The Impact of COVID-19 Pandemic on Ischemic Stroke Patients in a Comprehensive Hospital

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Purpose: This study aimed to investigate the impact of characteristic ischemic stroke and outcomes during the first COVID-19 pandemic lockdown.

Patients and Methods: A retrospective, observational cohort study of a comprehensive tertiary stroke center was conducted. Patients with ischemic stroke were divided into pre-COVID-19 lockdown (11/1/2019 to 1/30/2020) and COVID-19 lockdown (1/31/2020 to 4/30/2020) period groups. Patient data on stroke admission, thrombolysis, endovascular treatment, and 3-month routine follow-up were recorded. Data analysis was performed using SPSS according to values following a Gaussian distribution.

Results: The pre-COVID-19 lockdown period group comprised 230 patients compared to 215 patients in the COVID-19 lockdown period group. Atrial fibrillation was more predominant in the COVID-19 lockdown period group (11.68% vs 5.65%, p=0.02) alongside patients who were currently smoking (38.8% vs 28.7%, p=0.02) and drinking alcohol (30.37% vs 20.00%, p=0.012) compared with that of the pre-COVID-19 lockdown period group. For patients receiving thrombolysis, the median door-to-CT time was longer in the COVID-19 lockdown period group (17.0 min (13.0, 24.0) vs 12.0 min (8.0, 17.3), p=0.012), median door to needle time was 48.0 minutes (35.5, 73.0) vs 43.5 minutes (38.0, 53.3), p=0.50, compared with that of the pre-COVID-19 lockdown period group. There were no differences for patients receiving mechanical thrombectomy. The median length of hospitalization (IQR) was no different. Discharge mRS scores (IQR) were higher in the COVID-19 lockdown period group (1.0 (1.0, 3.0) vs 1.0 (1.0, 2.0), p=0.022). Compared with the pre-COVID-19 lockdown period, hospitalization cost (Chinese Yuan) in the COVID-19 period group was higher (13,445.7 (11,009.7, 20,030.5) vs 10,799.2 (8692.4, 16,381.7), p=0.000). There was no difference observed in 3-month mRS scores.

Conclusion: Patients presenting with ischemic stroke during the COVID-19 pandemic lockdown period had longer median door-to-CT time and higher hospitalization costs. There were no significant differences in 3-month outcomes. Multidisciplinary collaboration and continuous workflow optimization may maintain stroke care during the COVID-19 pandemic lockdown.

Keywords: ischemic stroke, COVID-19 pandemic, thrombolysis, thrombectomy, hospitalization cost

Introduction

Stroke accounts for the second most common cause of death globally, and the most common etiology contributing to increased mortality in China.1 The World Health Organization (WHO) declared the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for the Coronavirus Disease 2019 (COVID-19), to be a pandemic on 11th March 2020.2 Since then, the pandemic has been associated with a global reduction of overall
ischemic stroke and intracranial hemorrhages, and fewer endovascular thrombectomy procedures,\textsuperscript{3,4} with higher-volume COVID-19 centers experiencing steeper declines during the first wave of the pandemic.\textsuperscript{5} While there is no conclusive evidence and further studies are required, the falling stroke rates may be due in part to a reduction of non-COVID systemic infection as a trigger for acute stroke,\textsuperscript{6} but also due to patients avoiding medical care in the setting of milder symptoms.\textsuperscript{7} As a corollary, patients who have not sought medical attention for cerebrovascular disease are surviving with more disability and are likely to experience accumulated cerebral and cardiovascular events in the setting of suboptimal secondary prevention.\textsuperscript{8,9} This study primarily aimed to investigate the characteristic ischemic stroke clinical admission demographic and benchmark data, door-to-needle time (DNT), door-to-puncture time (DPT), and patient outcome during the COVID-19 pandemic lockdown.

