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Journal of the Neurological Sciences 423 (2021) 117348

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Characteristics and outcomes of 100 consecutive patients with acute stroke and COVID-19

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic started as a respiratory illness. Now, there are increasing reports of its hypercoagulable and thrombotic complications [1] leading to stroke [2,3]. Initial studies suggested strokes to be a feature of severe and late COVID-19 [2,4]; usually occurring in the second week of illness after the onset of typical respiratory symptoms [4]. Recent studies identified these even in mild to moderate infection [5,6]. A recent meta-analysis also noted that 24.5% of patients with stroke symptoms did not experience any of the other typical COVID-19 symptoms [6]. These patients can be a risk for nosocomial spread of infection and need to be identified and isolated. Stroke in COVID-19 though uncommon, results in significant morbidity and mortality [6,7].

As recent research indicates that stroke can be a presenting feature of COVID-19 [6] and there is limited data from the Indian subcontinent [8], we evaluated 100 consecutive acute stroke patients with COVID-19 from western India. We also included patients with cerebral venous thrombosis and intracerebral haemorrhage associated with COVID-19 as the information on these stroke subtypes is scant [5,9–12].

The areas of interest to us included stroke as an initial presentation of COVID-19, stroke in non-severe COVID-19 patients and their outcome. We also compared patients with COVID-19 and ischemic strokes with non COVID-19 infected ischemic strokes.

2. Methods

2.1. Study design and participants

This is a retrospective, multi centre observational study. The data was collected for the patients who were confirmed for COVID-19 and acute stroke during 4th April to September 15, 2020 from ten centres in Mumbai, India. Consecutive patients more than 18 years of age who had a radiological evidence of acute stroke [acute ischemic stroke (AIS), intra cranial haemorrhage (ICH) and cerebral venous thrombosis (CVT)] manifesting as focal neurological dysfunction, seizure or alteration of sensorium] and a positive real time reverse transcriptase polymerase chain reaction (RT PCR) for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) were included. The data was anonymized and waiver of written consent for patients was granted. The study protocol was approved by the Fortis hospital institutional academic ethics committee.

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https://doi.org/10.1016/j.jns.2021.117348
Received 20 October 2020; Received in revised form 6 January 2021; Accepted 12 February 2021
Available online 17 February 2021

2.2. Data collection

The authors reviewed the literature to arrive at a consensus to formulate a uniform data capture form, ensuring the standardisation process for the analysis of the data, incorporating the insights from the contemporary literature.

All the patients were tested for SARS-CoV-2 infection by RT-PCR on the first day of presentation to the hospital.

Data was collected by utilising a uniform Google ™ form. The demographics and the clinical information were collated. The parameters that were evaluated included the following:

1. Age (young (≤45 years) versus non young (>45 years)) [13] and sex of the patients.
2. Presenting complaint of the patient: Neurological or Non neurological (fever, breathlessness, cough or diarrhea).
3. In those with neurological presentation: Was it with focal neurological dysfunction or seizure or altered sensorium?
   Time from onset of neurological presentation to hospital admission was noted.
4. In those with non-neurological presentation: After how many days of hospitalisation was the neurological dysfunction noted?
5. Other associated features were noted: Headache, myalgia, abnormality of smell and taste.
6. Comorbidities/Risk factors: Diabetes mellitus (DM), hypertension (HTN), chronic renal failure (CRF), immunosuppression and underlying malignancy, past history of TIA/stroke, use of oral contraceptives.
7. Use of pre-exposure HCQS (hydroxychloroquine).
8. Glasgow Coma Scale (GCS) on admission for all stroke types. (GCS of 3–12 was considered low GCS).
9. National institute for health stroke scale/score (NIHSS) during admission for all types of strokes (NIHSS ≥ 16 was considered severe stroke).
10. Imaging data for lung involvement (HRCT chest was done on the day of admission): It was considered abnormal if there were changes typical of COVID-19 [14].
11. CT and/or MRI of the brain to confirm the stroke and sub classify as ischemic stroke, intra cerebral haemorrhage and cerebral venous thrombosis based on the radiologic findings.
12. For AIS additional information was collected: Stroke territory on imaging; watershed or single or multiple territory stroke (more than one territory) and presence of large vessel occlusion (LVO) (Large vessel occlusion was defined as occlusion of the intracranial internal carotid artery, M1/M2 segments of the middle cerebral artery, basilar artery, or P1 segment of the posterior cerebral artery).
13. Relevant laboratory data: Electrocardiogram, platelet counts, creatine kinase (CK) levels; D dimer and C reactive protein (CRP) levels closest to the occurrence of stroke and maximum level of Interleukin 6 (IL 6). Platelet count <1,50,000 thou/μL, CK > 200 U/L, D dimer >0.5 mg/L, CRP > 10 mg/L and IL-6 > 7 pg/mL were taken as abnormal.
14. Treatment given to these patients was also noted (specific for the stroke and that used for COVID-19) including if they needed ventilation (invasive or non-invasive). Standard medication changed as the pandemic evolved. In the initial months, it was a combination of HCQS and azithromycin; currently it is ivermectin and doxycycline. The use of special medications for COVID-19 like steroids, remdesivir and tocilizumab was noted.

