Short Communication

New-onset acute ischemic stroke following COVID-19: A case–control study

Fariborz Khorvash[1], Mohammad Amin Najafi[1], Mohsen Kheradmand[1], Mohammad Saadatnia[1], Rojin Chegini[2], Farideh Najafi[3]

[1]Department of Neurology, Al Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Orthopedic, Rothman Institute, Thomas Jefferson University, Philadelphia, Pennsylvania

Background: Neurological manifestations of coronavirus disease 2019 (COVID-19) have been highlighted. COVID-19 potentially increases the risk of thromboembolism. We aimed to compare patients with COVID-19 with and without new-onset acute ischemic stroke (AIS). **Materials and Methods**: In this single-center retrospective case–control study, demographics, clinical characteristics, laboratory findings, and clinical outcomes were compared between 51 patients with both COVID-19 and AIS (group A) and 160 patients with COVID-19 and without AIS (group B). **Results:** Patients in group A were significantly older, more likely to present with critical COVID-19 ($P = 0.004$), had higher rates of admission in the intensive care unit ($P < 0.001$), more duration of hospitalization ($P < 0.001$), and higher in-hospital mortality ($P < 0.001$). At the time of hospitalization, O_2 saturation ($P = 0.011$), PH ($P = 0.04$), and HCO3 ($P = 0.005$) were lower in group A. White blood cell count ($P = 0.002$), neutrophil count ($P < 0.001$), neutrophil-lymphocyte ratio ($P = 0.001$), D-Dimer ($P < 0.001$), blood urea nitrogen (BUN) ($P < 0.001$), and BUN/Cr ratio ($P < 0.001$) were significantly higher in patients with AIS. **Conclusion:** Stroke in COVID-19 is multifactorial. In addition to conventional risk factors of ischemic stroke (age and cardiovascular risk factors), we found that patients with more severe COVID-19 are more prone to ischemic stroke. Furthermore, leukocyte count, neutrophil count, neutrophil-lymphocyte ratio, D-Dimer, BUN, and BUN/Cr ratio were higher in patients with AIS following COVID-19 infection.

Key words: Acute ischemic stroke, blood urea nitrogen, coronavirus disease 2019, D-dimer

How to cite this article: Khorvash F, Najafi MA, Kheradmand M, Saadatnia M, Chegini R, Najafi F. New-onset acute ischemic stroke following COVID-19: A case–control study. J Res Med Sci 2022;27:31.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a global concern and causes different clinical characteristics and complications; Neurologic manifestations have been highlighted in numerous studies.[1]

Previous studies reported that infectious agents increase the risk of ischemic stroke due to the prothrombotic effect of the inflammatory response, thus according to hypercoagulopathy state and the increase of thrombotic events in COVID-19 infection, the increased risk of stroke could be predicted.[2]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.jrms_255_21

The literature is increasingly being focused on acute ischemic stroke (AIS) characteristics following COVID-19 infection.[3-6] Studying the characteristics of stroke in patients with both COVID-19 and stroke may help to better understand the relation between these two diseases. The aim of this study is to compare clinical characteristics, laboratory data, and comorbidities between patients with COVID-19 with and without new-onset AIS.

MATERIALS AND METHODS

This was a single-center retrospective case–control study between October 22, and December 1, 2020. Fifty-one patients with confirmed COVID-19 and new-onset AIS were admitted to the Al Zahra Hospital (group A). One

Address for correspondence: Dr. Mohammad Amin Najafi, Department of Neurology, Al Zahra Hospital, Sofeh Street, Isfahan, Iran.
E-mail: najafi.ma1372@gmail.com
Submitted: 13-Mar-2021; **Revised:** 28-Oct-2021; **Accepted:** 10-Nov-2021; **Published:** 15-Apr-2022

hundred and sixty-one confirmed COVID-19 patients, hospitalized in the same period in our center, were randomly selected as the control group (group B). Patients gave informed consent before take part in this trial. All patients tested positive for SARS-CoV-2 reverse transcription-polymerase chain reaction, had respiratory symptoms, had viral pneumonia findings on chest computed tomography (CT). AIS was diagnosed according to clinical symptoms and imaging studies (brain CT scan or Magnetic resonance imaging). The severity of the disease was determined according to the COVID-19 Treatment Guidelines Panel, which describes critical COVID as "patients with respiratory failure, multiple organ dysfunction, and septic shock."

