Original Article

# Brain and COVID: A Case Series of Neurovascular Complications

**Rajagopal Srinath, Subrat Kumar Nanda[1], Vikram Asturkar[1], FMH Ahmad[1], Vinny Wilson, Uday Yanamandra, Anil Menon**

Department of Internal Medicine, AFMC, [1]Department of Neurology, Command Hospital (SC), Pune, Maharashtra, India

## Abstract

**Introduction:** COVID-19 is caused due to infection with severe acute respiratory syndrome-coronavirus-2. A change in the epidemiological pattern of neurovascular diseases has been observed among patients who have had COVID-19 infection. There are not enough studies which have evaluated the neurovascular manifestations among patients of COVID-19 infection. **Materials and Methods:** This single-center observational study was intended to evaluate the correlation between various COVID-19-related parameters with the outcomes of vascular events among patients of COVID-19 who developed neurovascular complications. The study was conducted at a tertiary hospital in Pune, India, from February 01, 2021, to October 10, 2021. The study population involved patients with COVID-19 of varying severity and associated neurovascular complications. The total number of patients was 22 in number. The deidentified data were analyzed using JMP version 10.040. **Results:** Among a total of 22 patients, 16 (73%) had arterial infarcts, 5 (23%) had venous infarcts, whereas 1 (4%) had intracerebral hemorrhage. Four (18%) patients had features of severe COVID-19 and 2 (9%) of them had a modified Rankin Scale of six. There was a strong correlation between the severity of COVID infection and the severity of neurovascular complications. A positive correlation was observed between the time duration from Reverse transcriptase polymerase chain reaction (RT-PCR) positivity to neurovascular complications with the duration of >45 days having a poorer outcome. **Conclusion:** COVID-19 is more likely to cause thrombotic vascular events including stroke. The severity of COVID-19 is directly correlated with poorer outcomes. The duration between RT-PCR positivity and neurovascular symptoms if >45 days, has a poorer outcome.

**Keywords:** Arterial, COVID-19, stroke, thrombosis, venous

## Introduction

COVID-19 is caused due to infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).[1] Atypical clinical presentations including neurological presentations are not uncommon.[2] An important neurological problem is neurovascular thrombotic disorder. Evidence has shown that both arterial and venous thrombosis have been reported in pulmonary as well as systemic circulation which contribute to the severity of disease.[3] The prevalence of arterial thrombosis has been estimated between 2.8% and 3.8%.[4] The viral pathogen activates the innate immune system which is hypothesized to be the first event in the pathogenesis of thrombosis which is termed "immunothrombosis."[5] The COVID-19-associated coagulopathy involves a possible interplay between the activation of intravascular tissue factors, innate immune cells, platelets, and endothelial cells, and releases neutrophil extracellular traps which can activate the contact pathway of coagulation. Subsequently, with the activation of the cytokine storm from the innate immune system, thrombotic microangiopathy, endotheliopathy, and multifactorial activation of coagulation would ensue to cause various manifestations.[6]

A change in the epidemiological pattern of neurovascular diseases has been observed among patients who have had COVID-19 infection observed both during acute infection as well as in the patients who have recovered from COVID-19. An increasing number of strokes in younger patients have been reported among patients who had COVID-19 infection which includes individuals who have no previous risk factors.[7] The possible putative mechanisms include

**Address for correspondence:** Dr. Rajagopal Srinath, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.
E-mail: srinath290775@gmail.com

**Submitted:** 16-Jan-2022 **Revised:** 03-May-2022
**Accepted:** 12-May-2022 **Published:** 27-Jun-2022

Access this article online

Quick Response Code:

Website: www.actamedicainternational.com

DOI: 10.4103/amit.amit_5_22



**How to cite this article:** Srinath R, Nanda SK, Asturkar V, Ahmad FM, Wilson V, Yanamandra U, *et al*. Brain and COVID: A case series of neurovascular complications. Acta Med Int 2022;9:6-9.