The primary outcome of these patients; whether dead or discharged from the hospital was noted. Parameters in those with severe and non-severe COVID-19 disease were also compared for all stroke subtypes.

Patients were defined as severe COVID-19 when they developed any of the following criteria during the course of their hospital stay (those fulfilling the criteria for severe and critical disease as per the Chinese clinical guidelines were considered to have severe COVID-19 in this study) [15]:

1. Respiratory distress (≥ 30 breaths/min).
2. Oxygen saturation ≤ 93% at rest.
3. $PaO_2/FiO_2 \leq 300$ mmHg (l mm Hg = 0.133 kPa).
4. Chest imaging shows obvious lesion progression >50% within 24–48 h.
5. Respiratory failure requiring mechanical ventilation.
6. Shock and with other organ failure that requires ICU care.

All patients with AIS were also studied for any statistically significant parameters in those with young (≤45 years) as compared to the patients who were categorised as non-young (>45 years) strokes, severe versus non-severe COVID-19 disease and dead versus discharged. Patients with acute ischemic stroke (AIS) and COVID-19 were compared with records of AIS patients without COVID-19 during the same period of study.

2.3. Statistical analysis

The data was initially collected using the Google forms ™ and was transferred to Microsoft excel for analysis. Online statistical software GraphPad, Epi Info and SPSS (version 25), were used for analysing the data. Comparison of proportions between the two groups was done using Fisher's Exact Test. The association between two non-parametric variables was evaluated using Pearson Chi-square test and comparison of means between the two groups was done using Unpaired '*t*' test. Receiver's Operating Characteristic (ROC) was used to find out the cut-off values of CRP and D-dimer against outcomes (dead/discharge). Multivariable logistic regression model was utilised for the evaluation of the binary outcomes. p value of <0.05 was considered statistically significant.

3. Results

3.1. Demography and clinical features of all stroke sub types (Table 1)

Table 1 contains the details of the various aspects studied and salient points of that data are mentioned in the text below.

The mean age among the cohort ($n = 100$; 63 males, 37 females) was 57 years (±14, minimum 27, maximum 85, range 58, 95% CI 55 to 60).

Of the 100 consecutive patients with acute stroke and COVID-19; 78 were diagnosed as acute ischemic stroke (AIS), 13 were diagnosed as cerebral venous sinus thrombosis (CVT) and nine patients were diagnosed with an Intra Cerebral Haemorrhage (ICH).

The mean duration in these patients (n = 100) for reporting a neurological symptom was 2 days (±3, minimum 2 days prior and maximum 13 days post hospitalisation, range 15, 95% CI 1.4 to 2.6).

Stroke was the only manifestation of COVID-19 in 67% of the patients. The mean duration from the onset of neurological symptoms to hospitalisation in these patients ($n = 67$) was 0.64 days (±0.93, ranged from two days prior to the day of hospitalisation and maximum on the day of admission, 95% CI 0.41 to 0.89). Majority ($n = 58$) had stroke on the day of hospitalisation.

