

Research Paper

The Epidemiologic Features of Patients With Acute Stroke During COVID-19 Pandemic in a COVID-19 Center in Qazvin City, Iran



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ABSTRACT

Background and Aim: The novel coronavirus 2019 (COVID-19) disease is a global pandemic with different presentations ranging from mild respiratory problems to severe septic shock. Previous studies have established the association between acute stroke and COVID-19. Herein, we describe the characteristics of patients with stroke during the COVID-19 pandemic.

Materials and Methods: In this cross-sectional study, all patients with acute stroke referred to Bouali Hospital were enrolled from March to June 2020. The patients were categorized into two groups with and without COVID-19. Then, the demographic and clinical characteristics of stroke patients in both groups were evaluated. Eventually, SPSS software, version 22 was used to analyze the data.

Results: A total of 61 patients with acute stroke were identified, of which 22 patients were positive for COVID-19. Except for the in-hospital mortality ($P=0.07$) and type of hemorrhagic transformation ($P=0.02$), we did not find a significant difference in the demographic and clinical characteristics of patients in both groups. The majority of patients with COVID-19 were severely symptomatic. However, the severity of chest CT involvement was significantly correlated with the mean modified Rankin scale ($P=0.05$).

Conclusion: In this study, we revealed that acute stroke affected COVID-19 patients with traditional stroke risk factors at an age typically seen in non-COVID populations, which mainly constitute cryptogenic acute ischemic stroke. We also noted a higher in-hospital mortality rate in patients with COVID-19-associated stroke, which reflects a worse outcome of COVID-19. These results highlight the possible hypercoagulopathy state associated with COVID-19, which predisposes patients to develop stroke.

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1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in China, which soon turned into a global pandemic affecting more than 35 million people worldwide [1, 2]. The classic clinical presentation of SARS-CoV-2 infection ranges from asymptomatic disease to life-threatening acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure, and eventually death. However, there is increasing evidence suggesting the non-respiratory manifestations of COVID-19 in which neurological complications are noticeable [3-5].

Although stroke has been recognized as a complication of COVID-19, the exact pathophysiology is still poorly understood. Nonetheless, a cascade of cytokine storm and hypercoagulability with subsequent macrothrombi and microthrombi formation in the endothelial cells might contribute to acute stroke [6-10].

Given the unknown prognosis of stroke in patients with COVID-19 and limited data in our country, we aimed to describe the characteristics of patients with acute stroke due to COVID-19 compared to isolated stroke cases during the COVID-19 pandemic to provide a more comprehensive knowledge of the underlying pathophysiology of stroke in patients with COVID-19.

2. Materials and Methods

Study design

This cross-sectional study was conducted from March to June in Bouali Hospital, Qazvin, Iran. The study was approved by the Local Ethics Committee (Code: IR.QUMS.REC.1399.264). In addition, written informed consent forms were obtained from all patients before they participated in this study.

Study population

We enrolled all patients with the acute focal neurological deficit with a diagnosis of cerebrovascular accident. We excluded the patients who were infected after the onset of stroke given to the uncertainty attributing the occurrence of COVID-19 to superimposed nosocomial infection or incubation period of the disease. The diagnosis of cerebrovascular accident (CVA) was made based on clinical symptoms, neurological examinations, and neuroimaging studies. COVID-19 was diagnosed based on

WHO interim guidance [11]. A confirmed case of COVID-19 was defined as a positive result on a real-time reverse transcription–polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens.

Intervention and data gathering

Following the hospitalization of patients, the data collection was prospectively performed by a checklist consisting of demographic features such as age, sex, past medical history, habitual file, and clinical symptoms according to the national institutes of health stroke scale (NIHSS) score. The paraclinical assessment, including brain and chest computed tomography (CT) and laboratory testing on admission, was recorded. Laboratory assessments included a complete blood count, blood chemical analysis, coagulation testing, and measures of electrolytes and C-reactive protein. Additionally, the nasopharyngeal PCR and chest CT were performed for all patients at admission.

Based on the laboratory testing and chest CT, the patients were categorized into two groups: CVA associated with COVID-19 and CVA without COVID-19. Subsequently, we assessed the CVA characteristics in the two groups of CVA type, the Alberta stroke programmed early CT score (ASPECTS) in patients with ischemic stroke, vascular territory, and outcome status with the modified Rankin scale (mRS). Additionally, brain and cervical sonography and echocardiogram were performed for all patients.

