BIOLOGICAL MARKERS WITH STROKE SEVERITY

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Abstract

Background: The Covid-19, an infection caused by SARS-CoV 2 originated in Wuhan province of China in December 2019 and later it became pandemic by rapidly spreading to all parts of the world and caused death of millions of people in the first wave and second wave by its variant with less severity in the subsequent waves which is still ongoing in different parts of the world. According to WHO report, more than 100 millions cases were infected so far with the virus and about 4 million deaths were reported from Covid-19. This outbreak was comparable to other coronavirus SARS CoV 1 and MERS CoV which caused pandemics in the year 2002 and 2012 respectively. Materials and Methods: This is a retrospective cross sectional study, conducted at single centre Mc-Gann teaching hospital, Shimoga, Karnataka during the time period 01-01-2021 to 30-06-2021. Study population selected from the patients who are admitted to the above mentioned hospital by applying following inclusion and exclusion criteria. Neurodeficit was assessed using NIHSSS and grouped into severe and non-severe group. Neuro-imaging was done for all the study subjects. Covid-19 bio-markers was sent for all subjects. HRCT thorax for all patients having moderate to severe respiratory illness or low SpO2 and probability of Covid-19 pneumonia assessed using CT severity index. Results: Total 3256 Covid-19 patients admitted during the study period, among them, only 28 are incubed in the study(0.85%). Mean age of the population was 53 yrs. 17 were males(48.6%) and 11 were females(31.4%). 6 were having stroke in young. 10 presented with only neurological illness others respiratory illness followed by neurodeficit. Mean time of onset of neurodeficit was 6 ± 5 days. 7 were having severe hypoxia(25%) 19 were having ischemic stroke(67.85%), 4 were having Cortical vein Thrombosis (14.28%), 3 were having Intra Cerebral Hemorrhage(10.7%) and one each were having SAH and Bell’s palsy(3.5%). Neurodeficit was assessed using NIHSSS and grouped into severe(21.5%) and non-severe(78.5%). In stroke, hemiparesis was more common and majority had single large vessel involvement in the anterior circulation and in CVT majority were having superior sagittal sinus thrombosis. Intra Cranial bleed patients had normal blood pressure and coagulation profile. Mean CRP in the study population was 46±24 mg/dL and was significantly raised in the severe stroke group (P<0.05). Similarly, mean serum ferritin and LDH were significantly raised in the severe group(P<0.05) Mean D-dimer was 4.33± 3.49 mg/dL and is also significantly raised in the severe group(P<0.05) 5 patients were having severe lung injury and all of them were having ischemic stroke. Severity of lung injury when compared to stroke severity using Chi-square test was not statistically significant (P=0.37). Conclusion: Both central and peripheral nervous system involvement can be seen in Covid-19 patients. Ischemic stroke is the commonest form of involvement. Covid-19 patients with severe lung injury had severe neuro-deficit, however neurological manifestations can be independent of respiratory illness. Biological markers of Covid-19 can also be used as prognostic indicators for neurodeficit. Prophylactic anti-coagulation could have prevented the thrombotic complications in Covid-19 patients with mild symptoms.
INTRODUCTION

The Covid-19, an infection caused by SARS-CoV 2 originated in Wuhan province of China in December 2019 and later it became pandemic by rapidly spreading to all parts of the world and caused death of millions of people in the first wave and second wave by its variant with less severity in the subsequent waves which is still ongoing in different parts of the world.[1]

According to WHO report, more than 100 million cases were infected so far with the virus and about 4 million deaths were reported from Covid-19. This outbreak was comparable to other coronavirus SARS CoV 1 and MERS CoV which caused pandemics in the year 2002 and 2012 respectively.[2]

Majority of Covid-19 cases presented with symptoms of fever, cold, cough, sore throat, myalgia, like flu. Few with diarrhea, loss of taste and anosmia. Severe cases with shortness of breath, extreme fatigue because of hypoxemia, respiratory failure requiring mechanical ventilation.[3]

As the pandemic evolved, several studies conducted at various parts of the world revealed it is not only the respiratory system affected by the virus, other systems like cardiovascular, nervous system, musculoskeletal systems also involved.[4]

This was also supported by the pathogenesis of the Covid-19 i.e. activation of immunological system and coagulation cascade by the virus leading to cytokine storm and tissue destruction, hypercoagulable state causing acute myocardial destruction, pulmonary thrombosis, deep vein thrombosis, ischemic stroke and cortical vein thrombosis.