The rest ($n = 33$) presented with typical COVID-19 related symptoms (fever, cough, breathlessness, or diarrhea), that were the notified symptoms by Indian Council of Medical Research (ICMR), Government of India for the identification of COVID-19 cases. These patients developed their neurological symptoms along with other typical COVID-19 symptoms or while in the hospital. The mean duration among these patients for reporting a symptom of stroke was 4.8 days (±3.9, minimum 2 days prior to hospitalisation and maximum 13 days after hospitalisation, range 15, 95% CI 3.8 to 6.1).

Table 1
Characteristics and outcome of all stroke sub types.

Parameters	ICH (n = 9)	CVT (n = 13)	AIS (n = 78)
Age			
≤45 years	2	9	9
>45 years	7	4	69
Gender			
Female	3	7	27
Male	6	6	51
Risk factors			
Hypertension	3	2	39
Diabetes mellitus	2	1	40
Chronic renal failure	2	1	3
Immunosuppressant use	0	0	1
Underlying malignancy	0	0	1
HCQS prophylaxis	0	0	10
Other clinical features			
Headache	2	12	7
Altered sensorium	6	4	26
Seizures	6	9	3
Abnormality of smell	2	3	5
Abnormality of taste	0	4	4
GCS on admission			
13–15	2	9	47
3–12	7	4	31
Stroke severity: NIHSS			
1–4: Mild	2	7	22
5–15: Moderate	5	4	37
16–20: Moderate-severe	2	2	16
21–42: Severe	0	0	3
Ischemic stroke characteristics:			n=78
Arterial territory on imaging			
ACA			3
MCA			60
Watershed			5
Posterior circulation			10
Large vessel occlusion (LVO)			36
Number of territory involved on imaging			
Single territory stroke			58
More than 1 territory stroke			15
Laboratory findings			
Abnormal HRCT	(n = 8) 4	(n = 8) 5	(n = 57) 50
Abnormal ECG	2	0	11
Thrombocytopenia (<1,50,000 thou/μL)	0	1	13
Raised D-dimer: (>0.5 mg/L)	5	13	68
Raised CRP: (>10 mg/L)	6	4	72
Raised IL-6: (>7 pg/mL)	(n = 4) 1	(n = 9) 7	(n = 65) 60
Treatment and outcome			
tPA given			
No	–	–	72
Yes	–	–	6
Medications used			
Remdesivir	0	1	27
Tocilizumab	0	0	11
Steroids	5	6	59
Standard	5	13	69
Ventilation			
Invasive	4	2	21
Non-invasive	2	1	17
Outcome			
Deceased	6	1	22
Discharged	3	12	56

n = number of patients.

3.1.1. Risk factors

Hypertension was more common in those with AIS (50%) and ICH (33.3%) as compared to those who presented with CVT (15.4%). The prevalence of diabetes mellitus was higher in AIS (51.3%) as compared to those with CVT (7.7%). 29 patients had concomitant HTN and DM. Six patients had concomitantly all three co-morbidities of HTN, DM and chronic renal failure (CRF). The mean duration (years) of diabetes and hypertension was 7.2 (±5.3, minimum 1, maximum 20, range 19, 95% CI 5.6 to 8.8) and 7.7 (±5.3, minimum 1, maximum 20, range 19, 95% CI 6.1 to 9.3), respectively ($p = 0.648$ NS). One patient had pre-existing myeloma and another patient was on immunosuppressive therapy. 10 (12.8%) patients with AIS were on weekly HCQS pre-exposure prophylaxis.

3.1.2. Other clinical features and investigations

Headaches were common in those with CVT (92.31%); least in those with AIS (8.97%). Seizures were a common feature in those with ICH and CVT (66.7% and 69.2% respectively); least in those with AIS (3.85%).

HRCT of chest was done in 73 patients; it was abnormal in 59 patients. Two patients with AIS were diagnosed with atrial fibrillation on the ECG and one had a left ventricular thrombus on 2D ECHO. Four (5.13%) patients with AIS also had raised CK levels with myalgia (range 359–1032 U/L). D-dimer level was raised (more than 0.5 mg/L) in all patients with CVT, 87.2% in those with AIS and in only 55.6% with ICH. A raised C Reactive Protein (CRP) was more common in AIS (92.3%) and ICH (66.7%) than in those with CVT (30.8%).

3.1.3. Treatment and outcomes

Only six patients (7.7%) with AIS received intravenous thrombolytic therapy with tPA (recombinant tissue plasminogen activator-alteplase) and one patient underwent mechanical thrombectomy (perfusion was established but later succumbed to COVID-19 related respiratory complications).

