ischemic stroke in infected individuals (i.e COVID induced arrhythmias giving rise to embolus) and appropriate preventive measures ought to be taken early on (e.g antiarrhythmics) [23].

From each of the studies analyzed, the sample populations were mostly brought into emergency and very little history was taken or available before treatment was initiated. So it is not known whether all these patients had any pre-existing coagulopathy before being admitted for COVID-19. Qureshi²⁴ suggested that those patients who developed ischemic stroke were probably already at risk for large vessel atherosclerosis and small vessel disease. In the same study, the prevalence rate of ischemic stroke in COVID-19 patients was given between 1-3%. Nevertheless, the presence of such a complication even in a small percentage of the affected gave rise to the protected code stroke (PCS) for screening and treating such patients [25]. Because no specific guidelines exist on the ideal usage of antithrombotics and intravenous thrombolysis in patients of COVID (with regards to dosing and combinations), there needs to be further testing on the role played by such drugs in such a setting as well as advancement in new therapeutic modalities such as drugs targeting neutrophil extracellular traps (NET) which have potential to propagate microvascular thrombosis in COVID infections [26].

4. CONCLUSION

Platelets and white blood cell levels were not predictive of developing acute ischemic stroke in COVID-19 infection, however, CRP levels may potentially have a connection with coagulation markers. The most reliable of all markers remains D-dimer, but alone does not dictate course of management in patients cerebrovascular injury. Current management strategies, including the use of intravenous thrombolysis and antithrombotics, are not effective in improving the prognosis for such patients, and the development of new forms of drug treatment should be pursued.

CONSENT (WHEREEVER APPLICABLE)

We declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

We hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

REFERENCES

1. Madabhavi I, Sarkar M, Kadakol N. COVID-19: a review. *Monaldi Arch Chest Dis*. 2020 May 14;90(2). doi: 10.4081/monaldi.2020.1298. PMID: 32498503.
2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* [Internet]. 2020;8(4):420–422. Available from: [http://dx.doi.org/10.1016/S2213-2600\(20\)30076-X](http://dx.doi.org/10.1016/S2213-2600(20)30076-X)
3. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl Sci Rev* [Internet]. 2020;7(6):998–1002. Available from: <http://dx.doi.org/10.1093/nsr/nwaa041>
4. Hafeez A, Ahmad S, Siddiqui SA, Ahmad M, Mishra S. A review of COVID-19 (Coronavirus Disease-2019) diagnosis, treatments and prevention. *EJMO*. 2020;4(2):116–125.
5. Rieg S, von Cube M, Kalbhenn J, Utzolino S, Pernice K, Bechet L, et al. COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. *PLoS One* [Internet]. 2020;15(11):e0242127. Available from: <http://dx.doi.org/10.1371/journal.pone.0242127>
6. Akshay HM, Vaidya G, M. Shetty S, Dharmashekara C, Shreevatsa B, V. Siddalingegowda S, et al. Effect of anticoagulants on the survival rate in critically ill COVID-19 patients. *J Pharm Res Int* [Internet]. 2021 [cited 2021 Dec 20];6–11. Available from: <https://www.journaljpri.com/index.php/JPRI/article/view/33550>
7. Dahiwele A, Patil S, Zilate S, Salankar H, Rode S. Effective response to DPP-4 inhibitors in patients of COVID – 19 triggered uncontrolled type 2 DM – A case report. *J Pharm Res Int* [Internet]. 2021 [cited 2021 Dec 20];34–38. Available from: <https://www.journaljpri.com/index.php/JPRI/article/view/33803>
8. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* [Internet]. 1999;53(1):126–131. Available from: <http://dx.doi.org/10.1212/wnl.53.1.126>
9. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study: The Northern Manhattan Stroke Study. *Neurology* [Internet]. 1994;44(4):626–634. Available from: <http://dx.doi.org/10.1212/wnl.44.4.626>