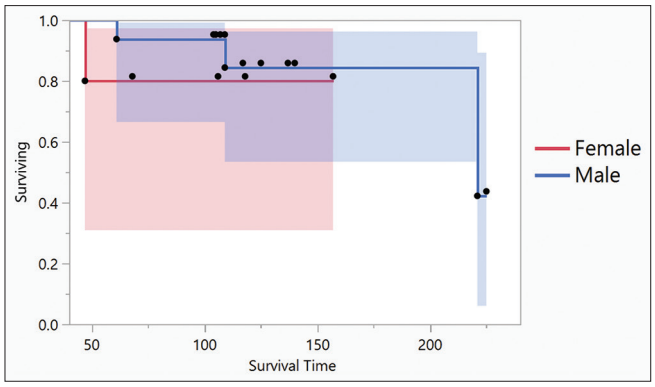


**Figure 1:** The survival plot with sex distribution

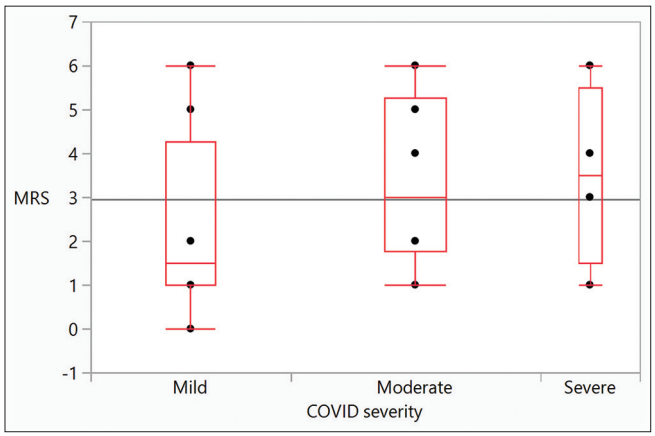


**Figure 3:** mRS with COVID-19 severity. mRS: Modified Rankin Scale

renin–angiotensin system disturbance, downregulation of angiotensin-converting enzyme (ACE-2) receptors, endothelial cell damage, coagulopathy, cytokine storm, and platelet abnormality inducing abnormality in the coagulation system, resulting in a direct cytotoxic effect on the nervous system related to angiotensin ACE-2 receptor uptake of SARS-CoV-2 virus. There have been proposed mechanisms such as embolic phenomena in preexisting or new-onset arrhythmias, hypoxia-induced ischemia secondary to severe pulmonary disease, hypoxemia related to cardiorespiratory failure, and metabolic derangements leading to hypoxia.[8]

There have been not many studies which have evaluated the neurovascular manifestations among patients of COVID-19 infection. We intend to enumerate various neurovascular complications among patients who had COVID-19 infection of varying severity and discuss the possible pathophysiological mechanisms.

## Materials and Methods

### Study design, study setting, population, and sampling methods

An observational study was conducted at a tertiary hospital in Pune, Maharashtra, from February 01, 2021, to October 10, 2021. The study population involved patients with