66.7% of those with ICH needed ventilation as compared to 23.1% with CVT and 48.7% with AIS.

3.1.4. Outcome

Those with ICH had the worst outcome (i.e. mortality in 66.7%). Outcome was better with AIS and CVT where 56 (71.8%) and 12 (92.3%) patients recovered, respectively.

3.2. Characteristics of patients with non-severe compared with severe COVID-19 for all stroke subtypes (Table 2)

47 patients went on to develop severe COVID-19 during their stay in the hospital; 78.7% among them were more than 45 years of age. The number of patients with diabetes mellitus and hypertension were comparable in both the groups. Table 2 contains details of the parameters studied.

3.3. Comparison of various parameters in all stroke subtypes to outcome (dead or discharged)

29 patients (29%) died of which 75.9% were more than 45 years. The number of patients with diabetes mellitus and hypertension were comparable in both the groups. Those who died presented with an altered sensorium (55.2% versus 28.2%; $p = 0.011$), had a low GCS on admission (69% versus 31.0%; $p = 0.001$) and more severe stroke (51.7% versus 11.3%; $p = 0.001$). Though D dimer and CRP were raised in both the groups; the mean D dimer (1.74 ± 0.82 versus 1.33 ± 0.74; $p = 0.016$) and CRP (38.89 ± 21.65 versus 24.64 ± 14.92; $p = 0.001$) levels were more elevated in those in those who died. LVO was more in those who died, but it was not statistically significant (44.8% versus 32.4%; $p = 0.259$). The use of invasive ventilation was more in those who died as compared to those who were discharged (65.5% versus 11.3%, $p = 0.001$).

4. Acute ischemic stroke (AIS) and COVID-19

78 patients who were diagnosed as AIS were analysed further. Prior history of TIA or stroke was observed in only seven patients (8.97%) with AIS. 76.9% ($n = 60$) of patients had stroke in the MCA territory. 19.2% ($n = 15$) patients had acute infarcts in more than one territory and 46.2% ($n = 36$) patients with AIS had large vessel occlusion (LVO).

Table 2
Characteristics of patients with non-severe compared with severe COVID-19 for all stroke subtypes.

Parameter	Non-severe COVID-19 (n = 53)	Severe COVID-19 (n = 47)	p value*
Age			0.764, NS
≤45 years	10 (18.9%)	10 (21.3%)	
>45 years	43 (81.1%)	37 (78.7%)	
Gender			0.159, NS
Female	23 (43.4%)	14 (29.8%)	
Male	30 (56.6%)	33 (70.2%)	
Other clinical features			
Headache	13 (24.5%)	8 (17.0%)	0.358, NS
Altered sensorium	9 (17.0%)	27 (57.4%)	0.001*
Seizures	9 (17.0%)	9 (19.1%)	0.778, NS
Abnormality of smell	3 (5.7%)	7 (14.9%)	0.125, NS
Abnormality of taste	6 (11.3%)	2 (4.3%)	0.194, NS
Risk factors			
Diabetes mellitus	22 (41.5%)	21 (44.7%)	0.749, NS
Hypertension	24 (45.3%)	20 (42.6%)	0.784, NS
Chronic renal failure	3 (5.7%)	3 (6.4%)	0.879, NS
Immunosuppressant use	1 (1.9%)	0 (0.0%)	0.344, NS
Malignancy	1 (1.9%)	0 (0.0%)	0.344, NS
HCQS prophylaxis	3 (5.7%)	7 (14.9%)	0.125, NS
GCS on admission			<0.001*
13–15	45 (84.9%)	13 (27.7%)	
3–12	8 (15.1%)	34 (72.3%)	
Stroke severity: NIHSS			<0.001*
1–15	51 (96.2%)	26 (55.3%)	
16–42	2 (3.8%)	21 (44.7%)	
Investigations			
Abnormal ECG	7 (13.2%)	6 (12.8%)	0.948, NS
Thrombocytopenia	5 (9.4%)	9 (19.1%)	0.248, NS
Raised D-dimer (> 0.5 mg/L)	42 (79.2%)	44 (93.6%)	0.046*
Raised CRP (>10 mg/L)	39 (73.6%)	43 (91.5%)	0.035*
Raised IL-6 (>7 pg/mL)	36 (67.9%)	32 (68.1%)	1.000, NS
Abnormal HRCT	24 (45.3%)	35 (74.5%)	0.004*
Treatment and outcomes			
Medications used			0.001*
Steroid	29 (54.7%)	41 (87.2%)	
Remdesivir	6 (11.3%)	22 (46.8%)	
Standard	50 (94.3%)	37 (78.7%)	
Tocilizumab	0 (0.0%)	11 (23.4%)	
tPA given	3 (5.7%)	3 (6.4%)	0.879, NS
Outcome (Death)	5 (9.4%)	24 (51.1%)	0.001*

