Impact of the 2019 Coronavirus Infectious Disease (COVID-19) pandemic on onset to door time and admissions of new onset acute ischemic stroke in a tertiary care level hospital in North India

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Abstract

Context: Coronavirus infectious disease (COVID-19) pandemic disrupted the already marginalized healthcare provision in resource limited countries like India. Aims: This study compared onset to door time and temporal trends of admissions to seek medical care in new onset acute ischemic stroke during the COVID-19 period with a representative pre-COVID-19 period in rural background. Settings and Design: Prospective Cross-sectional study in a tertiary level hospital in North India. Methods and Material: Study included new onset acute ischaemic stroke admitted within first 2 weeks of symptoms onset. Subjects were divided into: Group A – Pre-COVID-19 stroke, Group B - Non-COVID-19 Stroke, and Group C - Stroke, positive for COVID-19. Detailed epidemiological, clinical profile, onset to door time and temporal trends of admissions were recorded. Statistical Analysis Used: Chi square/Fisher’s exact test and Independent Samples T test or Mann–Whitney U test were used for categorical and continuous variables. Results: Onset to door time in new onset acute ischaemic stroke was significantly prolonged by 6 h in COVID-19 period (median (interquartile range), 19 (12–27) h) as compared with pre-COVID-19 period. Admissions of new onset acute ischaemic stroke were significantly less in COVID-19 period. Comorbidities and severity of stroke (mean National Institutes of Health Stroke Scale, 20 ± 4) were more during the COVID-19 period. Incidence and mortality of COVID-19 positive new onset acute ischaemic stroke were 0.95% and 38%. Conclusions: Onset to door time in new onset acute ischaemic stroke was significantly prolonged in COVID-19 as compared with pre-COVID-19 period. The admissions were fewer with more severity and comorbidities in COVID-19 period. COVID-19 positive stroke patients had more severity and mortality as compared with non-COVID-19 stroke.

Keywords: 2019 coronavirus infectious disease, acute ischaemic stroke, COVID-19, COVID and stroke, new onset acute ischaemic stroke, onset to door time

Introduction

Stroke is one of the leading causes of mortality (40% deaths) and morbidity (72% disability adjusted life years (DALYs)) among non-communicable diseases in India and worldwide with 12% of all deaths and the third most common cause of disability (4.5% of DALYs from all cause).[1-4]
The management of acute ischaemic stroke requires a well-organized, multidisciplinary approach and dedicated hospital systems to provide timely treatment within requisite window periods. In resource-limited countries like India, in which the non-communicable disease burden is enormous yet neglected, the occurrence of the 2019 coronavirus infectious disease (COVID-19) pandemic disrupted the already marginalized healthcare provision.

The COVID-19 outbreak was declared as global pandemic by World Health Organization on March 11, 2020.[3] In India, the first confirmed case of COVID-19 was a 20-year-old from Kerala on January 27, 2020.[4] The first confirmed case was admitted in our facility on February 21, 2020. Since then, the COVID-19 has emerged as a serious challenge to healthcare systems with resources for non-communicable diseases being diverted for management of COVID-19 worldwide.

The manifestations of the virus are not only limited to respiratory system but also involve the nervous system. Plausible mechanisms of neurovirulence of severe acute respiratory syndrome coronavirus (SARS-CoV-2) might include brain injury due to hypoxia, inflammation via a cytokine storm, release of interleukin-6, and binding of virus to Angiotensin Converting Enzyme-2 (ACE-2) in the blood–brain barrier, meninges, and cerebral blood vessel.[5‑9] Neurological manifestations occur in 14% to 36% of COVID-19 infection.[10,11] The features are diverse with severe manifestations including stroke, and its incidence varies from 2% to 17% of COVID-19 infection.[11,12] Ischaemic stroke is most common and occurs in 0.9% to 2.7% of the cases.[5,10,13]

Regulatory orders were issued by the government and authorities in the form of lockdown in India and across the world in view of highly infectious nature of SARS-CoV-2. The studies from western world had shown that COVID-19 and lockdown affected the management of non-COVID-19 diseases considerably.[14,15] In a study from Italy, there was a decline in the number of percutaneous coronary interventions for acute coronary syndrome by 32%.[14] Similarly, in other countries, hospital admissions due to transient ischaemic attacks and stroke decreased during the COVID pandemic.[15] Various other challenges were encountered in management of acute stroke during the COVID-19 pandemic.[15] Amongst them was the reluctance of the people to seek medical care in the hospital out of fear of the contagion. It is unclear whether this behavior impacted the time from symptom onset to presentation to the hospital (Onset to Door time). The average onset to door time in India ranges from 7.66 to 26 h and favorable functional outcomes were associated with early arrival of stroke patients to hospital.[16] There is limited data from India which compared the onset to door time, epidemiology, and management of new onset acute ischaemic stroke in pre-COVID-19 to COVID-19 period.[17,18]