Demographic characteristics, patient's medical history, duration of hospitalization (ward or intensive care unit [ICU]), mortality rate, vital signs in admission, baseline laboratory findings, and pulmonary thromboembolism (PTE) rate were extracted from electronic medical records and compared between two groups.

Statistical analysis

Statistical analyses were carried out using the SPSS (SPSS statistic package, version 21.0.0, IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) statistical software. The Pearson Chi-square test and the *t*-test were used to determine whether there were any significant differences. The level of statistical significance was set at $P < 0.05$.

RESULTS

Fifty-one patients (24 males and 27 females) with both COVID-19 and new-onset AIS (group A) and 160 COVID-19 patients (86 male and 74 female) without new-onset AIS (group B) were surveyed. Table 1 shows the comparison of the demographics and clinical characteristics between these groups. Group A patients were significantly older (73 ± 13 years vs. 66 ± 14 years, $P < 0.001$) and were more likely to present with critical COVID-19 (51% vs. 30%, $P = 0.004$). In-hospital mortality was significantly higher in group A (52.9% vs. 18.1%, $P = 0.001$). Group A were more likely to have other underlying disorders, including hypertension (HTN) (74.5% vs. 55%, $P = 0.013$), diabetes mellitus (DM) (54.9% vs. 36.2%, $P = 0.017$), previous stroke (21.5% vs. 5% $P \leq 0.001$), ischemic heart disease (IHD) (39.2% vs. 20% $P = 0.008$), and atrial fibrillation (AF) rhythm (31.4% vs. 5% $P \leq 0.001$). Group A was more likely to admit to the ICU (60% vs. 26.2% <0.001). The duration of hospitalization in both ward and ICU was greater

Table 1: Demographics and clinical characteristics of patients with coronavirus disease-2019 with or without new-onset acute ischemic stroke

	Total (*n*=211)	COVID-19 with AIS (*n*=51)	COVID-19 without AIS (*n*=160)	*P*	OR
Age	66.28±14.8	73.1±13	64.1±14.7	<0.001*	-
Gender, *n* (%)					
Male	110	24	86	0.425	0.76
Female	101	27	74		
Death in hospital, *n* (%)	56 (26)	27 (52.9)	29 (18.1)	<0.001*	5.49
Medical history, *n* (%)					
Any	164 (77.7)	46 (90.2)	118 (73.7)	0.010*	3.27
Stroke risk factor					
Hypertension	126 (59.7)	38 (74.5)	88 (55)	0.014*	2.39
Diabetes mellitus	103 (48.8)	28 (54.9)	58 (36.2)	0.022*	2.14
Previous stroke	19 (9)	11 (21.5)	8 (5)	0.001*	5.22
Ischemic heart disease	53 (25.1)	20 (39.2)	33 (20.6)	0.010*	2.48
Hyperlipidemia	40 (18.9)	10 (19.6)	30 (18.7)	1	1.05
Atrial fibrillation	24 (11.3)	16 (31.4)	8 (5)	<0.001*	7.91
Malignancy	10 (4.7)	4 (7.8)	6 (3.7)	0.201	2.18
Other					
Hypothyroidism	19 (9)	5 (9.8)	14 (8.7)	0.783	1.13
Chronic kidney disease	39 (18.5)	11 (21.6)	28 (17.5)	0.667	0.75
Critical COVID, *n* (%)	74 (35.1)	26 (51)	48 (30)	0.004*	2.62
Admission to ICU, *n* (%)	74 (35.07)	32 (62.7)	42 (26.2)	<0.001*	4.73
Duration of ICU hospitalization	8.95±7.32	11.4±8.8	7.1±5.2	0.011*	-
Duration of hospitalization	9.35±9.29	15.7±15.4	7.3±4.8	<0.001*	-
Systolic blood pressure in admit	130.6±21.5	135.7±28.07	129±18.9	0.06	-
diastolic blood pressure in admit	78.3±13.1	78.8±15.4	78.2±12.3	0.76	-
O_2 saturation in admission	84.9±8	82.8±8.3	85.7±7.8	0.011*	-
Pulmonary thromboembolism, *n* (%)	7 (3.3)	6 (11.7)	1 (0.6)	0.001*	23.8