**Materials and Methods**

**Study Design**

This was a retrospective, observational cohort study of a comprehensive tertiary stroke center that provides healthcare services to approximately 800,000 individuals in the Sanshui region, including intravenous thrombolysis (IVT) and endovascular therapy (EVT). China commenced lockdown at the end of January of 2020. Sanshui region, located in Foshan City in China, went into lockdown from 1/31/2020 to 5/1/2020. Patients with ischemic stroke were divided into pre-COVID-19 (11/1/2019 to 1/30/2020) and COVID-19 (1/31/2020 to 4/30/2020) period groups. The COVID-19 period in this study reflects the time of the initial wave of the pandemic in our region. As a consequence of the COVID-19 pandemic, our institution became a designated COVID-19 and fever-outpatient designated hospital. The study was approved by the Foshan Sanshui District People’s Hospital institutional review board and due to the retrospective nature of this study and in accordance with the guidelines of the review board, patient informed consent was waived, patient data was confidential and compliance with the Declaration of Helsinki. Inclusion criteria were consecutive patients with the diagnosis of acute ischemic stroke within seven days of symptom onset. Exclusion criteria were patients who did not have a diagnosis of ischemic stroke.

**Data Collection**

Patient data on stroke admission, thrombolysis, endovascular treatment, and 3-month routine follow-up were recorded from our stroke center patient database. One patient was excluded because of loss to follow-up and data. Additionally, baseline patient demographics regarding age, sex, cerebrovascular risk factors, last known normal-to-door time, DNT, admission National Institutes of Health Stroke Scale (NIHSS), length of hospitalization, and cost of hospitalization were included. All patients were assessed by the modified Rankin Scale (mRS) score at discharge and 3-months follow-up. An mRS score of 0 to 2 at 3-month follow-up was defined as a favorable outcome and an mRS score of 3 to 6 at 3-month follow-up was defined as an unfavorable outcome. The 3 month outcomes were collected by a stroke nurse during routine follow-up. The investigators were not blinded to baseline characteristics. Data on diabetes mellitus, dyslipidemia, atrial fibrillation, hypertension, coronary heart disease, smoking status, and alcohol consumption were collected based on medical records. Current smoker or alcohol consumption were defined if the patient had consumed alcohol or smoked within one month of admission. The costs comprised of the hospitalization expenses as calculated by the hospital administration team.

**Statistical Analysis**

Data analysis was performed using SPSS according to values following a Gaussian distribution. Quantitative differences between groups were analyzed using Student’s \( t \)-test or non-parametric Mann–Whitney \( U \)-test to analyze differences between groups. If data followed a normal distribution, values were shown as mean± standard deviation (SD). If the data did not follow a normal distribution, the median was applied (25%, 75% interquartile range (IQR)). A \( p \)-value \(< 0.05\) was considered statistically significant. Missing data were not imputed, there was one patient data missed and lost to follow-up. All analyses were performed at the two-sided level. No adjustments were made for multiple hypothesis testing. These results were described according to the Strengthening of Observational Studies in Epidemiology guidelines. Data will be made available to an investigator upon reasonable request of the corresponding author.
Results

Baseline patient characteristics are illustrated in Table 1. The pre-COVID-19 lockdown group comprised of 230 consecutive patients compared to 215 consecutive patients during the COVID-19 lockdown group. A diagnosis of atrial fibrillation (AF) was more common in the COVID-19 lockdown group (11.7% vs 5.7%, p=0.02), as well as patients who were currently smoking (38.8% vs 28.7%, p=0.02) and drinking alcohol (30.4% vs 20.0%, p=0.01) compared with that of the pre-COVID-19 group. No significant differences were observed between groups regarding age, sex, prior ischemic stroke or TIA, diabetes mellitus, dyslipidemia, hypertension, coronary heart disease, and posterior circulation stroke type. Because infection control measures were implemented by health authorities, there were only 13 positive COVID-19 cases confirmed in the Sanshui city during the period and none of the stroke patients had COVID-19 infection.