We compared onset to door time to seek medical care in new-onset acute ischaemic stroke during the COVID-19 pandemic with a representative pre-COVID-19 period. A secondary outcome was to determine the trends of monthly admissions and clinical profile of patients with new-onset acute ischaemic stroke admitted to hospital during the COVID-19 pandemic as compared with pre-COVID-19 period and to determine the incidence of new-onset ischaemic stroke associated with COVID-19. This would provide an insight into impact of COVID-19 pandemic on non-communicable diseases and guide healthcare planners and policy makers in the management of omnipresent diseases like stroke during the COVID-19 times.

Subjects and Methods

This prospective cross-sectional study was conducted in the Division of Neurology in a tertiary level hospital from resource limited rural belt of North India. This 600 bedded hospital is a dedicated Level 3 center for the management of COVID-19 in the area.

We used the period from May 2019 to December 2019 as pre-COVID-19 period and May 2020 to December 2020 as COVID-19 period in accordance with the highest numbers of cases of COVID-19 reported in the district. The two corresponding time intervals were selected assuming stable population and to avoid assessment bias due to seasonal variation in incidence of acute ischaemic stroke. Subjects with new onset acute ischaemic stroke were divided into three groups: Group A - pre-COVID-19 period stroke, Group B - Non-COVID-19 Stroke, and Group C - Stroke with positive COVID-19. In all three groups, we included patients admitted to the hospital with new onset acute stroke as per WHO definition within first 2 weeks of onset of symptoms.[19]

Group A: Pre-COVID-19 period - Ischaemic Stroke

These subjects were included from a hospital-based stroke registry based on WHO step wise approach for stroke surveillance maintained in the division of Neurology in the institute since 2019.[24] We included all patients from May 2019 to December 2019. Written informed consent was taken from all subjects before entry into the registry.

Group B: COVID-19 period - Non-COVID-19 Ischaemic Stroke

These subjects were enrolled prospectively from May 2020 to December 2020. All the subjects were screened for any symptoms of COVID-19 using the validated Screening questionnaire used in our Institution for suspecting clinical COVID-19 infection. We included patients who were negative for any symptoms of fever, cough, breathlessness, sore throat, expectoration, diarhorrea, bodyaches, haemoptysis, nasal discharge, and chest pain in the preceding 2 weeks of onset of stroke symptoms.

Group C: COVID-19 period - COVID-19 positive Ischaemic Stroke
These subjects were also enrolled prospectively from May 2020 to December 2020. These subjects were positive for SARS-CoV-2 on reverse-transcription polymerase chain reaction analysis in the nasopharyngeal or oropharyngeal swabs. Medical records of these subjects were reviewed regularly by the investigators for any features suggestive of stroke as per WHO definition.[19] Those who were suggestive for stroke underwent neurological examination with all the precautions. Verbal informed consent was taken from patient and written informed consent was taken from patients’ guardians.

The detailed demographic profile of all the subjects was recorded: age, gender, and address to assess the distance from hospital with reference being their primary healthcare center. Time from symptoms onset to presentation in the hospital (onset to door time) was recorded (hours). If the subject awakened with symptoms of stroke, then the time of onset was defined as the time at which the patient was last seen to be without symptoms or the last known normal time.

We also recorded the detailed history and clinical examination including neurological examination, National Institutes of Health Stroke Scale (NIHSS), diagnosis of stroke, and comorbidities of Stroke: Hypertension, Diabetes Mellitus, Carotid Artery stenosis, and Cardiac related-Atrial Fibrillation and Coronary artery disease. All the subjects underwent neuroimaging, Computerized tomography scan (CT scan) or Magnetic resonance imaging (MRI scan) of brain and Bilateral Carotid doppler, and only those subjects who had acute ischemic lesion on the scans were included. Subjects in group C had their neuroimaging done before presentation to the hospital and in others, it was done in the hospital taking all precautionary measures. The routine laboratory findings including Blood cell count, Liver and Renal function tests, Fasting Lipid profile, and Chest X ray were also recorded. We recorded the revascularization treatment given to the eligible patients across all three groups in the form of intravenous Thrombolysis with recombinant Tissue plasminogen activator (tPA).