COVID-19=Coronavirus disease 2019; ICU=Intensive care unit; AIS=Acute ischemic stroke; OR=Odds ratio; O_2=Oxygen

in group A (15.7 ± 15.4 vs. 7.3 ± 4.8, $P \leq 0.001$ and 11.4 ± 8.9 vs. 7.1 ± 5.2, $P = 0.011$, respectively). Group A showed significantly lower O_2 saturation in the emergency room (82.4 ± 8.3 vs. 85.7 ± 7.8, $P = 0.011$). During hospitalization, pulmonary thromboendarterectomy (PTE) occurred in 6 (11.7%) patients in group A and 1 (0.6%) patient in group B ($P < 0.001$).

Table 2 summarized the laboratory findings in two groups. Patients in group A had higher white blood cell count (10323 ± 6093 vs. 7865 ± 4447 × 109/L, $P = 0.002$), higher neutrophil count (8788.2 ± 5759.2 vs. 6248.7 ± 3823.9; $P < 0.001$), lower lymphocyte percentage (11 ± 7% vs. 15 ± 10, $P = 0.007$), and higher neutrophil-lymphocyte ratio (NLR) (13.9 ± 17.2 vs. 8.03 ± 8.31, $P = 0.001$). Lymphocyte count, erythrocyte sedimentation rate, and C-reactive protein level showed no statistically significant differences between the two groups. Moreover, D-Dimer levels (2876 ± 2479 vs. 1344 ± 1196, $P < 0.001$), BUN, and BUN/Cr ratio were significantly higher in group A ($P < 0.001$). The analysis of venous blood gases variables in the emergency room revealed lower PH and HCO3 in group A (7.23 ± 0.42 vs. 7.30 ± 0.07, $P = 0.040$ and 19.33 ± 5.47 vs. 22.75 ± 7.92, $P = 0.005$, respectively). Serum level of albumin was significantly lower in AIS patients (3.31 ± 0.46 vs. 3.70 ± 0.45, $P < 0.001$).

DISCUSSION

In agreement with previous literature, patients with AIS were older and more likely to die and have cardiovascular and cerebrovascular risk factors including HTN, DM, IHD, AF, and previous stroke.[4,5,7] The high prevalence of common vascular risk factors could be independently associated with the occurrence of stroke among patients with COVID-19 and play a significant role in the pathogenesis of this condition.

In brief, the binding of human angiotensin-converting enzyme 2 receptor and SARS-CoV-2 surface protein

Table 2: Laboratory findings of patients with coronavirus disease-2019 with or without new-onset acute ischemic stroke

