Ref: Ro J Neurol. 2022;21(2)
DOI: 10.37897/RJN.2022.2.14

# Spectrum of neurological manifestations among acute COVID-19 and long COVID-19 – A retrospective observational study

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## ABSTRACT

**Objective.** Preliminary clinical data indicate that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with neurological symptoms. To compare the clinical features, imaging and treatments in patients with and without COVID-19. To compare the mortality and in-hospital stay among patients with and without COVID-19 and negative patients.

**Materials and methods.** In this retrospective, single-center study, we included all the patients who attended the department of neurology with neurologic symptoms with confirmed COVID-19 and long COVID-19 from June 2020 to January 2021. Data on clinical signs, diagnosis, laboratory findings were collected and analyzed from the records for positive patients and compared with neurologic patients without COVID-19 admitted in the same period.

Statistical analysis: The mean values between study groups were compared using an independent sample t-test and Mann Whitney u test. Categorical outcomes were compared using the Chi square test. Data was analyzed using coGuide software.

**Results.** Headache was the common neurologic manifestation present in COVID positive patients compared to COVID negative patients (39.13%). There was no statistically significant difference between the two groups in baseline parameters. Laboratory parameters like CRP, Serum Ferritin, LDH, D-dimer, ESR, and IL-6 showed a significant increase in COVID positive patients ($P < 0.05$). In-hospital mortality was more in COVID positive patients than COVID negative patients ($P < 0.011$).

**Conclusion.** The study showed varied neurologic symptoms in COVID patients, with headache as the common symptom. Hospital stay, morbidity, mortality, and inflammatory parameters were more in COVID positive patients compared to COVID negative patients.

**Keywords:** COVID-19, encephalopathy, headache, pandemics, seizures

**Abbreviations**
AKI – Acute Kidney Injury
ARDS – Acute Respiratory Distress Syndrome
CNS – Central Nervous System, CoV - coronaviruses
COVID-19 – Coronavirus disease 2019
GBS – Guillain-Barre´ syndrome
MV – mechanical ventilation
SARS-CoV-1 – Severe Acute Respiratory Syndrome
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
RT-PCR – Reverse-Transcriptase Polymerase Chain Reaction

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and caused human coronavirus disease 2019 (COVID-19), which has now spread into a worldwide pandemic [1]. There are diverse clinical manifestations of COVID-19 in humans which can affect various organs/systems with varying degrees of severity. The

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*Article history:*
Received: 23 May 2022
Accepted: 3 June 2022

manifestations range from asymptomatic or mild symptoms like fever, headache, myalgia, sore throat, anosmia to the more severe and life-threatening complications like pneumonia, Acute Respiratory Distress Syndrome (ARDS), myocarditis, Acute Kidney Injury (AKI), stroke, encephalitis, multi-organ failure, and even death [2,3].

Even though severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system, there is growing evidence of neurological presentations/complications in patients with COVID-19 [4]. These neurological manifestations include encephalopathy, meningoencephalitis, ischemic stroke, acute necrotizing encephalopathy, and Guillain-Barre syndrome (GBS). Radiological series have shown infarcts, microhemorrhages, features of posterior reversible encephalopathy syndrome, or nerve root enhancement [5]. Two similar human coronaviruses (CoV), Severe Acute Respiratory Syndrome (SARS-CoV-1) in 2002 and the Middle East Respiratory Syndrome (MERS-CoV) in 2012, have established that coronaviruses can directly affect the nervous system due to their neurotropic and neuroinvasive potential. Coronaviruses enter the central nervous system (CNS) using a hematogenous pathway or through the olfactory bulb or peripheral nerves. They can also cause neurological symptoms indirectly through the activation of cytokine cascade and immune-mediated mechanisms [6,7].

In a case series by Mao et al., out of 214 patients, one-third had neurological symptoms, including stroke, encephalopathy, and myopathy [8]. In a French case series of 58 COVID-19 patients, it was observed that one-third of the patients had neuropsychiatric manifestations at the time of discharge [9]. Other smaller studies have reported possible hypercoagulable states resulting in strokes in COVID-19 patients [10].