In the second group, we determined the severity of COVID-19 and chest CT involvement. The severity of clinical symptoms was evaluated based on China's National Health Commission on February 5, 2020, COVID-19, and the severity of chest CT involvement based on the chest CT Severity Score Assessment [12].

Statistical analysis

Eventually, we used SPSS software version 22 (SPSS Inc., Chicago, IL, USA) to analyze the data. Data are presented as Mean±SD for continuous or frequencies for categorical variables. The Chi-square and Fisher exact tests were used to compare quantitative and qualitative variables. A P-value less than 0.05 was considered significant.

3. Results

During the 4 months study period, 86 patients with clinically suspected acute CVA were presented to our

healthcare system in which 61 patients with a mean age of 68.15 years were hospitalized with a definite diagnosis of acute CVA. Among 61 patients, 39 patients (63.9%) were negative for COVID-19 PCR, and 22 patients (36.1%) were positive. It is noteworthy that, as our hospital was a tertiary center for both infectious and neurological diseases, the total number of COVID-19-positive patients in this period was estimated to be 131.

Based on our results, there was not a significant difference between positive and negative COVID-19 groups regarding age ($P=0.4$) and sex ($P=0.5$). Although the total number of identifiable vascular risk factors, including smoking, hypertension, diabetes mellitus, ischemic heart disease, arrhythmia, and prior cerebrovascular accident, was higher in the second group, it was not significant ($P=0.06$). The patients' characteristics in both groups are summarized in [Table 1](#).

The radiographic evidence of hemorrhage was seen in 15 patients (24.6%), in particular, 18.2% in the positive COVID-19 group and 28.2% in the negative COVID-19 group, at presentation, which was not significantly different in both groups ($P=0.1$). The vascular territory most frequently affected was the middle cerebral artery (37%). We also did not find a difference between the two groups in the prevalence of large-artery and lacunar stroke ($P=0.1$) ([Figures 1 and 2](#)). In patients with ischemic stroke, the ASPECT score averaged 8.18 (8.42 in the first group and 8.05 in the second group) on admission and 6.30 (6.25 in the first group and 6.33 in the second group) at discharge which was not significantly different between the two groups ($P=0.2$). Additionally, the difference between the initial and final ASPECT scores in the two groups was also not significant ($P=0.2$).

In the second group, the median delay between the initiation of COVID-19 symptoms and stroke onset was 4.68 days. Five patients (22.7%) had mild symptoms of COVID-19, while 40.9% were severely affected, and 36.4% were in the critical stage of the disease. Additionally, only 9.1% of patients revealed mild pulmonary involvement based on chest CT findings, and most chest involvements were considered moderate (40.9%) and severe (50%). The main stroke symptoms were motor deficits in both groups (76.4%). At arrival, the median NIHSS scale was 11.59 in the negative COVID-19 group and 12.79 in the positive COVID-19 group, which was not significantly different ($P=0.2$). In terms of laboratory tests, we did not show a significant difference between the WBC counts in the two groups ($P=0.18$). Nevertheless, the lymphocyte count was considerably lower in the positive COVID-19 group ($P=0.02$). The erythrocyte

sedimentation rate level was significantly higher in the positive COVID-19 group ($P=0.025$).

In the following, we assessed the therapeutic approaches in both groups. In 46 patients with acute ischemic stroke, intravenous recombinant tissue plasminogen activator (rTPA) was administered in 8 (17.4%) patients, and 38 patients (82.6%) were under antiplatelet therapy. Any hemorrhagic transformation of the infarct was diagnosed in 3 patients (1 in group 1, 2 in group 2), of whom 3 had been treated with intravenous rTPA, which was significantly different between the two groups ($P=0.02$). Malignant brain edema was present in 9 patients, mainly patients with complex hemorrhagic CVA. Notably, no significant difference was evident in both groups ($P=0.12$), and none of these patients were treated with hemicraniectomy. The summary of medical treatment is presented in [Table 2](#).

Notably, 46 patients (18 patients in group 1, 28 patients in group 2) had a complete diagnostic workup towards stroke cause. Regarding the cardiac investigation, the echocardiogram was abnormal in 6 patients (13%), in particular 2 patients in group 1 and 4 in group 2. In addition, we recorded 11 patients (23.9%), in particular, 3 patients in group 1 and 8 in group 2, with atherosclerotic stenosis of the internal carotid artery in cervical sonography.