Initial studies suggested stroke to be a feature of severe and late Covid-19,[5], usually occurring in the second week of illness after the onset of typical respiratory symptoms. But meta-analysis, showed stroke patients without typical symptoms of Covid-19 showing throat swab test positive for Covid-19.[6]

There was limited data from our part of the country in this field, hence we have conducted a cross-sectional study in the District Covid-19 Hospital, Shimoga which is a tertiary center in the Malnad region of Karnataka India which has referrals from 5 surrounding districts.

The association between neurological severity and levels of biochemical markers was not clearly delineated in the earlier studies hence, we made an attempt to find the relation between biochemical markers level and stroke severity and also compared the stroke severity with severity of lung injury.

Objectives
1. To describe the neurological manifestations of Covid-19.
2. To correlate biological markers of Covid-19 with stroke severity.

MATERIALSANDMETHODS

Study Design
This is a retrospective cross sectional study, conducted at single centre Mc-Gann teaching hospital attached to Shimoga Institute of Medical Sciences, Shimoga, Karnataka which was designated as ‘District Covid Hospital’ during Covid pandemic in the time period from 01-01-2021 to 30-06-2021.

Study population selected from the patients who are admitted to the above mentioned hospital by applying following inclusion and exclusion criteria.

Inclusion Criteria
1. Age ≥ 18
2. Throat swab positive for Covid-19 either by RTPCR or Rapid Antigen Test.
3. Symptoms or signs of definite neurological involvement either central or peripheral nervous System
4. And patients who gave consent for the study

Exclusion Criteria
1. Past H/O stroke
2. Family H/O stroke in young
3. Atrial fibrillation

Study protocol was approved by the institutional ethical committee.

Data Collection
Among the study population following clinical, laboratory and imaging information collected from hospital medical records and data was reviewed by a team of physicians and a neurologist.

Age, sex, comorbid conditions, vitals,SpO2 clinical presentations, routine blood investigations, Covid-19 profile including serum C-reactive protein (CRP), Lactate Dehydrogenase(LDH), Ferritin, D-dimer levels and arterial blood gas analysis (ABG) and brain imaging reports are collected and analyzed.

Clinical stroke severity was assessed using the NIHSS Scoring system which includes 11 parameters covering all neuro deficits and scores ranging from 0-42. Based on score, patients were subgrouped into minor stroke(1-4 score), moderate stroke(5-15), moderate to severe stroke(16-20) and severe group(21-42). For analysis purpose they were simply grouped into non-severe stroke group(NIHSS Score <21) and severe stroke group(NIHSS Score ≥21).

HRCT thorax for all patients having moderate to severe respiratory illness or low SpO2 and probability of Covid-19 pneumonia assessed using CORADS scoring and further severity estimated using CT severity index, scoring from 0 to 25.

Scoring 0-8 were considered as mild pneumonia, 9-17 as moderate pneumonia and ≥18 as severe pneumonia.

Statistical Analysis
The data was initially collected using the Google forms and was transferred to Microsoft excel for analysis. Online statistical software Graph Pad,
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.

RESULTS

During the aforementioned period, totally 3256 got admitted to our hospital for Covid-19, but only 28 patients (0.85%) were having neurological manifestations during the course of illness and satisfied inclusion criteria. Their demographic and clinical characteristics were shown in the table below.

Mean age of the study population was 52.95yrs. 6 patients were below 45yrs attributing to “stroke in Young” and 22 patients were above 45yrs. Mean age of patients below 45yrs was 41± 8 yrs, minimum of 22yrs and maximum of 87 yrs. Mean age of patients above 45yrs was 64±10yrs, minimum of 51 yrs and maximum of 87 yrs.

In the study population, 17 were males(48.61%) and 11 patients were females(31.4%). Among males 4 were below 45yrs(23.5%) and among females 2 were below 45yrs(18%).