	Total (*n*=211)	COVID-19 with AIS (*n*=51)	COVID-19 without AIS (*n*=160)	*P*
ESR	52.52±25.6	46.8±24.3	54.3±25.8	0.069
CRP	88.38±45.81	94.2±49.9	86.4±44.3	0.290
D-Dimer	1712.65±1724	2876.5±2479.8	1344.3±1196.8	<0.001*
Ferritin	724.69±535.98	777.9±575.4	708.5±524.8	0.492
WBC count	8465.07±4997	10323.5±6093.6	7865.1±4447.9	0.002*
Neutrophil count	6868.4±4495.1	8788.2±5759.2	6248.7±3823.9	<0.001*
Lymphocyte count	1088.74±1724	915.8±415.2	1144.5±1968.1	0.412
Lymphocyte percentage	14.92±10.06	11.65±7.91	15.98±10.46	0.007*
Neutrophil-to-lymphocyte ratio	9.48±11.42	13.9±17.2	8.03±8.31	0.001*
Hgb	12.57±2.3	12.3±2.4	12.6±2.2	0.482
PLT	195.51±84.64	207.1±102.1	191.7±78.1	0.261
Cpk	357.16±906.63	469.6±894.07	321.9±910.6	0.331
LDH	877.54±485.30	983.45±688.4	847.8±408.9	0.102
Troponin	572.8±4153	1334±6333	325.6±3128	0.132
PT	13.27±5.11	14.3±7.3	12.9±4.1	0.078
PTT	31.88±7.91	33.3±13.6	31.4±4.7	0.120
Albumin	3.61±0.48	3.31±0.46	3.70±0.45	<0.001*
ALT	48.36±48.27	51.9±68.6	47.2±39.8	0.547
AST	57.75±58	66.5±77.98	54.9±49.99	0.218
BUN	26.5±20.6	35.3±25.06	23.6±18.1	<0.001*
Cr	1.68±1.58	1.58±0.8	1.71±1.75	0.602
BUN/Cr ratio	16.63±6.77	21.7±7.5	14.96±5.5	<0.001*
Na	139.23±9.85	138.9±18.5	139.3±4.46	0.831
K	4.6±0.65	4.71±0.72	4.67±0.63	0.694
Ca	8.59±0.60	8.4±0.6	8.6±0.6	0.090
Ph	3.32±0.95	3.48±0.89	3.28±0.97	0.227
Mg	2.01±0.27	2.04±0.28	2.01±0.27	0.467
PH1	7.28±0.21	7.230±0.423	7.302±0.071	0.040*
Pco2	40.97±11.25	41.84±10.93	40.70±11.38	0.535
Hco3	21.93±7.54	19.33±5.47	22.75±7.92	0.005*
BS	178.34±116.02	194.58±126.88	172.93±112.08	0.249

ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; WBC=White blood cell; Hgb=Hemoglobin; PLT=Platelet; Cpk=Creatine kinase; LDH=Lactate dehydrogenase; PT=Prothrombin time; PTT=Partial thromboplastin time; ALT=Alanine transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; Cr=Creatinine; Na=Sodium; K=Potassium; CA=Calcium; Ph=phosphor; Mg=Magnesium; BS=Blood sugar; AIS=Acute ischemic stroke; COVID-19=Coronavirus disease 2019

spike that cause endothelial apoptosis and neuronal damage mentioned as a probable association of COVID-19 severity and neurological symptoms.[8] Furthermore, hyperinflammatory state from cytokine storm followed by a prothrombotic state is frequently complicated by both venous and arterial thromboembolism.[9] Critical COVID and hypoxia in admit were more common in group A. Patients with critical illness were 2.5 fold more likely to be at risk of AIS. Bhatia *et al*. reported critical illness in 74% of patients with COVID and cerebrovascular disease (CVD).[3]

We showed higher leukocytosis and neutrophil count, lower lymphocyte percentage, and higher NLR in group A. Previous reports are almost the same, for example, Yao *et al*. compared 25 COVID-19 patients with new stroke and 2361 COVID-19 patients without stroke; they found that patients with stroke are more likely to have leukocytosis, neutrophilia, and lymphocytopenia and anemia.[6] Leukocytosis, lymphopenia, and high NLR are all inflammatory biomarkers that could be used as an indicator of systemic inflammation.[10] These blood parameters are independent predictors for the disease severity and survival of patients with COVID-19.[5,10,11]

D-dimer was significantly higher in group A. D-dimer is both a thrombus indicator and an acute phase reactant factor. D-dimer rise is basically due to a severe underlying COVID-19 infection.[12] Several studies have reported elevated levels of D-dimer in patients with COVID-19 and stroke.[13-16] As mentioned elevated D-dimer levels in critically ill patients with COVID-19 could be the causes of abnormal blood coagulation function in the early stage and could render patients prone to acute CVD. Accordingly, AIS patients more tended to develop PTE during hospitalization.

