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Concomitant COVID-19 and acute ischemic stroke in patients transferred by emergency medical service during first wave of pandemic in Tehran, Iran; a cross-sectional study

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Abstract: **Objective:** We conducted this study to evaluate the prevalence of concomitant COVID-19 in acute ischemic stroke (AIS) patients admitted to stroke centers of Tehran, Iran.

Methods: We conducted a retrospective cross-sectional study in a 45-day period. AIS patients transferred by emergency medical service (EMS) to all medical centers of the city were included. Information was recorded and compared in two groups: patients who tested positive for COVID-19 and those who were negative.

Results: Emergency medical technicians (EMTs) screened 348 patients as AIS cases, of whom, AIS was ultimately confirmed in 311 (89.4%) patients; and 58 (18.6%) of the 311 AIS patients were diagnosed with concomitant COVID-19 infection. The National Institutes of Health Stroke Scale (NIHSS) scores of COVID-19 positive AIS patients were significantly higher than non-COVID-19 AIS patients (16.3±3.7 vs. 11.8±4.3; p<0.001). There was also a significant difference in length of hospital stay between the two groups (11.1±1.8 vs. 8.8±4.3 days; p<0.001). However, data showed no significant difference regarding prevalence of in-hospital mortality between the two groups (1.6% vs. 3.5%; p=0.320).

Conclusion: Our study results showed that AIS patients with concomitant COVID-19 infection had higher NIHSS scores and longer length of hospital stay compared to patients without concomitant COVID-19 infection.

Keywords: Acute; COVID-19; Emergency Medical Services; Ischemic Stroke; Length of Stay; Severity of Illness Index

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1. Introduction

In December 2019, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing an unusual respiratory illness, COVID-19, was detected in Wuhan, China. Since then it has become a worldwide disease, resulting in the COVID-19 pandemic (1, 2). Although it was believed that COVID-19 mainly involves the respiratory system, it is becoming increasingly difficult to ignore its other, extra-pulmonary, manifestations and the multisystem inflammatory disorder caused by the virus (3-5). Recent literature report neurological manifestations in COVID-19 patients including headache, weakness, hypogeusia, hyposmia, dizziness, seizure, encephalitis, and acute ischemic stroke (AIS) (6-8). In the primary reports from China, AIS was diagnosed in around 5% of the COVID-19 patients (8). Although there have been increasing reports of AIS in COVID-19 patients of all ages, severe AIS occurring in young patients with no pre-existing risk factors is becoming a major concern (9, 10). Even though, AIS seems to be an infrequent complication amongst COVID-19 patients, it leads to significant morbidity and mortality (11).

Severe COVID-19 has the potential to disrupt most physiological systems and cause various multi-systemic thromboembolic incidents including AIS (12). Inflammation largely contributes to AIS pathogenesis in COVID-19 patients. However, other mechanisms such as coagulopathy, endothelial dysfunction, cardio embolism,

renin–angiotensin system disruption, and direct viral-mediated neuronal injury also play a role in the physiopathology of AIS in COVID-19 patients (13-16). Current literature and our experiences during the COVID-19 pandemic suggest that further investigations are needed to assess the probable association between COVID-19 and AIS (12).

Therefore, we conducted this study to evaluate the prevalence of COVID-19 in AIS patients admitted to all stroke centers of Tehran, Iran.

2. Method

2.1. Study design and setting

This is a retrospective cross-sectional study performed using the records in the databank of Tehran emergency medical service (EMS) center, recorded from 20 February 2020 until 12 May 2020. We obtained institutional board review approval from Tehran University of Medical Sciences to conduct this study (IR.TUMS.VCR.REC.1399.314).