We also compared the clinical course of the disease between the groups. The mean hospitalization time in the positive COVID-19 group was 11.55 days compared to 11.03 days in the negative COVID-19 group which was not statistically significant ($P=0.6$). Furthermore, in the positive COVID-19 group, 11 patients (50%) needed invasive oxygenation, which was significantly higher compared to 2 patients (5.1%) in the negative COVID-19 group ($P=0.01$). Regarding in-hospital mortality, a considerable difference was found between the two groups (25 mortalities in group 1 versus 15 in group 2). However, we did not observe a considerable difference in the mean modified Rankin scale (mRS) between the groups ($P=0.07$). The summary of the mRS score of the two groups is presented in [Tables 3 and 4](#) and [Figure 3](#). Eventually, based on the Chi-square test results, we did not find a significant difference between the clinical severity of COVID-19 and any of the following variables: NIHSS ($P=0.5$), initial ASPECT ($P=0.3$), final ASPECT ($P=0.3$) and mean mRS (0.07). We also did not notice a significant difference between the chest CT involvement and NIHSS ($P=0.3$) or ASPECT ($P=0.1$ for initial ASPECT and $P=0.3$ for final ASPECT). However, a considerable difference was observed between the severity of

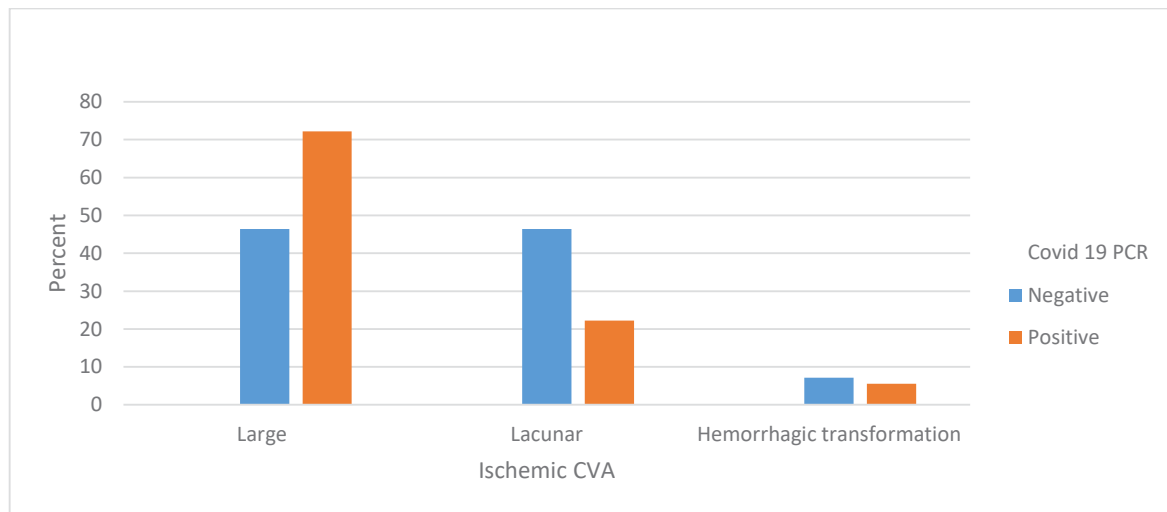


Figure 1. Frequency of ischemic Cerebrovascular Accident (CVA) types in both groups

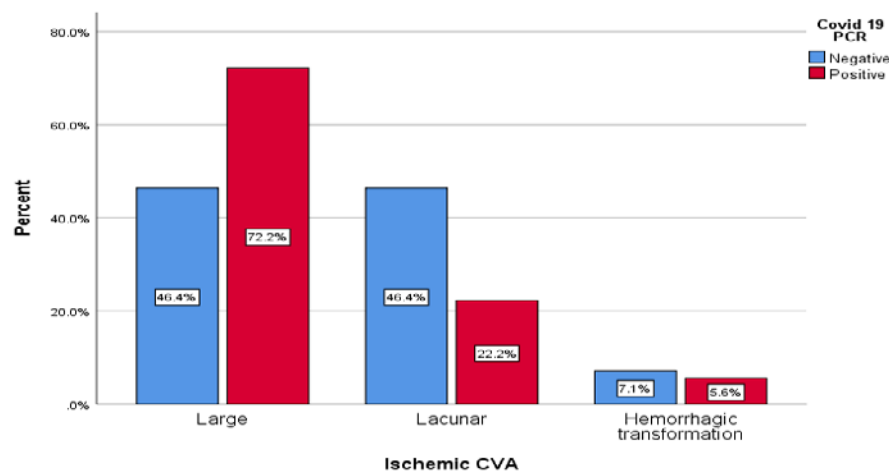


Figure 2. Frequency of hemorrhagic Cerebrovascular Accident (CVA) types in both groups