The primary outcome of the study was to determine the impact of COVID-19 on onset to door time in new onset acute ischemic stroke cases admitted to the hospital in COVID-19 as compared with pre-COVID-19 period. The secondary outcome of the study was to assess the temporal trends of admissions and clinical profile of patients with new onset acute ischemic stroke admitted to hospital in COVID-19 period as compared with pre-COVID-19 period and to find the incidence of new acute onset ischemic stroke associated with COVID-19.

The study and prospective stroke registry (ERB/UCER/2019/4/12) had the approval from the Institutional Ethics Committee-GGS/IEC/20/107. The patient data pertaining to socio-demographic and other clinical variables were entered in the form of a data matrix in Microsoft® Excel® and analyzed using IBM® SPSS® v 20.0.0. The descriptive statistics were presented as frequencies and percentages or means and standard deviations as appropriate. Chi square/Fisher’s exact test was used to assess association among categorical variables and Independent Samples T test or Mann–Whitney U test were used for continuous variables. A two-sided P value of < 0.05 was considered statistically significant.

The study showed significantly fewer admissions (52 subjects) with new onset acute ischaemic stroke over a period of 8 months in COVID-19 period (May to December 2020) as compared with pre-COVID-19 period (96 subjects) (P < 0.0005) [Figure 1]. Figure 2 shows a steep downward temporal trend in the number of admissions for new onset acute ischaemic stroke during August to November 2020 in the COVID-19 period as compared with the similar time in pre-COVID-19 period.

A total of 1468 COVID-19 positive patients were admitted in the hospital during May 2020 to December 2020, out of which 14 had new onset acute ischaemic stroke (Group C) [Figure 3]. Incidence of COVID-19 positive new onset acute ischaemic stroke was 0.95%. Figure 4 shows an increase in number of COVID-19 positive patients during the months of August and September 2020. However, there was no significant temporal trend in the new onset acute ischaemic stroke during this time.

Table 2 shows that there was no significant difference in mean age of subjects in group A (60 ± 14 years) (pre-COVID-19 period) as compared with group B and C (COVID-19 period). Males (70%, 64%, and 57% in groups A, B, and C, respectively) were more than females. Comorbidities were more frequent among stroke patients during the COVID period. Hypertension (P = 0.043) and

![Figure 1: New onset acute ischaemic stroke in Group A (pre-COVID-19 period) (May to Dec 2019), Group B (non-COVID-19), and Group C (COVID-19 positive) during COVID-19 period (May to Dec 2020)](https://example.com/figure1.png)
Sulena, et al.: Onset to door time in acute ischemic stroke and COVID-19

Table 1: Onset to door time and distance travelled to reach hospital in new onset acute ischaemic stroke in pre-COVID-19 (Group A) and COVID-19 period (Group B + C)

|                          | Group A pre-COVID-19 period Median (IQR) | Group B + C COVID-19 period Median (IQR) | P    |
|--------------------------|------------------------------------------|-----------------------------------------|------|
| Onset to door time (hrs) | 13 (12-15)                               | 19 (12-27)                              | <0.0005|
| Distance travelled to reach hospital (kms.) | 32 (3-48)                               | 41 (2-50)                               | 0.214|

Figure 2: Temporal trend of monthly admissions for new onset acute ischaemic stroke monthlywise in pre-COVID-19 period (Group A) and COVID-19 period (Group B)

Diabetes mellitus (P = 0.006) were significantly more frequent in group B subjects as compared with group A; 92% of patients in group B and 91% of Group C had one or more comorbidities: Hypertension, Diabetes Mellitus, Carotid Artery Stenosis, and Cardiac-related factors, such as atrial fibrillation and ischaemic heart disease. The mean NIHSS was significantly higher in subjects of group B than group A (P = 0.019). The mean NIHSS in Group C was 20 ± 4 [Table 3].

Out of 14 patients of group C, one had in-hospital ischemic stroke. Thirteen patients presented with features suggestive of acute ischaemic stroke along with feature of respiratory symptoms. The mortality in these patients was 38% (n = 5). There was no statistically significant difference in the clinical profile of these patients as compared with non-COVID-19 strokes in the same period except NIHSS and mortality which were significantly more in COVID-19 positive stroke [Table 3].