2.2. Definition

Iran has launched a 724 system (7 days a week / 24 hours a day) to rapidly screen patients with suspected AIS and to enhance coordination between EMS and designated thrombolytic therapy facilities. Once a call is made to the EMS center, emergency medical dispatchers (EMDs) decide whether the patients is suspected to have AIS. If suspected, emergency medical technicians (EMTs) approach the patient and decide whether the patient needs to be transferred to a stroke unit or not (stroke units are facilitated with intravenous thrombolytic treatment and patients will be treated under the direct supervision of a neurologist in less than 15 minutes). This decision is made using the FAST (Facial drooping, Arm weakness, Speech difficulties, and Time) clinical tool, within the defined 3-hour golden time (17).

According to the established national protocol during the COVID-19 pandemic, all stable AIS patients underwent both spiral brain and lung computed tomography (CT) scan. Reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal test for COVID-19 was performed for all patients with positive findings for COVID-19 on lung CT scan.

2.3. Study population and data gathering

All adult patients with suspected stroke transferred by EMS to any of the medical centers in Tehran city were included in the census sample data. Patients with a final diagnosis other than AIS and those transferred to hospitals without stroke units were later excluded. The required information was gathered from EMS operation forms and hospital records. Age and gender of the patient, referred hospital, the severity of symptoms on admission based on the National Institutes of Health Stroke Scale (NIHSS), administration of intravenous thrombolytic, lung computed tomography (CT) scan findings, results of reverse transcription polymerase chain reaction (RT-PCR) test, length of hospital stay, and in hospital mortality were documented in a pre-prepared checklist. The final diagnosis of AIS was made by a neurologist, based on the patient's symptoms and neuroimaging findings.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp; 2015). The results of the statistical analyses of descriptive data were reported in the form of mean and standard deviation (SD) for continuous variables and absolute frequencies and percentages for categorical variables. We compared variables between COVID-19 negative ischemic stroke patients and COVID-19 positive cases. Student t-test and chi-square test were applied for continuous and categorical variables, respectively. Any $P< 0.05$ was considered significant.

3. Results

A total of 381 patients (213 male) with symptoms resembling stroke were transferred by EMS to 17 hospitals; their mean age was 67.3±18.8 years. Demographics and clinical characteristics of the studied patients are presented in table 1. EMTs reassessed these patients and transferred 348 patients (out of the 381) as suspected AIS cases to 8 stroke centers in Tehran. The median number of suspected AIS patients transferred to the stroke centers was four patients per day (range of 0-10). AIS was confirmed by neurologists in 311 (89.4%) cases. Later, 235 (75.6%) cases received intravenous throm-

Table 1 Demographics and clinical characteristics of the studied patients

Variable	n (%)
Gender (n=381)	
Male	213 (55.9)
Female	168 (44.1)
Referred stroke center (n=348)	
Loghman	78 (22.4)
Firoozabadi	65 (18.7)
Shohadaye Tajrish	58 (16.7)
Imam Hossein	54 (15.5)
Rasool-e-Akram	45 (12.9)
Sina	23 (6.6)
Firoozgar	15 (4.3)
Shariati	10 (2.9)
Confirmed as acute ischemic stroke (out of 348)	311 (89.4)
Received intravenous thrombolysis (out of 311)	235 (75.6)
Chest CT scan with findings for COVID-19 (n=348)	
Positive	58 (16.7)
Negative	247 (70.9)
Not performed	43 (12.4)
RT-PCR (n=58)	
Positive	29 (50.0)
Negative	20 (34.5)
Unavailable	9 (15.5)

CT: computed tomography;
RT-PCR: reverse transcription polymerase chain reaction.

Table 2 Comparison of acute ischemic stroke variables between patients with and without positive findings for presence of concomitant COVID-19 on lung computed tomography (CT) scan (n=305)

Variable	Presence of findings of COVID-19 infection in lung CT scan		P
	Negative (n=247)	Positive (n=58)	
NIHSS score on Admission	16.3±2.1	11.8±4.3	<0.001
Length of hospital stay (days)	11.1±1.8	8.8±4.3	<0.001
In-hospital death	4 (1.6%)	2 (3.5%)	0.320

NIHSS: National Institutes of Health Stroke Scale.

bolytic therapy and 76 (24.4%) patients did not.