ICH: intracranial hemorrhage; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage; Complex: a combination of any type of ICH, SAH, and IVH

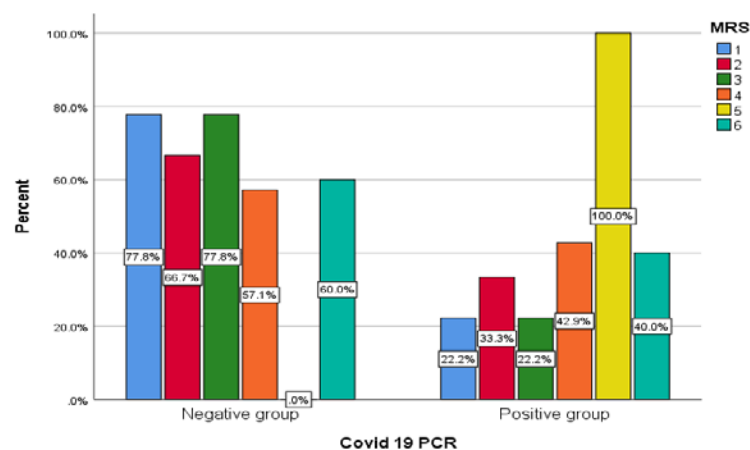


Figure 3. Frequency of modified rankin scale score in both groups

Table 1. Characteristics of patients with Cerebrovascular Accident (CVA) with or without simultaneous COVID-19 infection

Characteristics	COVID-19 Positive (group 1)	COVID-19 Negative (group 2)	All Patients
Mean age	66.32 years	69.18 years	68.15 years
Sex	59.1% male	56.4% male	57.4% male
	40.9% female	43.6% female	42.6% female
Habitual history	18.2%	23.1%	21.3%
Hypertension history	68.2%	82.1%	77%
Diabetes history	27.3%	35.9%	32.8%
Ischemic heart disease history	31.8%	46.2%	41%
AF history	36.4%	25.6%	29.5%
Previous CVA	9.1%	35.9%	26.2%

CVA: cerebrovascular accident; AF: atrial fibrillation.

chest involvement and the mean mRS ($P=0.05$). Moreover, there was no significant association between laboratory parameters and any of the variables of NIHSS, ASPECT, and mRS.

4. Discussion

With the paucity of evidence for the treatment and prevention of COVID-19 disease and the growing trend of its neurological manifestations, it is crucial to maintain vigilance in managing COVID-19 neurological complications.

In this study, we pooled all 61 consecutive patients hospitalized with an acute cerebrovascular accident within 4 months during the COVID-19 pandemic, in which 39 patients (63.9%) were negative for COVID-19 PCR and 22 patients (36.1%) were positive for COVID-19 PCR with an average lag period of 4.68 days between COVID-19 symptoms and the stroke. Notably, the total number of stroke admission in the last year before the COVID-19 pandemic was almost 240 patients.

Based on the results, 77.3% of patients with COVID-19-associated stroke were severe to critically symptomatic with moderate to severe involvement of the chest CT. Regarding the type of cerebrovascular event, we indicated that acute ischemic stroke (AIS) constituted 85% of all cases, consistent with previous reports [6, 13]. In patients with AIS, we found a prominent embolic pattern stroke primarily located in the middle cerebral artery without a clear source of stroke identified in 31 of the 46 (13 in the first group and 18 in the second group) meeting the criteria for cryptogenic strokes which was not significantly different between the two groups ($P=0.49$). This higher rate of cryptogenic stroke compared to the 17% overall rate found by others [14, 15] highlights the possible underlying hypercoagulable state in patients with COVID-19. A recent review article revealed a higher incidence of juvenile and cryptogenic stroke in multiple regions with high COVID-19 prevalence [16]. We also reported a case series of juvenile acute stroke in relation to COVID-19 early in the pandemic [17, 18].