Discussion

The study showed that the onset to door time in new onset acute ischemic stroke was significantly prolonged by 6 h in COVID-19 period (groups B and C) as compared with pre-COVID-19 period (group A) (P value < 0.005) with no significant difference in distance travelled by these subjects to reach hospital [Table 1]. Longer onset to door time may have been caused by the deficiencies in the knowledge about recognition of stroke symptoms and psychological factors leading to delayed response in seeking medical care. Moreover, subjects in COVID-19 period had come amid administrative regulatory restrictions in the form of Lockdown. Similar observation was noticed in other parts of the world like Italy and other countries where onset to door time was significantly more in the lockdown phase. Conversely, there was no significant difference in onset to door time in acute stroke during the first month of COVID-19 period and few other studies showed shorter onset to door time possible reasons being availability of caregivers at home and reduced road traffic and transportation times during pandemic. Even western countries, with well established stroke hub and spoke model showed a significant delay in transport time and reduction in transfers of patient for acute revascularization treatments. The medical services in local hospitals were overburdened by protocols for personal protection measures inpatients’ care and repeated sanitization leading to further delays. Further studies are needed at multicentre level and larger scale to study the detailed factors influencing onset to door time in acute ischaemic stroke. This study showed significant decrease in admissions (n = 52 subjects) of new onset acute ischaemic stroke over a period of 8 months in COVID-19 period as compared with pre-COVID-19 period (n = 96 subjects) [Table 2, Figure 1]. Earlier periods of pandemic onset in year 2020 had one-third decrease in total stroke codes as compared with year 2019. Moreover, countries from different parts of world (China, Italy, Brazil, and Spain) had a decrease in monthly admissions of acute stroke during peak period of pandemic. In United states of America (USA), admissions of other non-communicable diseases like cardiovascular events and interventional treatment including cardiac catheterization declined by 38%. There were no substantial expected causes for decrease in number of acute ischaemic stroke due to any nascent changes in etiology or etiopathogenesis and this fall may be attributed to the regulatory restrictions on public movement, transportation, and people’s choice to avoid public places including hospitals for the fear of acquiring the infection. The incidence of COVID-19...
positive new onset acute ischaemic stroke in our study was 0.95\% (n = 14) which is similar to reported incidence of 0.9\% to 2.7\%.[13,26]

In this study, males were more than females with maximum number of subjects being more than 45 years of age across all groups as seen in other studies.[24] Male predominance may be attributed to more incidence of SARS-CoV infection in them.[17] Comorbidities were more in subjects during the COVID-19 period than group A with Hypertension (P value = 0.043) and Diabetes Mellitus (P value = 0.006) being significantly more in Group B as compared with group A. Subjects with comorbidities were more sensitive to identifying stroke symptoms and seeking early help for supervised medical care in the hospital.[24] COVID-19 infection may be acting as a trigger for acute ischaemic stroke in these patients with known risk factors for ischaemic stroke.[11,26] This study signifies the need for increasing awareness about stroke, its comorbidities, and impact of COVID-19 on acute ischaemic stroke among physicians and primary healthcare doctors and general population. This would help improve the response in early recognition of acute stroke and management during third wave of COVID-19 pandemic. Since medical fraternity is novice to COVID-19, prospective, multicenteric studies at larger scales are needed to understand pathophysiology of stroke with COVID-19.

In this study, subjects with acute ischaemic stroke during COVID-19 period had more severe NIHSS (groups A and B, P value = 0.019) than pre-COVID-19 period modulating their decision to get admitted. Mean NIHSS in group C was significantly more than non-COVID-19 stroke (P value = 0.001) similar to a systematic review.[27] The discrepancy in the severity of stroke maybe because minor stroke did not report to the hospital amid implementation of social isolation policies.[15] SARS-COV-2 has thrombogenic and hypercoagulable potential

Table 2: Baseline characteristics of subjects admitted with new onset acute ischaemic stroke during pre-COVID-19 and COVID-19 period

|                                | Pre-COVID-19 period (May-Dec 2019) Group A | COVID-19 period (May-Dec 2020) Group B | P     |
|--------------------------------|-------------------------------------------|---------------------------------------|-------|
| No. of AIS admissions          | 96                                        | 52                                    | 0.000 |
| Age, Mean (SD) years           | 60±14                                     | 59±16                                 | 0.617 |
| Male, n (%)                    | 68 (71%)                                  | 33 (64%)                              | 0.357 |
| Co-Morbidities, n (%)          | 74 (77%)                                  | 48 (92%)                              | 0.197 |
| Diabetes Mellitus              | 28 (29%)                                  | 27 (52%)                              | 0.006 |
| Hypertension                   | 56 (58%)                                  | 39 (75%)                              | 0.043 |
| Cardiac - Atrial Fibrillation and Cardiac Artery Stenosis | 36 (38%) | 20 (39%) | 0.908 |
| NIHSS, Mean (SD)               | 12±6                                      | 14±6                                  | 0.019 |
| Intravenous Thrombolysis n (%) | 4 (4%)                                     | 2 (4%)                                |       |