Lung CT scan findings showed COVID-19-specific changes in 58 (18.6%) cases. Forty-three confirmed AIS patients did not undergo lung CT scan. RT-PCR test was performed on 49 cases (out of the 58 cases with positive lung imaging findings for COVID-19) and the results were reported to be positive in 29 (50.0%) cases.

The mean NIHSS score on admission day for all patients with a confirmed diagnosis of AIS was 13.4±3.7. As demonstrated in table 2, the NIHSS scores for AIS patients with concurrent COVID-19 infection were significantly higher than non-COVID-19 cases (16.3±2.1 vs. 11.8±4.3; p<0.001) (Table 2).

The mean length of hospital stay for all patients with a confirmed diagnosis of AIS was 10.1±2.3 days. Patients with concomitant AIS and COVID-19 infection had a longer length of hospital stay (11.3±1.8 vs. 8.8±4.3 days; p<0.001) (Table 2).

A total of six deaths were reported. Two of the six patients who died during hospital stay were COVID-19 positive. No statistically significant difference was detected in terms of in-hospital death between the two groups (p= 0.320) (Table 2).

4. Discussion

In this multicenter study, we found COVID-19 positive radiographic findings in around one-fifth of the patients admitted due to stroke signs and symptoms within 3 hours of onset. Half of these patients tested positive for COVID-19 on their RT-PCR test.

Since the beginning of the COVID-19 pandemic, a considerable number of articles have documented a relationship between COVID-19 and thromboembolic incidents such as ischemic stroke, but there is yet no clear neuropathogenesis (12, 18). A possible explanation might be that older people with various comorbidities and predisposing risks for stroke, are also more likely to be infected with COVID-19 (19). Several reports have shown a higher incidence of cerebrovascular events in patients hospitalized with COVID-19 than those without. Recent literature report increasing cases of acute ischemic stroke in COVID-19 positive young people with no pre-existing cerebrovascular risk factors (9, 20, 21).

Our study focused on patients with AIS, whose symptoms were initiated less than 3 hours before admission to a stroke center, and evidence of concomitant COVID-19 was observed in their lung CT scan imaging.

The findings of our study suggest that stroke severity (scored based on NIHSS) and length of hospital stay were significantly higher in those with concomitant COVID-19 compared to those without the disease. These findings are in line with the findings of a retrospective multicenter cohort study conducted by Fuentes et al. (22), in which they confirmed that patients with COVID-19 had more severe strokes and poorer outcomes despite similar acute management. Although they included all stroke patients and not only acute and ischemic strokes, we too point to the same conclusion. However, unlike Fuentes et al., we did not detect a significant difference regarding in-hospital mortality rates between AIS patients with concomitant COVID-19 and non-infected patients. However, this difference may be due to the small sample size of our study compared to Fuentes et al. study (22).

5. Limitations

In this observational study, we cannot determine the exact cause and effect of our findings: It cannot be determined whether COVID-19 has predisposed patients to face increased thromboembolic events or the patients' comorbidities. The present study lacked a control group, so our findings cannot confirm the relationship between COVID-19 and stroke with certainty.

6. Conclusion

Our study results showed that AIS patients with concomitant COVID-19 infection had higher NIHSS scores and longer length of hospital stay compared to patients without concomitant COVID-19 infection.

7. Declarations

7.1. Acknowledgment

We would like to express our commitment to the Prehospital and Hospital Emergency Research Center affiliated to Tehran University of Medical Sciences.

7.2. Authors' contribution

The conception and design of the work by PS, SS and MZ; Data acquisition by PS, MR, SM and SA; Analysis and in- terpretation of data by SS, MZ, SM and SA; Drafting the work by MZ and SA; Revising it critically for important intellec- tual content by PS, SS, MR and SM; All the authors approved the

final version to be published; AND agree to be account- able for all aspects of the work in ensuring that questions re- lated to the accuracy or integrity of any part of the work.

7.3. Conflict of interest

None declared.

7.4. Funding

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