Neither the prevalence of large-artery and lacunar stroke nor the traditional stroke risk factors were con-

Table 2. Frequency of medical treatment prescribed for patients with ischemic stroke

Type of Treatment	No. (%)	Valid Percentage in Ischemic Cerebrovascular Accident
rTPA	8(13.1)	17.4
Mono antiplatelet	23(37.7)	50.0
Dual antiplatelet	15(24.6)	32.6
Total	46(75.4)	100.0

Table 3. Frequency of modified rankin scale score in both groups

mRS	No. (%)
1	9(14.8)
2	9(14.8)
3	9(14.8)
4	7(11.5)
5	2(3.3)
6	25(41)
Total	61(100)


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siderably different in both groups ($P=0.1$, $P=0.06$). It is postulated that the mechanisms of stroke development include a hypercoagulable state from systemic inflammation and cytokine storm, post-infectious immune-mediated responses, and direct viral-induced endotheliopathy in which hypercoagulopathy is of paramount importance [16]. We assume that this difference might be due to ecological and cultural conditions, as the majority of our patients had a history of smoking. Moreover, given that this study was conducted early in the pandemic, the number of hospitalizations was low, patients with low-risk factors or mild symptoms were less likely to present at medical centers, and the presence of these comorbid conditions has been associated with a higher risk of having a COVID-19 infection which all contributed to interpretation bias. Similarly, in another case series, the presence of stroke risk factors in patients with COVID-19 and AIS was considered a confounding factor in stroke development [14].

In our study, the primary and final ASPECT score averaged 8.18 and 6.30, respectively, which was not significantly different between the two groups ($P=0.2$). The stroke severity was similar between the two groups, which was inconsistent with another case series in Iran [19]. The retrospective nature of their study, accompanied by small sample size (31 versus 61 in our study), might justify this difference.

Regarding the therapeutic methods, no difference was observed between the two groups. However, the hemorrhagic transformation was significantly higher in patients with COVID-19 ($P=0.02$). We also noted that the COVID-19 patients who experienced a stroke were considerably more likely to die than patients without concomitant COVID-19 infection ($P=0.07$). In this study, consistent with other case series, patients with COVID-19 had worse clinical outcomes than patients without COVID-19 [20-23]. Contrary to these findings, Mehrpoor et al. reported a significant difference in the type of stroke without a worse outcome in patients with COVID-19-associated stroke [19]. Neither the severity of the disease nor the laboratory investigations were significantly correlated with the NIHSS and mean mRS. However, a considerable difference was observed between the severity of chest involvement and the mean mRS ($P=0.05$).

The strength of our work is its prospective manner of collecting data, which provided a better understanding of COVID-19 and stroke. However, our study has some limitations. First, we had a small sample size from one center, which is not an accurate representation of the general population in Iran. Secondly, the results are mainly observational in which the casual association of COVID-19 and stroke is not ascertained. Thirdly, due to the limitations caused by COVID-19 infection, we could not perform occult arrhythmia screening for all patients, which contributed to the overdiagnosis of cryptogenic stroke.

Table 4. Modified rankin scale score in both groups

mRS score	1	2	3	4	5	6
Negative COVID-19 group	7	6	7	4	0	15
Positive COVID-19 group	2	3	2	3	2	10
Total	9	9	9	7	2	25


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Taking all considerations into account, we aimed to highlight the need to increase awareness regarding hypercoagulopathy related to COVID-19 infection, which might predispose patients to stroke predominantly in patients with identifiable risk factors. However, we are still in the early stages of recognizing neurological complications of COVID-19 disease. As many countries are facing the second peak of the disease with much more serious manifestations, larger multicenter studies are required to better understand the nature and management of neurological complications of COVID-19 disease.

5. Conclusion

In our study, acute stroke affected COVID-19 patients at the age of stroke presentation typically seen in non-COVID populations in which acute ischemic stroke accounted for the majority of cases. We also observed a higher rate of cryptogenic strokes. Additionally, the concomitant COVID-19 contributed to the worse outcome with a higher in-hospital mortality rate. These results highlight the possible hypercoagulopathy state associated with COVID-19, which predisposes patients to develop stroke. Further studies are needed to better understand COVID-19 associated with stroke, especially in developed countries facing the second peak of the disease.

Ethical Considerations

Compliance with ethical guidelines

The ethical principles observed in the article, such as the informed consent of the participants, the confidentiality of information, the permission of the participants to cancel their participation in the research and the code of ethics received from the ethics committee of the universities should be written as follows:

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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