* $p < 0.05$ was considered significant; NS: Non-Significant.

4.1. Young (≤45 years) as compared to the non-young (>45 years)

Nine patients were ≤ 45 years and 69 (88.5%) patients were more than 45 years of age (non-young). Those more than 45 years of age were more likely to have concomitant diabetes (56.5% versus 11.1%; $p = 0.010$) and hypertension (56.5% versus 0%; $p = 0.001$). Headache (33.3% versus 5.8%; $p = 0.007$) and strokes in more than one territory (55.6% versus 14.5%; $p = 0.011$) were more common in the young. Altered sensorium (55.6% versus 30.4%; $p = 0.133$), low GCS on admission (55.6% versus 37.7%; $p = 0.136$), severe stroke (44% versus 21.7%; $p = 0.136$) and LVO (66.7% versus 43.5%; $p = 0.288$) were also more common in the young but were not statistically different between the two age groups. D dimer and CRP levels were comparable in both the age groups.

4.2. Non-severe compared with cases of severe COVID-19 AIS

40 (51.3%) patients with AIS continued to have non-severe COVID-19 during their period of hospitalisation. 38 patients eventually developed severe COVID-19. The severity of developing COVID-19 was independent of age and sex of the patients. Diabetes and hypertension were comparable in the two groups. Those with severe COVID-19 were more likely to have altered sensorium (50% versus 17.5%; $p = 0.002$) and low GCS on admission (65.8% versus 15%; $p = 0.001$), severe stroke (44.7% versus 5%; $p = 0.001$), strokes involving more than one territory (31.6% versus 7.5%; $p = 0.009$), large vessel occlusion (63.2% versus 30%; $p = 0.006$) and raised D dimer (100% versus 75%; $p = 0.001$). Of the 73.1% of patients with AIS (57/78) who underwent a HRCT of chest on admission, an abnormal finding was found significantly in those with severe COVID-19 (78.9% versus 50%; $p = 0.010$). CRP levels were elevated in both the groups (97.4% versus 87.5%; $p = 0.201$). The use of steroids (94.7% versus 57.5%) and remdesivir (57.9% versus 12.5%; $p = 0.001$) was more in the severe COVID-19 group. There were more patients with severe COVID-19 and AIS who died as compared to those with non-severe COVID-19 (44.7% versus 12.5%; $p = 0.002$).

4.3. Comparison of various parameters to outcome (dead versus discharged) in AIS

22 patients (28.21%) with AIS died; 77.3% were above 45 years of age. Those who died were more likely to have a low GCS on admission (59.1% versus 32.1%; $p = 0.029$), severe stroke (54.5% versus 12.5%; $p = 0.001$) and need for invasive ventilation (63.6% versus 12.5%; $p = 0.001$). Those who died also had a higher mean D dimer (1.91 ± 0.62 versus 1.27 ± 0.71; $p = 0.001$) and CRP level (40.53 ± 20.49 versus 27.29 ± 13.91; $p = 0.002$). There was no significant difference in deaths between those with LVO and non LVO strokes (36.1% versus 21.4%; $p = 0.208$).