Mean Systolic BP among the study population was 130.5 mm of Hg and mean diastolic BP was 80.46 mm of Hg. 18 patients were having normal BP, 10 were having either systolic or diastolic high BP. 6 patients were having high systolic BP and 4 were having high diastolic BP and only 3 were having both high BP.

SpO2 measured using pulse oximeter, >95% was normal, 90-94% is mild hypoxia, 85-89% is moderate hypoxia and <85% is severe hypoxia. It was normal in 12 patients. 16 were having hypoxia, out of them 7 were having severe hypoxia which was further confirmed ABG.
When clinical presentation was observed 12 were having fever(42.85%), 7 were having cough(25%) and 10 were having shortness of breath(35.71%). Only 3 patients were having all these 3 symptoms(10.71%). One was having a cold and one was having diarrhea during the presentation.

At the time of initial presentation, 10 patients were having only neurological manifestations(35.71%), remaining presented with respiratory symptoms either as URI or LRI(64.28%), subsequently developed neurological symptoms. Mean time of onset of neurodeficit considering the onset of illness is 6± 5 days.

60% presented within the first week of illness, 25% presented on the second week of illness, ischemic stroke and CVT cases were seen even after 2 weeks of illness onset. Further, the majority of severe stroke patients presented within the first week itself.

Over all, 10 were having right hemiparesis(35.71%), 7 were having left hemiparesis(25%), 6 presented as loss of consciousness without definite focal sign(24.42%), 1 was having Bell’s palsy. 5 patients were having headache and 2 among them were having associated generalized seizures.

After CT brain, it was evident that 19 were having ischemic stroke(67.85%), 4 were having cortical vein thrombosis(14.28%), 3 were having intracerebral hemorrhage (10.71%), one each was having Subarachnoid hemorrhage(3.5%) and Bell’s palsy(3.5%). This was comparable to earlier studies(24-25)

Among ischemic stroke, 6 were below 45 yrs (4 were males and 2 were females) attributing to ‘Stroke in Young’(21%). 11 patients were having anterior circulation stroke(57.89%), 3 were having posterior circulation stroke(15.78%), 6 were having both anterior and posterior circulation stroke(31.57%).

When CT reports were analyzed in detail, 7 were having single large vessel strokes (25%), 3 were having multiple large vessel strokes(10.71%), 5 were having multiple small vessel strokes(17.85%) and 4 single small vessel strokes(14.28%). 13 patients were having unilateral involvement (46.42%) in imaging and 6 were having bilateral
involvement (21.42%) and overall only 3 were having high BP. In CVT all patients were below 60yrs, 50% were males and 50% were females. Only one was diabetic. 50% were below 50yrs and 2 patients presented with headache and seizures, one with only headache and one with hemiparesis. BP was normal in all patients and SpO2 was also normal in all these patients.

All were having involvement of superior sagittal sinus thrombosis. 2 patients were having only venous thrombosis, along with that one was having venous infarct also and another was having CVT with hemorrhage. All were having mild strokes only.

50% were having moderate lung injury and the remaining 50% didn’t show pulmonary involvement at all in HRCT thorax. D-dimer was elevated in majority of the patients.

In the brain hemorrhage group all were above 50yrs and all were males. Only one patient had hypertension history, 2 were having only neurological symptoms and one was having respiratory symptoms also. One was having normal systolic and diastolic BP and other two were having high diastolic BP. All were having normal SpO2 at room temperature.

Two patients presented with loss of consciousness and one with left hemiparesis. 2 were having cerebellar hemorrhage and one was capsuloganglionic bleed. All got admitted within 5 days of illness onset. 2 patients (60%) didn’t show any pulmonary involvement and one (33%) was showing only mild lung injury.

Only one elderly female was having Subarachnoid hemorrhage, whose systolic BP was high with no comorbidities. She presented as loss of consciousness on the 4th day of illness with moderate neuro deficit and the site of bleeding was a basal cistern extending into bilateral Sylvian fissure. She didn’t have any lung involvement.

One middle aged male was having Bell’s palsy presented on the 2nd day of illness. He was not having any comorbidity and BP was normal, but was hypoxic at admission and was having severe lung injury.

