

## ACUTE ISCHEMIC STROKE IN COVID-19: A STUDY ON LABORATORY PARAMETERS AS PREDICTIVE INDICATORS OF CLINICAL OUTCOMES

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### Abstract

**Background:** Stroke is the third-most common cause of disability and the second-most common cause of death worldwide. Stroke survivors frequently bear the burden of expensive rehabilitation, lost wages and productivity, restrictions on normal social interactions, and severe residual disability.

**Materials and Methods:** We analysed the data from 100 patients of acute ischemic stroke in COVID-19 in a tertiary healthcare hospital from the period between January 2020 and December 2020 using the COVID-19 dataset. The dataset included patients with an emergency department or inpatient encounter with discharge diagnosis codes that could be associated with suspicion of or exposure to COVID-19 or confirmed COVID-19. This analysis was carried out to determine whether there were any significant differences in demographic and clinical characteristics, in-hospital events, and outcomes between COVID-19 patients with and without acute ischemic stroke, and acute ischemic stroke patients with and without COVID-19. **Result:** There were 176 patients with confirmed COVID-19; among them, 100 patients who developed an acute ischemic stroke with COVID-19. Patients with COVID-19 who did not have an acute ischemic stroke (n = 76); patients who had an acute ischemic stroke but did not have COVID-19 (n = 19). In our study, patients with stroke admitted with more severe COVID-19 had significantly higher C-reactive protein, ferritin levels, elevated D-dimer levels, and neutrophil-lymphocyte ratio compared with patients positive for COVID-19 and without any acute ischemic stroke and patients with acute ischemic stroke without COVID-19.

**Conclusion:** Elevated C-reactive protein and ferritin levels, elevated D-dimer levels, lymphopenia, and an elevated neutrophil-lymphocyte ratio are the markers associated with poor prognosis in stroke patients with COVID-19 in our study.

## INTRODUCTION

Stroke is the third most common cause of disability and the second most common cause of death worldwide. Stroke survivors frequently bear the burden of expensive rehabilitation, lost wages and productivity, restrictions on normal social interactions, and severe residual disability. As of October 24, 2021, the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2)-caused coronavirus disease 2019 (COVID-19) pandemic

had killed more than 4.9 million people worldwide.<sup>[1]</sup> Acute cerebrovascular episodes are one of COVID-19's neurological side effects. One of the unusual, potentially fatal risk factors for COVID-19 infection is acute ischemic stroke.<sup>[2]</sup> Patients with COVID-19 have an incidence of acute ischemic stroke that varies from 0.9 to 2.7%. Compared to acute ischemic strokes without COVID-19, these strokes have a worse prognosis and increased mortality. Ischemic stroke is caused by thrombotic or embolic events. Blood flow to the

brain is obstructed in thrombotic aetiology due to vessel dysfunction, which may be secondary to atherosclerotic disease or inflammatory conditions.<sup>[3]</sup>

While the precise relationship between stroke and COVID-19 is still unknown, there is mounting evidence that the disease process may precipitate an ischemic stroke or worsen an existing stroke.<sup>[4]</sup> Male sex, advanced age, and comorbidities such as hypertension, diabetes, and heart disease are all risk factors for severe COVID-19. These factors are also risk factors for stroke, explaining the complicated relationship between the two conditions.<sup>[5]</sup> Furthermore, the current pandemic has direct and indirect consequences for stroke care. When infected with COVID-19, stroke patients have an increased risk of severe disease. Furthermore, patients with COVID-19 who have a stroke have a higher risk of an adverse outcome than non-COVID-19 stroke patients. On the other hand, the pandemic's impact on available healthcare resources may have a negative impact on stroke care delivery services, limiting stroke patients' access to prompt and time-sensitive intervention.

## MATERIALS AND METHODS

This was a retrospective observational study. This study was carried out in a tertiary healthcare hospital between January 2020 and December 2020 using the COVID-19 dataset. The dataset included patients with an emergency department or inpatient encounter with discharge diagnosis codes that could be associated with suspicion of or exposure to COVID-19 or confirmed COVID-19.