4.4. The comparison of the non COVID-19 AIS patients with COVID-19 and AIS (Table 3)

Data of 100 patients with acute ischemic stroke without COVID-19 was compared with 78 patients with COVID-19 and AIS. Both groups predominantly had strokes in the middle cerebral artery territory with comparable stroke severity. Parameters common to both the groups were compared. Deaths between the two groups were not statistically different (28.2% versus 17%; $p = 0.100$). Multivariate logistic regression model demonstrated that there was a positive association for the presence of diabetes in those with COVID-19 and AIS (OR 2.55, 95% CI 1.20–5.40, $p = 0.015$). Similarly, there was a positive association for LVO (large vessel occlusion) in patients with COVID-19 and AIS (OR 8.67; 95% CI 3.89–19.31, $p < 0.001$).

Table 3
Comparison of the non COVID-19 AIS patients with COVID-19 and AIS.

Parameters	Non COVID-19 AIS (n = 100)	Ischemic stroke + COVID-19 (n = 78)	p value*
Age			0.395, NS
≤45 years	16 (16.0%)	9 (11.5%)	
>45 years	84 (84.0%)	69 (88.5%)	
Sex			0.821, NS
Female	33 (33.0%)	27 (34.6%)	
Male	67 (67.0%)	51 (65.4%)	
Risk factors			
Hypertension	65 (65.0%)	39 (50.0%)	0.048*
Diabetes mellitus	36 (36.0%)	40 (51.3%)	0.048*
Other clinical/Lab features			
Headache	8 (8.0%)	7 (9.0%)	1.000, NS
Altered sensorium	19 (19.0%)	26 (33.3%)	0.037*
Seizures	3 (3.0%)	3 (3.8%)	1.000, NS
Abnormal ECG	25 (25.0%)	11 (14.1%)	0.091, NS
GCS on admission			0.006*
13–15	79 (79.0%)	47 (47.0%)	
3–12	21 (21.0%)	31 (39.7%)	
Stroke severity: NIHSS			0.225, NS
1–15	83 (83.0%)	59 (75.6%)	
16–42	17 (17.0%)	19 (24.4%)	
Stroke characteristics:			
LVO	22 (22.0%)	36 (46.2%)	0.001*
More than 1 territory stroke	8 (8.0%)	15 (19.2%)	0.041*
Outcome			
Dead	17 (17.0%)	22 (28.2%)	0.100, NS

* $p < 0.05$ was considered significant; NS: Non-Significant.

5. Intra cerebral haemorrhage (ICH)

Nine patients in our cohort (9%) presented with an ICH. The mean age with ICH was 55.7 years (range 43 to 72). None of them had thrombocytopenia or coagulopathy on admission. Only three patients had hypertension and two among them also had chronic renal failure and diabetes; rest of them (66.7%) had no risk factors for ICH. Six (66.7%) patients had seizures on presentation. Five patients (55.6%) had lobar haemorrhages (one patient had bilateral frontal haemorrhages: there was no evidence of CVT on the MR venogram). None with lobar haemorrhages had hypertension, diabetes or CRF. Four patients had basal ganglia bleed (putamen being the commonest). Majority (six patients) had severe COVID-19. The mean CRP was non significantly raised in those with severe COVID-19 and ICH as compared to those ICH patients without severe COVID-19 (35.03 ± 28.6 versus 16.7 ± 10.75).

6. Cerebral venous thrombosis (CVT)

Of the 100 patients with COVID-19 and acute stroke; 13 patients (13%) had CVT. Nine of these patients (69.23%) presented with seizures. The mean age was 39.8 years (range 27–67 years). Seven patients were females; none of them were on oral contraceptives nor was there a prior history of venous thrombosis. One patient also had an associated arterial stroke, her work up for anti-phospholipid antibody syndrome was negative. Majority with CVT had non severe COVID-19 (76.9%). All patients with venous infarcts had raised D dimer values; C reactive protein was raised in only 4 (30.77%) patients. One patient among our cohort died (had both superficial and deep venous thrombosis).

7. Discussion

This study presents a large cohort of 100 consecutive patients with COVID-19 and acute strokes. Our study is an epidemiological representation of the association of COVID-19 and stroke from Mumbai as the data is pooled from 10 different centres across the city which was worst affected during the height of the pandemic.