Based on NIHSS Score, the study population was grouped into a severe stroke group(score >21/42) and non-severe stroke group(<21/42). 22 patients were in a non-severe group and 6 were having severe strokes.

When demographic, clinical and laboratory findings compared in these 2 groups following observations were seen.

Mean age of the non-severe stroke group was 58±16 yrs and of the severe stroke group was 59±8yrs, this was not statistically significant (P-value 0.79).

In the severe group, only 1 was female and the remaining 6 were males compared to the non-severe group where 10 were females and 12 were males. This association tested using chi-square test with Yates’ correction, P-value was 0.41 which was not statistically significant.

Mean systolic BP among non-severe group was 129±20 mm Hg compared to severe group where it is 135±14 mm Hg which is not statistically significant (P-value 0.5)

Mean diastolic BP among non-severe groups was 78±11 mm Hg compared to the severe group where it is 86±10 mm Hg which is also not statistically significant (P-value 0.1).

Co-morbidities in the severe group were found in 50% individuals compared to 63.6% in the non-severe group, P-value found after Chi-square test using Yates’ correction was 0.548 which is statistically significant.

Mean Hb%, total leukocyte count, neutrophil %, lymphocyte%, platelet count, random blood sugar among severe stroke and non-severe stroke groups were compared as shown in the table below, but none had shown statistically significant correlation.

Mean CRP in the study population was 46.64 ± 24.56 mg/dL, in non-severe group it was 35.9 ± 13.95 mg/dL, compared to 86 ± 8.5 mg/dL in severe group which is statistically significant correlation (P-value <0.05).

Mean serum LDH in the study population was 823 ± 422 IU/mL, in non-severe group it was 622 ± 158 IU/mL, compared to 1562 ± 148 IU/mL in severe group which is statistically significant correlation (P-value <0.05).

Mean serum ferritin in the study population was 436 ± 46 mg/dL, in non-severe group it was 323 ± 159 mg/dL, compared to 853 ± 88 mg/dL in severe group which is statistically significant correlation (P-value <0.05).

Mean D-dimer in the study population was 4.33 ± 3.49 mg/dL, in non-severe group it was 2.9 ± 1.6 mg/dL compared to 9.6 ± 3.4 mg/dL in severe group which is statistically significant correlation (P-value <0.05).

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<td>Non-severe stroke</td>
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<td>Age</td>
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<tr>
<td>females 10(45%)</td>
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<td>SBP</td>
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<td>Mean Hb%</td>
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HRCT thorax was done for all patients. 4 were having mild lung injury (14%), 8 were having moderate lung injury (28%). Only 5 were severe lung injury (18%) and all of them were having an ischemic stroke.

11 patients were normal chest imaging (40%). All types of cerebrovascular accidents seen in these patients and 90% developed neurological symptoms within first week of illness.

23 patients (82%) were having non-severe Covid-19 and 5 were (18%) having severe Covid-19. Severity of lung injury when compared with severity of stroke using Chi-square test with Yate’s correction as shown in the table below co-relation was not statistically significant (P=0.37).

Table 4

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<tr>
<th>Stroke severity</th>
<th>Lung injury</th>
<th>Total</th>
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<tr>
<td></td>
<td>Non-severe</td>
<td>Severe</td>
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<tr>
<td>Non-severe</td>
<td>16(72.7%)</td>
<td>6(27.2%)</td>
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<tr>
<td>Severe</td>
<td>6(100%)</td>
<td>0(0%)</td>
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<tr>
<td>total</td>
<td>22</td>
<td>6</td>
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DISCUSSION

COVID-19 is a novel respiratory disease caused by SARS-CoV-2, which has become the biggest health concern worldwide. COVID-19 may accompany a wide range of signs and symptoms including fever, cough, rhinorrhea, chest pain, diarrhea, vomiting, nausea, confusion, etc. Whereas, some patients may be asymptomatic. The diagnosis of COVID-19 is made through suspicious clinical symptoms and imaging.[7] In this regard, some clinical and laboratory manifestations of the COVID-19 may be uncommon or neglectable, leading to the misdiagnosis and spread to others. Based on conducted studies, more than one-third of COVID-19 patients present neurological symptoms during the course of the disease. Even in some patients, neurologic symptoms may be the initial or only presentations of the COVID-19. Additionally, the prevalence of neurological signs and symptoms is higher in patients with severe COVID-19 infection.[8]