The stroke time metrics of patients in both the pre-COVID-19 and COVID-19 period groups are shown in Table 2. The median last known to arrival time was no different between groups, with 840 mins (263.8, 1752.5) and 821 mins (193.0, 1800.0) in the pre-COVID-19 lockdown and COVID-19 lockdown groups, respectively (p=0.91). Additionally, there was no difference in the proportion of patients who arrived within the pre-specified time windows of ≤4.5 hours, ≤6 hours, ≤24 hours, or >24 hours between groups.

Admission NIHSS scores between the pre-COVID-19 and COVID-19 groups are shown in Table 3. The COVID-19 group demonstrated numerically higher median baseline NIHSS scores than that of the pre-COVID-19 period group. However, no significance was observed (2 (1, 6) vs 2 (0, 5), p=0.12).

A comparison of the administration of thrombolysis and mechanical thrombectomy between the pre-COVID-19 and COVID-19 period groups is illustrated in Table 4. For patients receiving thrombolysis, the median door-to-CT time (DCT) was longer in the COVID-19 lockdown period group (17.0 min (13.0, 24.0) vs 12.0 min (8.0, 17.3), p=0.01) compared with the

Table 1 Baseline Characteristics of the Patients

|                              | Pre-COVID-19 Lockdown Period Group | COVID-19 Lockdown Period Group | P-value |
|------------------------------|-----------------------------------|-------------------------------|---------|
| Number                       | 230                               | 215                           | 0.48    |
| Median age ± SD              | 66.4±12.5                         | 67.3±12.6                     | 0.27    |
| Male, n (%)                  | 161 (70)                          | 133 (61.9)                    | 0.07    |
| Age ≥65 years, n (%)         | 129 (56.1)                        | 129 (60.0)                    | 0.40    |
| Age ≥ 80 years, n (%)        | 38 (16.5)                         | 40 (18.6)                     | 0.56    |
| Ages<50 years, n (%)         | 30 (13.0)                         | 22 (10.2)                     | 0.36    |
| Prior ischemic stroke/ TIA, n (%) | 55 (23.9)       | 54 (25.1)                     | 0.77    |
| Diabetes mellitus, n (%)     | 52 (22.6)                         | 47 (21.9)                     | 0.85    |
| Dyslipidemia, n (%)          | 80 (34.8)                         | 69 (32.1)                     | 0.54    |
| Atrial fibrillation, n (%)   | 13 (5.7)                          | 25 (11.7)                     | 0.02    |
| Hypertension, n (%)          | 183 (79.6)                        | 174 (80.9)                    | 0.72    |
| Current smoker, n (%)        | 66 (28.70)                        | 83 (38.8)                     | 0.02    |
| Alcohol consumer, n (%)      | 46 (20.00)                        | 65 (30.4)                     | 0.01    |
| TOAST                        |                                   |                               |         |
| Large artery atherosclerosis | 101 (43.91)                       | 75 (34.88)                    | 0.165   |
| Cardioembolic                | 19 (8.26)                         | 31 (14.42)                    |         |
| Small vessel disease         | 93 (40.43)                        | 93 (43.26)                    |         |
| Stroke of other determined etiology | 5 (2.17)   | 6 (2.79)                      |         |
| Stroke of undetermined etiology | 12 (5.22)  | 10 (4.65)                     |         |
| SARS-CoV-2 infection, n, (%) | 0 (0)                             | 0 (0)                         |         |

Notes: Quantitative differences between groups were analyzed using Student’s t-test or non-parametric Mann–Whitney U-test to analyze differences between groups. If data followed a normal distribution, values were shown as mean± standard deviation (SD). If data did not follow a normal distribution, the median was applied (25%, 75% interquartile range (IQR)). A p<0.05 was considered statistically significant. Missing data were not imputed, there was one patient data missed and lost follow-up. All analyses were performed at the two-sided level. No adjustments were made for multiple hypothesis testing.