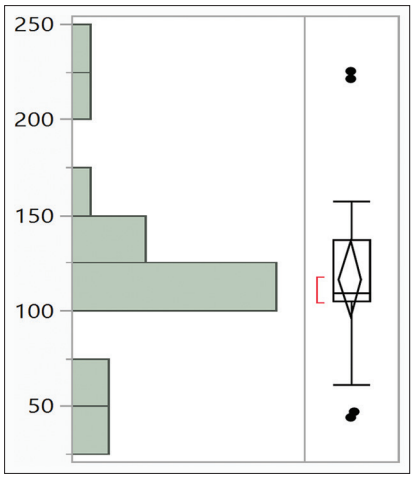


**Figure 2:** Survival time plot

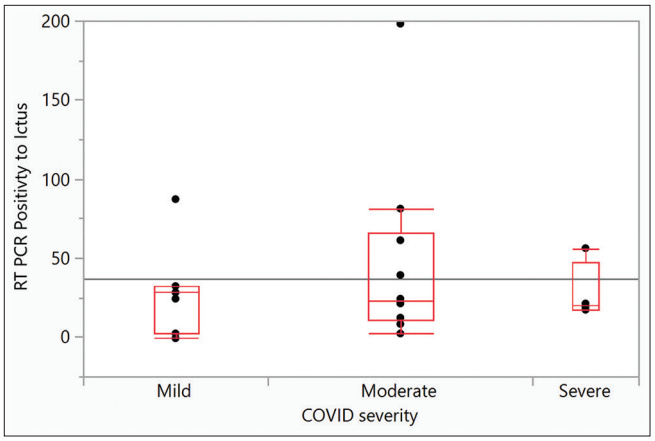


**Figure 4:** RT-PCR positive to ictus and COVID severity. RT-PCR: Reverse transcription-polymerase chain reaction

COVID-19 of varying severity and associated neurovascular complications. The total number of patients was 22 in number. The ethical approval was taken from institutional ethical committee, with letter number (IEC/2022/07).

### Inclusion criteria

Patients infected with COVID-19, either concurrently or those who have recovered presenting with any neurovascular manifestations in the form of stroke.

### Exclusion criteria

Those presenting with doubtful stroke or stroke mimics were excluded from this study.

### Variables evaluated

The severity of COVID-19, time from RT-PCR positivity, vaccination status, anticoagulation status, and neurovascular complications were correlated with functional outcomes.

### Follow-up

All the patients were followed up for a minimum of 90 days either by physical visit to the hospital or by telephonic interview done by the investigators.

### Statistical analysis

The data were analyzed in MS Excel. The data were analyzed using JMP version 10.040. The categorical variables were summarized using frequency, proportions, and ratios, whereas the Chi-square test was used to determine the association between study variables. A $P < 0.05$ was considered statistically significant.

## Results

There were 16 males and 6 females [Figure 1], and the median age of the patients was 56 years with oldest being 76 years and youngest 40 years. Only six had received (both doses) vaccination, whereas 16 had not received the same. All six of them had received COVISHIELD vaccine. About 18% of the patients had severe COVID, whereas 46% had moderate and 36% had mild disease. Therapeutic anticoagulation was received by eight patients for at least 1 week.

Among a total of 22 patients, sixteen (73%) had arterial infarcts, five (23%) had venous infarcts, whereas one (04%) had intracerebral hemorrhage. Four patients had features of severe COVID-19 and two of them had a modified Rankin Scale (mRS) of six. There were a total of four deaths one of them being a female.

The survival plot has time on the X-axis and number on Y-axis. It shows a total of four deaths with one of them being female [Figure 2].

The median survival was 109 days. The X-axis depicts the number of patients and Y-axis number of days. This shows a median survival of 109 days with a minimum of 44 days and a maximum of 225 days.

The median mRS for mild COVID-19 was 1.5, whereas for moderate, it was 3.0 and severe had 4 [Figure 3]. There was no statistically significant correlation of mRS with COVID-19 severity with $P = 0.3942$.

There was no statistically significant correlation of RT-PCR positivity to ictus with COVID-19 severity with $P = 0.9719$ [Figure 4]. However, a positive correlation was observed between the time duration from RT-PCR positivity to neurovascular complications with the duration of >45 days having a poorer outcome.

## Discussion

The neurological complications following COVID-19 infections which have been reported are viral meningitis and encephalitis, anosmia, postinfectious acute disseminated encephalomyelitis, postinfectious brainstem encephalitis, Guillain–Barre syndrome, myositis, and acute necrotizing hemorrhagic encephalopathy.[9] It is known that COVID-19 infection causes a 7.6% increase in the odds of stroke compared to influenza virus-related disease with a reported incidence of stroke in COVID-19 patients between 1% and 6%. The WHO panel review has pegged the risk of ischemic stroke during COVID to be about 5%. The possible reasons for increased vascular events during COVID-19 include state of generalized hypercoagulability, dysregulated immune response, leading to cytokine-release syndrome, damage to endothelial cells, leading to increased inflammation and thrombosis, dysregulation of the renin–angiotensin–aldosterone system, and a direct cytotoxic effect on the nervous system related to ACE-2 receptor uptake of SARS-CoV-2. COVID-19 infection has a definite correlation with adverse functional outcomes in strokes with severe COVID having poorer outcomes. Various studies have revealed that COVID-19-associated strokes have a higher propensity to cause large vessel disease which not only has reduced the success of intravenous recanalization therapy but also results in poor functional recovery.[10] Increased complications during hospitalization involving multiple systems among patients of COVID-19 with stroke have been reported. Not to mention the inadvertent use of steroids in some patients of COVID-19 which not only presents with glycemic issues but also delays the functional recovery.[11] There is evidence that COVID-19 infection has adverse implications on stroke management and outcomes, more so among severe COVID-19 patients.[12] It is worth noting here that almost all the patients of severe COVID-19 would have received heparin in therapeutic doses which theoretically might reduce stroke risk. This is a pertinent aspect which conveys that there may be other pathophysiological aspects other than thrombosis in the etiology of such vascular events.