The reported neurological sign and symptoms of COVID-19 include headache, dizziness, confusion, acute cerebrovascular disease, epilepsy, ataxia, anosmia, ageusia, and muscle pain demyelinating encephalomyelitis.[9] In this regard, CVDs are not only one of the main comorbidities of COVID-19 patients, but also individuals with risk factors may experience CVDs in the context of COVID-19 pathophysiology. The hyperactivation of inflammatory factors disrupts the coagulation system leading to D-dimer and platelet abnormalities,[10] which spikes the risk of CVDs. Furthermore, administration of anticoagulants is showed to decrease the mortality rate of hospitalized patients.[11]

Anosmia and ageusia are known to be a common PNS manifestation of COVID-19 especially in those assumed to be asymptomatic.[12] Some individuals with anosmia later develop respiratory symptoms while others remain asymptomatic. In this regard, these symptoms should raise the suspicion of COVID-19 diagnosis even in the absence of other typical symptoms in the current pandemic.[12] Anosmia and ageusia may be associated with the increased ACE-2 receptors expressed in nasal mucosa and tongue.[13] Whether anosmia and ageusia are the results of nerve injuries or inflammation of the olfactory nerves is still disputable. Since brain stem involvement has been reported previously in patients and animal models of severe acute respiratory syndrome coronavirus (SARS-CoV) infection, some researchers believe that peripheral trigeminal or olfactory nerves are pathways for coronaviruses to enter the CNS. However, further studies are required.[14]

Patients with severe CNS involvement present with lower lymphocytes and platelets counts beside higher blood urea nitrogen levels, while laboratory findings may not be helpful in patients with PNS involvement or individuals with non-severe CNS involvement.[15]

This study represents a retrospective cross sectional study at single large centre representing the population of Malnad region. Even though majority Covid-19 patients were presenting with fever, sore throat, coryza, cough, shortness of breath suggesting respiratory illness we observed different neurological manifestations in these patients appearing either during Covid-19 illness (60%) or found to be incidentally Covid-19 positive when they are admitted for neuro-illness (40%) which was comparable to earlier studies.[24-25]

Different forms neurological features are seen in Covid-19 patients either involving central nervous system or peripheral nervous system. Ischemic stroke was the most common form which was comparable to earlier studies Rajesh Benny et al. (25), conducted at Mumbai a multi-centre study and a case series Ling Mao et al., conducted at Wuhan, China (24), followed by Cortical vein thrombosis (CVT), Intra Cerebral Hemorrhage, sub-arachnoid hemorrhage and Bell’s palsy in descending order of percentage. Those having hemorrhage were having normal clotting profile and didn’t received anti-coagulation prior to event.

We grouped study population into severe and non-severe group to compare the demographic characters, co-morbid condition, hypoxic status, laboratory parameters and severity of lung injury. 21% of patients had severe neurodeficit, majority among them were having ischemic stroke. There was no statistically significant co-relation when age, sex, blood pressure, co-morbid conditions and hypoxic level was compared between these 2 groups. Hence, Covid-19 can be an independent risk factor for stroke and majority had neuro illness during first week of Covid-19.

But, when serum Covid-19 bio-markers like ferritin, lactate dehydrogenase, C-reactive protein and D-
dimer levels compared between the 2 groups, severe group were having significantly raised levels. This could be due to pro-coagulant nature of the disease leading to arterial or venous thrombosis. Majority of them were having moderate lung injury, but none of them were having severe Covid-19. This suggests that ‘Covid-19 with severe respiratory illness can lead to severe stroke but severe stroke need not have severe lung injury’.

‘Stroke in young’ in our study was 21% compared to 8.8% in general population and all were having ischemic stroke, this large difference could be due to thrombotic nature of the primary illness and suggests to consider it as independent risk factor for stroke(25).