Table 3: Demographic profile of Group B (Non-COVID-19) and C (COVID-19 positive) patients with new onset acute ischaemic stroke

|                                | COVID-19 period (May-Dec 2020) | P     |
|--------------------------------|-------------------------------|-------|
| Number of admissions           | 52                            | 14    | 0.000 |
| Age, Mean (SD) years           | 59±16                         | 59±16 | 0.991 |
| Male, n (%)                    | 33 (64%)                      | 8 (57%)| 0.187 |
| Co-Morbidities, n (%)          | 48 (92%)                      | 11 (91%)| 0.138 |
| Diabetes Mellitus, n (%)       | 27 (52%)                      | 8 (57%)| 0.728 |
| Hypertension                   | 39 (75%)                      | 11 (92%)| 0.781 |
| Cardiac - Atrial Fibrillation and Cardiac Artery Stenosis, n (%) | 20 (39%) | 6 (43%) | 0.765 |
| Mean NIHSS±S.D.                | 14±6                          | 20±4  | 0.001 |
| Intravenous thrombolysis, n (%)| 2 (4%)                        | 0     |       |
| Mortality, n (%)               | 4 (8%)                        | 5 (36%)| 0.024 |

Figure 4: Temporal trend of COVID-19 positive subjects and non COVID new onset acute ischaemic stroke (Group B) admitted in the Hospital from May to Dec 2020

Sulena, et al.: Onset to door time in acute ischemic stroke and COVID-19

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and odds of cerebrovascular events with COVID-19 being 7.6 folds more as compared with other viral infection.\cite{10} In a study from India, one fourth of stroke patients with COVID-19 had no comorbidities suggesting the role of SARS-CoV infection in pathogenesis of stroke.\cite{17} Stroke may be a feature of early or late stages, mild to moderate, or severe COVID-19 infection.\cite{10,18}

Stroke was the only clinical manifestation of COVID-19 in 67% of patients of as opposed to our study where 13 patients (93%) had presented with predominant stroke symptoms along with respiratory symptoms.\cite{18}

Mortality rate (n = 5, 36%) in subjects of COVID-19 with stroke was significantly more than non-COVID-19 stroke. Global COVID-19 stroke registry and Indian study from banglore had higher morbidity and mortality in COVID-19 stroke.\cite{17,20} Patients with stroke had more severe respiratory features of COVID-19 disease and patients with older age and comorbidities were more amenable to severe strokes and thus increased mortality.

Our study showed a decrease in the number of subjects undergoing revascularization treatment with intravenous thrombolysis with r-tPA during COVID-19 as compared with pre-COVID-19 period. Possible reasons being longer onset to door time with fewer subjects reporting within window period 4% and 8% in groups A and B + C in our study as observed in other study.\cite{21} However, yet another study showed a significant increase in thrombolysis therapy rate in COVID-19 as compared with pre-COVID-19 due to timely revision and implementation of newer acute stroke management protocol amid the pandemic.\cite{20}

The limitations of this study were small sample size and selection bias. Being a single center and not a population-based study, patients with mild stroke may not have been admitted. The lesser number of strokes in COVID-19 positive patients may be explained by the fact that they were isolated and may not have appreciated symptoms of stroke. The strength of the study is that it is a prospective continuum of new onset acute ischaemic stroke from pre-COVID-19 to COVID-19 period and simultaneous comparison with concurrent COVID-19 positive new onset acute ischaemic stroke cohort conducted over a longer duration in India.

**Conclusion**

Onset to door time in new onset acute ischaemic stroke was significantly longer in COVID-19 as compared with pre-COVID-19 period. The admissions of new onset acute ischaemic stroke were significantly low with more severe stroke and comorbidities as compared with pre-COVID-19. Longer onset to door time denotes prehospital delay which can be decreased by improving public awareness about stroke and encouragement of the patients to seek timely supervised medical care in stroke during third wave of COVID-19 pandemic. New protocols need to be adopted judiciously to manage stroke while coeval COVID-19 pandemic is handled. At the level of health policy makers and authorities, the utilization of the teleconsultation for the management of acute stroke should be advocated in view of third wave of COVID-19 pandemic.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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