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation; TIA, transient ischemic attack.
There were no differences observed in the thrombolysis number, median last known to arrival times, median CT-to-needle time, median DNT, and median last known normal-to-needle time between the two groups. For patients receiving mechanical thrombectomy, there were no significant differences in number, mean DPT, and mean door-to-recanalization time (DRT) (Figure 2).
The patient outcomes are summarized in Table 5. The median length of hospitalization (IQR) was not different in the COVID-19 period group compared with the pre-COVID-19 period group (8.0 (6.0, 10.0) vs 7.0 (6.0, 9.3), p=0.43). Discharge mRS scores (IQR) were higher in the COVID-19 period group (1.0 (1.0, 3.0) vs 1.0 (1.0, 2.0), p=0.02). Compared with the pre-COVID-19 lockdown period, hospitalization expense in the COVID-19 period group was higher (13,445. (11,009.7, 20,030.5) vs 10,799.2 (8692.4, 16,381.7) RMB, p<0.001). There were no statistically significant differences observed in 3-months mRS scores, including favorable outcome (mRS 0–2) (p=0.08), unfavorable outcome (mRS 3–6) (p=0.08), and mortality (p=0.72).

The patient outcomes comparing the COVID-19 group with the pre-COVID-19 group after adjusting confounding factors are shown in Table 6.
Discussion

Our study highlighted a prolonged door to imaging time and increase in hospitalization costs in patients presenting with stroke during the COVID-19 pandemic. An increase in hospitalization cost can be explained by the increased length of hospitalization, more alteplase thrombolysis, and more EVT in the COVID-19 lockdown group compared with the pre-COVID-19 lockdown group. The COVID-19 lockdown did not impact on DNT, DPT, and 3-month patient outcome.

Interestingly, we found that patients in the COVID-19 period group displayed an increased rate of AF (11.7% vs 5.7%, \( p = 0.02 \)), tobacco smoking (38.8% vs 28.7%, \( p = 0.02 \)) and alcohol consumption (30.4% vs 20.0%, \( p = 0.012 \)). Whether these factors reflect a population of patients with a higher probability of healthcare-seeking behavior or suggests such patients with vascular comorbidities were at greater risk of stroke during the first wave of the pandemic remains unclear.

A study of 184,017 patients from 114 hospitals in the United Kingdom showed that there was a 12% reduction (6923 versus 7902) in the number of acute stroke admissions between October 1, 2019, and April 30, 2020 compared with the same period in the 3 previous years.\(^{10}\) They also showed that admissions fell more for ischemic than hemorrhagic stroke, for older patients, and for patients with less severe strokes.\(^{10}\) In addition, a multinational study comprising 7 countries and 18 centers in Latin America showed that there was a mild decrease in admissions of ischemic stroke during the COVID-19 lockdown period (March-June 2020) compared to the same period in 2019, with a significant delay in time to consultations and worse hospitalization outcomes.\(^{11}\)

Government instructions involving stay-at-home, lockdown, curfew, and social distancing policies have proved effective in combating the COVID-19 dissemination.\(^{12-14}\) However, social distancing during the COVID-19 period lockdown may also play a central role in the delays of ischemic stroke patient referrals and escalated treatment to tertiary centers.\(^{15-17}\) Previous studies have demonstrated that there has been a significant decline in the number of acute ischemic