Our study has revealed that COVID-19 is more likely to cause thrombotic vascular events including stroke and the severity of COVID-19 are directly correlated with poorer outcome from the vascular events. Another finding from our study is that the duration between RT-PCR positivity and neurovascular symptoms if >45 days, having a poorer functional outcome from vascular complications even though statistically not significant, is possibly due to the waning effect of anticoagulation or antiplatelet received during the management of various COVID-19 subtypes. Our study did not show any correlation between vaccination status and functional outcome from vascular events even though the numbers were rather small to come to any conclusion. The jury is out on whether the COVID-19 and stroke have cause or association and further studies are needed to come to any conclusion on this.

Our study has revealed that COVID-19 infection results in increased risk of thrombosis with severe the COVID-19, poorer the functional outcome. A past history of COVID-19 infection is important to be taken among all patients presenting with stroke which might help in further elucidating the likely etiopathogenesis.

### Limitations

The sample size of our study was small which possibly have had a bearing on the results. The data collection at our center is still going on. The data on vaccination status and its correlation with outcome did not come up with any credible results due to the meager number.

## Conclusion

COVID-19 is more likely to cause thrombotic vascular events including stroke. The severity of COVID-19 is directly correlated with poorer outcomes. The duration between RT-PCR positivity and neurovascular symptoms if >45 days, has a poorer outcome.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al.* Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199-207.
2. Mungmunpuntipantip R, Wiwanitkit V. COVID-19, neurovascular thrombotic problem and short summary on blood coagulation disorder: A brief review. Egypt J Neurol Psychiatr Neurosurg 2022;58:6.
3. Chernysh IN, Nagaswami C, Kosolapova S, Peshkova AD, Cuker A, Cines DB, *et al.* The distinctive structure and composition of arterial and venous thrombi and pulmonary emboli. Sci Rep 2020;10:5112.
4. Markus HS, Brainin M. COVID-19 and stroke – A global World Stroke Organization perspective. Int J Stroke 2020;15:361-4.
5. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: An overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointerv Surg 2021;13:202-6.
6. Florez-Perdomo WA, Serrato-Vargas SA, Bosque-Varela P, Moscote-Salazar LR, Joaquim AF, Agrawal A, *et al.* Relationship between the history of cerebrovascular disease and mortality in COVID-19 patients: A systematic review and meta-analysis. Clin Neurol Neurosurg 2020;197:106183.
7. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke 2021;16:137-49.
8. Sagris D, Papanikolaou A, Kvernland A, Korompoki E, Frontera JA, Troxe AB, *et al.* COVID-19 and ischemic stroke. Eur J Neurol 2021;28:3826-36.
9. Vogrig A, Gigli GL, Bnà C, Morassi M. Stroke in patients with COVID-19: Clinical and neuroimaging characteristics. Neurosci Lett 2021;743:135564.
10. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, *et al.* Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382:e60.
11. Sedova P, Brown RD Jr., Bryndziar T, Jarkovsky J, Tomek A, Sramek M, *et al.* Treat COVID-19, but Not Only COVID-19: Stroke matters as well. Cerebrovasc Dis 2022;51:52-9.
12. Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, *et al.* Arterial and venous thromboembolism in COVID-19: A study-level meta-analysis. Thorax 2021;76:970-9.