Stroke is not a common complication of infection with SARS-CoV-2 virus: the incidence being 1.44% to 1.74% [6]. Earlier studies reported strokes to occur late in the disease course of COVID-19 and especially in those with severe infection [2,4]. As the pandemic evolved, studies reported the occurrence of strokes even in those with mild or asymptomatic infection [3,5,6,16–19]. The present study found that stroke as a clinical presentation of COVID-19 in 67% of the patients which is higher than that reported in the previous studies. This may be because patients may not have noticed or experienced mild COVID-19 symptoms. The fear of contagious nature of the pandemic may have prevented them from visiting a physician or hospital at the outset and they probably sought help only later in the disease course when they experienced a stroke. This may also reflect the local set up which involves out of pocket expenses due to lack of healthcare insurance in most of the patients and limited availability of government medical services due to the overwhelming pandemic.

45 of these patients with a neurological presentation had HRCT chest on the day of admission to triage for the presence of asymptomatic COVID-19; it was normal in 10 (22.2%) patients. These patients would have been misdiagnosed as non-COVID-19 strokes, if the hospital policies did not dictate the need for RT PCR testing for SARS-CoV-2 virus for all those needing hospitalisation. Stroke as distinctive presenting feature of COVID-19 needs to be recognised as these patients can be responsible for nosocomial spread of infection.

In our study, 51.3% with AIS had non-severe COVID-19 implying that even those with mild COVID-19 disease are at a risk to develop stroke. A recent study [5] reported 31% of their stroke patients to have mild to moderate COVID-19 disease. In our study, even those with non-severe COVID-19 and AIS had raised CRP and D dimer levels in 87.5% and 75% of the patients respectively. This perhaps explains the propensity to AIS even in those with mild to moderate COVID-19 as both CRP and D dimer are considered to be thrombogenic. CRP can induce thrombosis by initiating the extrinsic pathway of coagulation [20]. Raised CRP has also been known to predict aggravation from mild to severe COVID-19 as well [21]. D dimer is a broad biomarker of systemic thrombosis and a recent meta-analysis suggested higher levels even in those with ischemic strokes [22]. Increase in D dimer suggests the increase in inflammation and hyperfibrinolysis associated with COVID-19 [23]. Though traditionally used as a marker for venous thromboembolism, its pathophysiologic role in COVID-19 strokes needs to be explored further by larger studies.

In our study, patients who progressed to develop severe COVID-19 after admission were more likely to present with an altered sensorium and a low GCS on admission, had propensity for multiple territory strokes, large vessel occlusion and an abnormal finding on HRCT chest. The propensity for LVO and multiple territory strokes is probably due to multi vessel thrombosis or embolism as has been described earlier [3,18,24]. In our study, those with severe COVID-19 and AIS had elevated D dimer in all the patients and CRP in 97.4% of patients suggesting that the pro coagulant and inflammatory responses were more in those with severe COVID-19. Increase in procoagulants especially with severe COVID-19 has been described [25]. Increase in D dimer levels are not only associated with severe disease, but it is also a useful biomarker to predict increased in-hospital mortality in those with COVID-19 [23]. The prognosis was poor in those with severe COVID-19 and AIS with 44.7% deaths as compared to the death rate in the entire AIS cohort which was 28.2%. The increase in deaths in the severe COVID-19 group may be due to associated complications of severe COVID-19 like hypoxia, sepsis and multi organ failure.

Certain features were more likely in those with COVID-19 and ischemic strokes who died: Altered sensorium and low GCS on admission, severe stroke, need for invasive ventilation and elevated levels of D dimer and CRP.

We compared the data of 78 COVID-19 patients with AIS to 100 patients of non-COVID-19 AIS. Diabetes, altered sensorium and low GCS on admission, large vessel occlusion and multiple territory strokes were common in the COVID-19 group. The presence of moderate-severe and severe strokes was comparable in both the groups. Though deaths were higher in those with COVID-19 strokes (28.2% versus 17%), they did not differ statistically between the two groups. Ntaios et al. [7] in the Global COVID-19 stroke registry study compared COVID-19 AIS with non-COVID-19 strokes and found the mortality to be significantly higher in those with COVID-19. Mathew et al. [8] recently demonstrated similar findings of increased mortality and morbidity in those with COVID-19 as compared to the non-COVID-19 ischemic stroke controls. However, their control group had 54% patients with mild stroke and zero in hospital mortality. In our study the mortality in the non COVID-19 patients with AIS was high (17%) probably reflecting the changed scenario of overwhelming burden in the hospital due to the pandemic which necessitated the management of patients with mild stroke on an office-based setting. Also, probably patients were hesitant to report to the hospital for fear of contracting COVID-19 and those with minor symptoms reported only when their symptoms worsened.