This analysis was carried out to determine whether there were any significant differences in demographic and clinical characteristics, in-hospital events, and outcomes between COVID-19 patients with and without acute ischemic stroke and acute ischemic stroke patients with and without COVID-19. We compared patients' age, gender, race/ethnicity, cardiovascular risk factors, length of stay, medical complications, procedures performed, and discharge status (discharge home, discharge to a destination other than home, or death) in COVID-19 strata based on the presence or absence of acute ischemic stroke. We also analysed data from patients with acute ischemic stroke who did not have COVID-19 to see if there were any differences in the abovementioned variables between ischemic stroke patients with and without COVID-19.

To detect any significant differences in variables between COVID-19 patients with and without ischemic stroke, we used the  $\chi^2$  test for categorical data and the 2-sample t-test for continuous data. We used the Bonferroni correction to account for multiple comparisons. Any  $P < 0.05$  is regarded as significant.

## RESULTS

There were 176 patients with confirmed COVID-19; among them, 100 patients developed acute ischemic stroke with COVID-19. Seventy-six patients with COVID-19 and without acute ischemic stroke and 19 patients with acute ischemic stroke without COVID-19 were included in this study.

**Table 1: Patients characteristics**

Characteristics	Patients with COVID-19 and acute ischemic stroke (n=100)	Patients with COVID-19 and without any acute ischemic stroke (n=76)	Patients with acute ischemic stroke without COVID-19 (n=19)
Mean age (SD)	68.8±14.72	54.2±20.2	71±14.9
Age less than 35 years	2(2%)	15(19.6%)	1(8%)
Age 35-54 years	17(17%)	21(27.7%)	1(8%)
Age 55-70 years	32 (32%)	22(28.8%)	5(28%)
Age >70 years	50 (50%)	18(24%)	11(55%)
Men	44(44%)	36(47%)	11(55%)
Hypertension	84(84%)	36(48%)	15(82%)
Smoking	11(11%)	6(8.6%)	3(19%)
Hyperlipidemia	75(75%)	25(33%)	13(71%)
Atrial Fibrillation	28(28%)	8(10%)	7(36%)
Congestive heart failure	33(33%)	10(12.7)	7(36%)
In hospital events			
Mean length of hospitalization	10±8	7±6	9±7
Cerebral edema	4(4%)	1(0.5%)	1(2.5%)
Pneumonia	56(56%)	34(45%)	10(54%)
Deep venous thrombosis	7(7%)	2(3.7%)	2(11.1%)
Pulmonary Embolism	4(4%)	2(2.3%)	1(2.5%)
Intubation/Mechanical ventilation	7(7%)	3(3.5%)	2(12.6%)
Urinary tract infection	28(28%)	13(17.7%)	5(29.7%)
Acute kidney injury	50(50%)	17(22.8%)	9(47.7%)
Hepatic failure	4(4%)	1(1.2%)	1(5%)
Cardiac arrest	4(4%)	2(1.5%)	1(5%)
Acute myocardial infarction	10(10%)	3(4.6%)	3(18%)
Intracerebral hemorrhage	2(2%)	0(0)	1(3%)
Systemic Inflammatory response syndrome	2(2%)	2(1.5%)	1(2%)

Septic Shock	35(35%)	13(17.6%)	7(40%)
Respiratory Failure	52(52%)	22(29.6%)	8(49%)

**Table 2: Outcome of patients**

Outcome	Patients with COVID-19 and acute ischemic stroke (n=100)	Patients with COVID-19 and without any acute ischemic stroke (n=76)	Patients with acute ischemic stroke without COVID-19 (n=19)
Discharge Home	19(19%)	49(64.9%)	6(30%)
Discharge to destination other than to home	62(62%)	22(29.1%)	10(48%)
In hospital death	19(19%)	5(6.2%)	4(22%)

The in-hospital mortality among acute ischemic stroke patients with COVID-19 was similar to those without COVID-19 (19.4% versus 21.6%; P=0.66). There was a significantly higher rate of discharge to destination other than home among acute ischemic stroke patients with COVID-19 compared with those without it (62.1% versus 48.2%; P=0.02). In the multivariate model, COVID-19 (RR, 1.2 [95% CI, 1.0–1.3]; P=0.03) was associated with discharge to destination other than home or death in patients with acute ischemic stroke. Another factor associated with discharge to destination other than home or death was atrial fibrillation (RR, 1.2 [95% CI, 1.0–1.3]; P=0.014).