As shown in previous studies, the presence of multiple organ dysfunction and over-activated systematic inflammation is more common in COVID-19 patients with stroke than in those without stroke.[13] In our study, the BUN and BUN/Cr ratios were higher in group A patients. Yao *et al*. reported higher levels of BUN and Cr in patients with AIS.[6] Another study showed higher levels of BUN and Cr among 11 patients with COVID and CVD in comparison to those without CVD.[13] An increased BUN level is a predictive factor of extrapulmonary organ injuries. Higher initial levels of BUN together with D-dimer are associated with mortality in COVID-19 patients and are used as an assessment tool for the prediction of mortality and severity in patients with COVID-19. Furthermore, it is mentioned in previous studies that BUN/Cr ratio is an independent predictor for COVID-19 severity and can help to identify high-risk cases.[10,17]

Limitations

First, it would be better to include more patients. Second, we did not measure other coagulation-and inflammatory-related indices, i.e., antiphospholipid antibodies, fibrinogen, interleukin-6, factor VIII, and Von Willebrand factor.

CONCLUSION

Patients with AIS were older, had a more critical infection, more cardiovascular, and cerebrovascular risk factors (HTN, DM, IHD, AF, and previous stroke). Furthermore, we found that COVID-19 patients with higher leukocytosis, neutrophil count, NLR, D-Dimer, BUN, and BUN/Cr are more likely to develop stroke. These findings suggest that stroke in COVID-19 are probably multifactorial, and physicians should pay more attention to patients with critical infection, vascular risk factors, and those with higher mentioned laboratory markers.

Acknowledgments

This article has been approved by the ethics committee of the Isfahan University of Medical Sciences under the registration # IR. MUI. MED. REC.1400.300.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: A review and a call for action. J Neurol 2020;267:1573-6.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al.* COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
3. Bhatia R, Pedapati R, Komakula S, Srivastava MV, Vishnubhatla S, Khurana D. Stroke in coronavirus disease 2019: A systematic review. J Stroke 2020;22:324-35.
4. 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. Stroke 2021;52:905-12.
5. Tan YK, Goh C, Leow AS, Tambyah PA, Ang A, Yap ES, *et al.* COVID-19 and ischemic stroke: A systematic review and meta-summary of the literature. J Thromb Thrombolysis 2020;50:587-95.
6. Yao X, Liu S, Wang J, Zhao K, Long X, He X, *et al*. The clinical characteristics and prognosis of COVID-19 patients with cerebral stroke: A retrospective cohort study. Eur J Neurosci. 2021 Feb;53(4):1350-1361. doi: 10.1111/ejn.15007. Epub 2020 Dec 21. PMID: 33052619; PMCID: PMC7675674.
7. Arienti C, Brambilla L, Campagnini S, Fanciullacci C, Giunco F, Mannini A, *et al.* Mortality and characteristics of older people dying with COVID-19 in Lombardy nursing homes, Italy: An observational cohort study. J Res Med Sci 2021;26:40.
8. Jain A, Jafri F, Manglani R, Al-Mufti F, Aronow WS, Chandy D. Stroke in critical COVID-19 patients: A cautionary tale from the frontlines. Arch Med Sci Atheroscler Dis 2020;5:e263-70.
9. Klein DE, Libman R, Kirsch C, Arora R. Cerebral venous

thrombosis: A typical presentation of COVID-19 in the young. J Stroke Cerebrovasc Dis 2020;29:104989.
10. Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. J Med Virol 2021;93:786-93.
11. Katz JM, Libman RB, Wang JJ, Filippi CG, Sanelli P, Zlochower A, *et al.* COVID-19 severity and stroke: Correlation of imaging and laboratory markers. AJNR Am J Neuroradiol 2021;42:257-61.
12. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, *et al.* Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;87:18-22.
13. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, *et al.* Acute cerebrovascular disease following COVID-19: A single center, retrospective, observational study. Stroke Vasc Neurol 2020;5:279-84.
14. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. Stroke 2020;51:e124-7.
15. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, *et al.* SARS-CoV-2 and stroke in a New York healthcare system. Stroke 2020;51:2002-11.
16. Lee KW, Yusof Khan AH, Ching SM, Chia PK, Loh WC, Abdul Rashid AM, *et al.* Stroke and novel coronavirus infection in humans: A systematic review and meta-analysis. Front Neurol 2020;11:579070.
17. Liu Q, Wang Y, Zhao X, Wang L, Liu F, Wang T, *et al.* Diagnostic performance of a blood urea nitrogen to creatinine ratio-based nomogram for predicting in-hospital mortality in COVID-19 patients. Risk Manag Healthc Policy 2021;14:117-28.