The number of patients in the ICH and CVT groups were small and hence these interpretations have limitations, but the following observations could be made in these two groups of patients:

7.1. ICH and COVID-19

The mean age of our cohort (55.5 years) was less as compared to those with conventional ICH (73.89 years) [26]. A majority of those with ICH went on to develop severe COVID-19 disease. It is noteworthy that most of these patients did not have traditional risk factors for ICH ($n = 6$); none had coagulopathies ($n = 0$) on admission to the hospital. A previous study found ICH to occur more frequently in their patients who we on prophylactic or therapeutic doses of anticoagulation in view of their rising D dimer levels by median day 17 of hospitalisation [27]. In our study only 2 patients developed symptomatic ICH on day 7 and 13 of hospitalisation; both had severe COVID-19 by then. Rest of our patients presented on the day of hospitalisation with ICH related symptoms. The absence of conventional risk factors for lobar haemorrhages and occurrence early in the disease course of COVID-19 probably lends some credence to the causal relationship between COVID-19 and ICH. Though the mechanisms leading to ICH with COVID-19 are evolving, two theories are proposed. Firstly, there may be a direct [28] and indirect endothelium dysfunction (by way of inflammatory and thrombotic responses). Secondly, there may be COVID-19 induced disruption of the renin angiotensin system [29] leading to loss of cerebral blood flow autoregulation and ICH.

7.2. CVT and COVID-19

All our CVT patients had raised D dimer levels, but only a few had elevated CRP levels. This observation indicates the dominant role of procoagulant mechanism as against the inflammatory mechanisms observed in other types of stroke. Also, most patients were young, had non severe COVID-19 (76.9%) and low mortality. This is contrary to the older age and higher mortality reported in other studies [11,12]. However, the number of patients is small to draw meaningful conclusions.

7.3. Our study has limitations

The retrospective nature of the study, overwhelming patient burden, highly contagious nature of COVID-19 and risk of nosocomial spread limited a detailed history and examination. Therefore, we were unable to apply disability scoring in most of the patients who were discharged and hence, this parameter was not part of the analysis. Ancillary tests for risk factor evaluation couldn't be done in most of the patients (e.g. 2D ECHO/Transoesophageal ECHO especially in those with LVO and multiple territory strokes). Due to the retrospective nature of study, presence of deep vein thrombosis (DVT) or pulmonary embolism (PE) was not tested in all but was evaluated only when clinically suspected. We could test for DVT/PE in 22 patients; it was negative in all. We could have missed thrombosis in patients where it was not clinically suspected or who were sick to be shifted to the radiology suite. There was a limitation in the data capturing tool, which did not allow us to assess other traditional risk factors for stroke like obesity, tobacco abuse/smoking, dyslipidaemia, alcohol abuse and hyperhomocysteinemia.

Despite these limitations, the strength of our study is the large cohort of patients with COVID-19 and acute strokes of various sub types (AIS, ICH and CVT). Also, the patients in our study represented a multi-ethnic population across several centres as patients from several remote geographies converge to the mega-metropolis of Mumbai for specialist care.

8. Conclusions

Strokes can be a presenting feature in those with COVID-19. Even those with non-severe COVID-19 disease are at a risk to develop acute ischemic stroke. Those with ischemic strokes and severe COVID-19 had a higher mortality as compared to those with non-severe COVID-19. Certain parameters like altered sensorium and poor GCS on admission, severe stroke, need for invasive ventilation, an elevated D-dimer and raised CRP were more likely to predict death in those with COVID-19 and ischemic strokes. Although patients who were diagnosed positive for COVID-19 with ischemic strokes were more likely to present on admission with an altered sensorium and poor GCS, large vessel occlusion and multiple territory involvement; the mortality in these patients was comparable to the patients with ischemic stroke who did not have COVID-19.

Declarations of Competing Interest

None.

Financial disclosures

None.

Acknowledgement

Data accuracy and verifying its completeness was ascertained by SGP and MB. We thank Prof. Satish V Khadilkar for his technical insights, editing and valuable suggestions.

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