10. Randolph SA. Ischemic Stroke. *Workplace Health Saf.* 2016 Sep;64(9):444. doi: 10.1177/2165079916665400. PMID: 27621261.
11. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J ThrombHaemost.* 2020 Jul;18(7):1738-1742. doi: 10.1111/jth.14850. Epub 2020 Jun 24. PMID: 32302438.
12. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of covid-19 in New York city. *N Engl J Med* [Internet]. 2020;382(24):2372-2374. Available from: <http://dx.doi.org/10.1056/NEJMc2010419>
13. Merkle AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with Coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol* [Internet]. 2020;77(11):1366-1372. Available from: <http://dx.doi.org/10.1001/jamaneurol.2020.2730>
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* [Internet]. 2021;372:n71. Available from: <http://dx.doi.org/10.1136/bmj.n71>
15. Xu P-C, Lin S, Yang X-W, Gu D-M, Yan T-K, Wei L, et al. C-reactive protein enhances activation of coagulation system and inflammatory response through dissociating into monomeric form in antineutrophil cytoplasmic antibody-associated vasculitis. *BMC Immunol* [Internet]. 2015;16(1):10. Available from: <http://dx.doi.org/10.1186/s12865-015-0077-0>
16. Hussein AM, Taha ZB, Malek AG, Rasul KA, Hazim DQ, Ahmed RJ, et al. D-Dimer and Serum Ferritin as an Independent Risk Factor for Severity in COVID-19 Patients. In: *Materials Today: Proceedings.* 2021 Apr 13.
17. Hsu P-J, Chen C-H, Yeh S-J, Tsai L-K, Tang S-C, Jeng J-S. High plasma D-dimer indicates unfavorable outcome of acute ischemic stroke patients receiving intravenous thrombolysis. *Cerebrovasc Dis* [Internet]. 2016;42(1-2):117-121. Available from: <http://dx.doi.org/10.1159/000445037>
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *stroke.* 2018 Mar;49(3):e46-99.
19. Qureshi AI, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: Report of an international panel. *Int J Stroke* [Internet]. 2020;15(5):540-554. Available from: <http://dx.doi.org/10.1177/1747493020923234>
20. Escalard S, Maier B, Redjem H, Delvoye F, Hébert S, Smajda S, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: Experience from Paris: Experience from Paris. *Stroke* [Internet]. 2020;51(8):2540-2543. Available from: <http://dx.doi.org/10.1161/STROKEAHA.120.030574>
21. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* [Internet]. 2020;395(10234):1417-1418. Available from: [http://dx.doi.org/10.1016/S0140-6736\(20\)30937-5](http://dx.doi.org/10.1016/S0140-6736(20)30937-5)
22. Abdulkadir TU, Ünlübaş Y, Alemdar M, Akyüz E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. *Journal of Clinical Neuroscience.* 2020;77:227-229.
23. Jillella DV, Janocko NJ, Nahab F, Benameur K, Greene JG, Wright WL, et al. Ischemic stroke in COVID-19: An urgent need for early identification and management. *PLoS One* [Internet]. 2020;15(9):e0239443. Available from: <http://dx.doi.org/10.1371/journal.pone.0239443>

24. Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, et al. Acute ischemic stroke and COVID-19: An analysis of 27 676 patients: An analysis of 27 676 patients. *Stroke* [Internet]. 2021;52(3):905–912. Available from: <http://dx.doi.org/10.1161/STROKEAHA.120.031786>
25. Yang B, Wang T, Chen J, Chen Y, Wang Y, Gao P, et al. Impact of the COVID-19 pandemic on the process and outcome of thrombectomy for acute ischemic stroke. *J Neurointerv Surg* [Internet]. 2020;12(7):664–668. Available from: <http://dx.doi.org/10.1136/neurintsurg-2020-016177>
26. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. *JCI Insight* [Internet]. 2020;5(11). Available from: <http://dx.doi.org/10.1172/jci.insight.138999>

UNDER PEER REVIEW