Table 5 Comparison of Patient Outcomes in the Pre-COVID-19 Lockdown and COVID-19 Lockdown Period Groups

| Outcome                  | Pre-COVID-19 Lockdown Period Group (n=230) | COVID-19 Lockdown Period Group (n=215) | \( \chi^2/z \) | \( P \)-value |
|--------------------------|-------------------------------------------|----------------------------------------|----------------|--------------|
| Length of hospitalizations, day (IQR) | 7.0 (6.0, 9.3) | 8.0 (6.0, 10.0) | -0.795 | 0.43         |
| Expense (RMB, IQR)       | 10,799.2 (8692.4, 16,381.7) | 13,445.7 (11,009.7, 20,030.5) | -5.037 | <0.001       |
| Discharge mRS (IQR)      | 1.0 (1.0, 2.0) | 1.0 (1.0, 3.0) | -2.29  | 0.02         |
| Discharge mRS (0–2), n (%) | 181 (78.7) | 154 (71.6) | 2.983  | 0.08         |
| Discharge mRS (5–6), n, % | 11 (4.8) | 15 (7.0) | 0.972  | 0.32         |
| 3-months mRS (IQR)       | 0.0 (0.0, 2.0) | 0.0 (0.0, 3.0) | -0.975 | 0.33         |
| 3-months mRS (0–2), n, % | 182 (79.13) | 155 (72.09) | 2.994  | 0.08         |
| 3-months mRS (3–6), n, % | 48 (20.87) | 60 (27.91) | 2.994  | 0.08         |
| 3-months death, n, %     | 17 (7.39) | 14 (6.51) | 0.133  | 0.72         |

Notes: Quantitative differences between groups were analyzed using Student's \( t \)-test or non-parametric Mann–Whitney \( U \)-test to analyze differences between groups. If data followed a normal distribution, values were shown as mean± standard deviation (SD). If data did not follow a normal distribution, the median was applied (25%, 75% interquartile range (IQR)). A \( p<0.05 \) was considered statistically significant. Missing data were not imputed, there was one patient data missed and lost follow-up. All analyses were performed at the two-sided level. No adjustments were made for multiple hypothesis testing.

Abbreviations: RMB, Renminbi (Chinese Yuan); mRS, modified Rankin Scale.

Table 6 Comparison of Patient Outcomes in the COVID-19 Lockdown Period VS Pre-COVID-19 Lockdown Groups After Adjusting Confounding Factors

| Outcome                  | OR            | \( P \)-value |
|--------------------------|---------------|--------------|
| Discharge mRS score (0–2), n, % | 0.69 (0.44, 1.09) | 0.113        |
| Discharge mRS score (5–6) | 1.32 (0.56, 3.11) | 0.533        |
| 3 months mRS (0–2), n, % | 0.67 (0.42, 1.07) | 0.094        |
| 3 months mRS (3–6), n, % | 1.49 (0.93, 2.39) | 0.094        |
| 3 months death, n, %     | 0.86 (0.40, 1.86) | 0.707        |
stroke admissions during the COVID-19 pandemic and subsequent lockdown.\textsuperscript{18,19} Although this correlation has been well recognized internationally, patients presenting on admission were noted to be in poorer health with longer onset to door time.\textsuperscript{20} Similar trends were also observed in non-designated COVID-19 hospitals nationally in China, with higher patient NIHSS scores on admission reflecting longer DCT, DNT, and DPT.\textsuperscript{21,22}

Hospitals responsible for treating COVID-19 patients for the management of pandemic had greater declines in ischemic stroke patient admissions.\textsuperscript{18} Reasons include apprehension and reluctance to seek medical attention due to the potential risks of nosocomial contraction of COVID-19.\textsuperscript{21} Additionally, a mandatory screen for COVID-19 during pre-hospital admission may delay CT or MRI imaging.\textsuperscript{23} In our hospital, we observed a prolonged time to request and perform head CT scans for patients undergoing thrombolysis due to our facility holding both COVID-19-designated and fever-outpatient hospital status. Patients with suspected COVID-19 presenting from areas of high disease burden were screened with CT chest scans, thereby delaying diagnostic imaging for patients with ischemic stroke. Sterilization of the CT apparatus and room was required after each suspected COVID-19 patient received a scan, thus prolonging waiting times. While one retrospective cohort study of 14 comprehensive stroke centers in the United States demonstrated a similar delay in CT to needle time, they also reported no delay in patients receiving endovascular thrombectomy during the COVID-19 pandemic in an overlapping data set.\textsuperscript{24} Adopting measures to reduce delays from head imaging to needle time may attenuate collateral effects during the pandemic.\textsuperscript{8} Multidisciplinary collaboration and continuous workflow optimization may shorten overall DNT despite the challenges and reallocation of resources during the COVID-19 pandemic. We should seize every opportunity to maintain care and optimize workflow during the COVID-19 pandemic.\textsuperscript{25,26} Referral of Code Stroke patients by emergency medical services was an effective tool for stroke care despite the COVID-19 pandemic lockdown. Continued education of the public about seeking stroke care remains essential.\textsuperscript{27} Tele-stroke networks may extend virtual care and resources to patients in remote or rural areas without rapid access to acute stroke care.\textsuperscript{28}