**Table 3: Laboratory Parameters**

Laboratory parameter (mean)	Patients with COVID-19 and acute ischemic stroke (n=100)	Patients with COVID-19 and without any acute ischemic stroke (n=76)	Patients with acute ischemic stroke without COVID-19 (n=19)	P Value
C-reactive protein	7.9 mg/l	4.4 mg/l	3.6 mg/l	0.001
Ferritin	308 ng/ml	300 ng/ml	250 ng/ml	0.023
D-Dimer	227 ng/ml	200 ng/ml	190 ng/ml	0.012
Neutrophil- lymphocyte ratio	3.9	3.3	2.1	0.002

In our study, patients with stroke admitted with more severe COVID-19 had significantly higher C-reactive protein, ferritin levels, elevated D-dimer levels, and neutrophil-lymphocyte ratio compared with patients positive for COVID-19 and without any acute ischemic stroke and patients with acute ischemic stroke without COVID-19. Among the different presenting symptoms, fever, cough, and dyspnea were associated with a substantially increased risk for ICU admission and patients with comorbid conditions. For other laboratory biomarkers, anemia, a high neutrophil count, a low lymphocyte count, and impaired liver and kidney function tests carried an increased risk for ICU admission.

## DISCUSSION

Several findings emerged from a study of 100 patients with COVID-19 who had an acute ischemic stroke. Patients with COVID-19 who had an acute ischemic stroke were older and had higher rates of hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure.<sup>[6]</sup> Patients with COVID-19 who developed an acute ischemic stroke had more cardiovascular events during hospitalization, including cerebral edema, intracerebral hemorrhage, and myocardial infarction, compared to those who did not develop an acute ischemic stroke. Patients with COVID-19 and acute ischemic stroke were more likely to have multisystem involvement, including acute kidney injury, hepatic failure, and respiratory failure, than those without acute ischemic stroke.<sup>[7]</sup>

Patients with COVID-19 and acute ischemic stroke had significantly higher in-hospital mortality and discharged to a location other than home than those without stroke. After adjusting for potential confounders, patients with acute ischemic stroke had a 2-fold higher risk of discharge to a location other than home or death compared to those without acute ischemic stroke among all COVID-19 patients.<sup>[8]</sup> When acute ischemic stroke patients with and without COVID-19 were compared; there were only minor differences in baseline and clinical characteristics.<sup>[9]</sup>

When ischemic stroke patients with COVID-19 were compared to those without COVID-19, there was a higher rate of discharge to a location other than home or death. After controlling for potential confounders, COVID-19 was associated with a 1.2-fold higher risk of discharge to a location other than home or death in ischemic stroke patients.<sup>[10]</sup>

We discovered a low incidence of acute ischemic stroke (1.3%) among COVID-19 inpatients. In our study, patients without COVID-19 had a similar (1%) risk of ischemic stroke. According to preliminary estimates, those hospitalized with COVID-19 had a higher proportion (5%) of acute ischemic stroke. Other studies have suggested that the proportion of patients with acute ischemic stroke among those hospitalized with COVID-19 and receiving standard thromboprophylaxis may range between 1% and 3%.<sup>[11]</sup> According to the study by Yagi et al., 0.9% of 3556 COVID-19 hospitalized patients had an acute ischemic stroke.

Leukocytosis and lymphopenia have also been linked to severe COVID-19 infection and a poor outcome.<sup>[12]</sup> A recent meta-analysis of a few studies

found that lower lymphocyte and higher leukocyte counts were associated with severe infection.<sup>[13]</sup> Lymphopenia was formerly used as a prognostic biomarker in other infectious diseases such as influenza. Association between lymphopenia and severe disease may be the consequence of direct infection of the lymphocyte, lymphatic tissue destruction, lymphocyte apoptosis due to inflammation, or some metabolic abnormalities, for instance, lactic acidosis, causing lymphocyte inhibition.<sup>[14]</sup> Despite being associated with severe COVID-19 infection in this study, neither leukocytosis nor lymphopenia were significant risk factors by multivariate regression analysis.

## CONCLUSION

According to our findings, COVID-19-associated ischemic strokes were more severe, with poorer functional outcomes and higher mortality than non-COVID-19-associated ischemic strokes. However, the association between COVID-19 and severe stroke highlights the urgent need for studies aimed at uncovering the underlying mechanisms. From our study, elevated C-reactive protein and ferritin levels, high D-dimer levels, lymphopenia, and an elevated neutrophil-lymphocyte ratio were the markers associated with poor prognosis in stroke patients with COVID-19. It can be considered while treating patients, as it is associated with a poorer outcome.

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