CVT and Covid-19
Both youngers and olderers were equally affected, also males and females are equally affected they presented with seizures and hypoxia was not there in any patient. All were having normal chest imaging suggesting purely thrombotic pathophysiology in these patients this was comparable to earlier studies(25). Superior sagittal sinus was commonly involved in all patients.

ICH and Covid-19
All those who had hemorrhage were older and all were males with high diastolic blood pressure and majority were having only neurological illness and were not having hypoxia.

Though the mechanisms leading to ICH with COVID-19 are evolving, two the-ories are proposed. Firstly, there may be a direct [22] and indirect endothelium dysfunction (by way of inflammatory and thrombotic re-sponses). Secondly, there may be COVID-19 induced disruption of the renin angiotensin system [23] leading to loss of cerebral blood flow autoregulation and ICH. Because of only each case of SAH and Bell’s palsy we can’t draw any conclusion.

40% of the study population were having normal lungs. 40% were having mild to moderate lung injury and 20% were having severe lung injury. Ischemic stroke was very common in severe respiratory illness. Most of the Ischemic stroke patients were showing some concurrent pulmonary involvement unlike CVT and ICH patients.

In Covid-19 treatment protocol, anti-coagulation was given to all patients having hypoxia or moderate to severe lung injury in chest imaging. 40% of our study population were not receiving anti-coagulation in view of mild nature of illness, but they subsequently developed infarct and some developed CVT. When we looked into their laboratory reports, D-dimer was elevated along with other biomarkers. This further strengthens the pro-thrombotic pathophysiology of the primary disease and to consider prophylactic anti-coagulation in Covid-19 patients when their serum D-dimer is elevated even though they are having mild illness. Contrary to this, many patients with moderate to severe Covid-19 in our study who were already receiving anti-coagulation, but yet developed ischemic stroke suggests the possibility of severe inflammatory nature of the disease that can damage vascular endothelium (22).

Various mechanisms are proposed for explaining the possible CNS involvement of the SARS-COV-2 including direct invasion of the virus via disruption of BBB through release of cytokines and retro- or anterograde neuronal transport via dynein and kinesins’ proteins. [16] In addition, possible nerves injuries may also be mediated by the immune system, hypoxia resulted by pneumonia, and/or through attaching to ACE2 receptors. [17] These receptors are known to be expressed in different organs including CNS, lungs, arteries, heart, kidney, and intestines. ACE2 receptors regulate blood pressure and according to the studies, SARS-CoV-2 spike protein could interact with ACE2 receptors, leading to elevated blood pressure and increase the risk of cerebral haemorrhage. [18] With similar mechanism, SARS-COV-2 binding with ACE2 receptors of capillary endothelium may disrupt the BBB and enter the CNS. In a study, Steardo et al. indicated that coronaviruses infect brain stem neurons, which are responsible for the cardio-respiratory regulation, resulting in the respiratory failure and hypoxia. [19] It seems that on one hand, SARS-COV-2 leads to both pneumonia and impairment of brain stem cardio-respiratory regulation center, which both leads to hypoxia. On the other hand, hypoxia may exacerbate the neural damage leading to a deadly vicious cycle. [20] This supports the higher prevalence of neurological symptoms in severely ill patients. Considering the lack of evidences and the importance of possible CNS roles in the COVID-19 pathophysiology, further studies are encouraged. [21]

Limitations of the study
The retrospective nature of the study, overwhelming patient burden, highly contagious nature of COVID-19 and risk of nosocomial spread limited the data collection. Because of very small sample size and study conducted at single centre we can’t draw the conclusions to the general population.

Ancillary tests for risk factor evaluation like 2D-ECHO, arterial and venous colour Doppler was not done for all patients. 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. We couldn’t also follow up the patient to look for the outcome.
CONCLUSION

Both central and peripheral nervous system involvement can be seen in Covid-19 patients. Ischemic stroke is the commonest form of involvement. Covid-19 patients with severe lung injury had severe neuro-deficit, however neurological manifestations can be independent of respiratory illness. Biological markers of Covid-19 can also be used as prognostic indicators for neurodeficit. Prophylactic anti-coagulation could have prevented the thrombotic diseases in Covid-19 patients with mild symptoms.

REFERENCES