The Society of Vascular and Interventional Neurology issued guidance regarding ischemic stroke and subarachnoid hemorrhage management during the COVID-19 pandemic.\textsuperscript{29,30} We cannot underestimate the needs of our patients with stroke or at risk of cerebrovascular disease. Neurological disorders of COVID-19 can be explained in terms of both “loss and gain of function” states for the nervous system.\textsuperscript{31} Our hospital maintained our stroke emergency care workflow smooth and categorize normal patients and patients at risk of SARS-CoV-2 infection: 1) we continuously reinforced rapid throughput of stroke patients who presented to the emergency department during the pandemic; 2) we rapidly acquired head CT in at-risk individuals; 3) we reinforced stroke education to the public; 4) we prioritized mechanical thrombectomy in patients who might benefit; 5) patients with suspected COVID-19 (eg, those with fever and pending SARS-CoV-2 screening) were kept segregated from patients without SARS-CoV-2. We have previously shown that a multidisciplinary collaboration and continuous process optimization, such as engaging the Hospital chief, establishing a secure Hospital web-based notification system (WeChat), prioritizing suspected stroke patients by emergency room nurse and physicians, providing monthly training for stroke and emergency nurses and emergency room physicians, notifying relevant stroke teams, including emergency healthcare, via a prenotification service before performing head CT scans, prioritizing CT scan and transfer to radiology, facilitating interpretation of head CT by stroke team physicians without requiring formal radiology reports (radiology reports can be given priority in certain circumstances), connecting with the regional Health Bureau and media department of the hospital to raise awareness and public education of acute stroke, can result in overall shortened door-to-needle despite the challenges incurred by the COVID-19 pandemic.\textsuperscript{25} These experiences could be used for preparation for future challenges by lockdown and pandemics. Consistent and adaptable strategies to combat the COVID-19 pandemic should be reconciled with the stroke patient to provide the best possible treatment.\textsuperscript{32–34}

\textbf{Study Strengths and Limitations}

While our findings may guide other centers seeking to improve their stroke throughput, our work has limitations. Our study was a retrospective single-center study, and our findings may not be transportable to other single-center facilities with distinct resources. Furthermore, this study was exploratory, and the results should be hypothesis-generating. Multiple results were summarized, without adjustment for multiple hypothesis testing. Statistically, significant differences should therefore be interpreted with caution.
Conclusion
We found that patients presenting with ischemic stroke during the COVID-19 period to our center had a prolonged median door-to-CT time associated with a higher economic burden. There were no differences in other treatment times, 3-month outcomes, and mortality. Multidisciplinary collaboration and continuous workflow optimization may maintain stroke care during the COVID-19 pandemic lockdown. Further large-scale, multi-center studies are warranted to confirm these findings.

Data Sharing Statement
Data will be made available to an investigator upon reasonable request of the corresponding author.

Ethics and Consent Statements
The study was approved by the Foshan Sanshui District Hospital institutional review board and due to the retrospective nature of this study, patient informed consent was waived accordingly.

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Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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