However, to our knowledge, the literature on neurologic manifestations in COVID-19 patients is scarce, especially in an Indian setting. Also, mild complaints and sub-clinical findings are not uncommon, which might indicate that neurological manifestations are common and also may be underdiagnosed. Hence, the present study intends to evaluate the spectrum of neurological manifestations in COVID-19 patients who reported to the Department of Neurology. The objectives were to assess the neurologic symptoms of COVID-19 patients attending the Neurology department. And to compare the presenting symptoms, laboratory parameters, length of hospital stay, and treatment between COVID positive and COVID negative patients.

## MATERIALS AND METHODS

### Study population and Study site

COVID positive and negative patients with neurologic symptoms who attended the Department of Neurology in a tertiary care hospital.

### Study duration

Eight months, from June 2020 to January 2021.

### Inclusion Criteria

Patients who were having neurologic symptoms with COVID-19 positive results by means of real-time reverse-transcriptase polymerase chain reaction testing (RT-PCR) for SARS-CoV-2/ CT chest score.

Non-COVID-19 patients with neurologic symptoms admitted in the same period were taken as a comparator group.

### Exclusion criteria

Patients below 18 years were excluded.

### Study design

Retrospective study

### Sample size and sampling method

All 69 patients fulfilling the study criteria and all 66 patients fulfilling the criteria for the comparator group who attended the Department of Neurology during the study period were selected by convenient sampling

### Ethical considerations

The study was approved by the institutional review board and the ethics committee of the hospital and data confidentiality was maintained.

### Data collection tool

Demographic, clinical, laboratory, imaging, and treatment details were extracted from both printed and electronic medical records with standardized anonymized data collection forms. All data were imputed and checked by three neurologists for both COVID-19 positive and negative patients.

### Demographic data

The age and gender of both groups were recorded.

### Clinical features

Clinical symptoms, diagnosis, comorbidities, and the symptoms while presenting to the hospital (neurological or non-neurological) were de-identified and recorded.

### Laboratory investigations, imaging, and treatment

The laboratory tests and imaging available for both groups such as CRP (mg/L), Serum ferritin (ng/ml), LDH (IU/L), D-dimer (mg/ml), ESR (mm/hr), IL-6 (pg/ml), CT brain, MRI brain, NCS, EEG, LP-CSF, MRI

spine were collected. Details of the imaging and treatment data were also recorded for both groups.

### Modified Rankin score (mRS) [11]

Numerous studies demonstrated the construct validity of the mRS to be moderate to strong [12]. Modified Rankin scores at admission and discharge were analyzed.

### Statistical methods

Clinical symptoms, investigation reports, imaging, CT Chest, treatment, comorbidity, hospital stay, and mRS score at admission and discharge were considered as primary outcome variables. Group-I (COVID positive and post-COVID) vs. Group-II (COVID negative) was considered as a primary explanatory variable. For normally distributed quantitative parameters, the mean values were compared between study groups using an independent sample t-test (2 groups). For non-normally-distributed quantitative parameters, medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). Categorical outcomes were compared between study groups using the Chi square test. P value <0.05 was considered statistically significant. Data was analyzed using coGuide software, V.1.0 [13].

## RESULTS

A total of 135 subjects were included in the final analysis.

There was no statistically significant difference between the two groups in demographic parameters like age (in years), gender (p >0.05). The RT PCR was positive for 66 (96.65%) participants. Headache was reported more in COVID positive patients 27 (39.13%) than in non-COVID patients 17 (25.76%). The seizure was reported in 4 (5.8%) patients in group-I and 12 (18.18%) patients in group-II, and ischemic stroke reported in 11 (15.94%) patients in group-I and 12 (18.18%) patients in group-II. In COVID positive group, the majority 44 (63.77%) of the patients' primary symptom to seek medical care was neurological. (Table 1)

The mean/median of inflammatory parameter investigations was higher in COVID positive group as compared to COVID negative group for CRP (5mg/L), serum ferritin (21.8-274.66ng/ml), LDH (180-360IU/L), D-dimer (0-0.5mg/ml), ESR (1-19mm/hr) and IL-6 (0-7pg/ml). There was a statistically significant difference between the study groups with an increase in all laboratory parameters in COVID positive group (p-value <0.05). The common imaging done was MRI brain. The CT Chest showed mild abnormality for the majority of the patients, 56 (81.16%) in the COVID positive group, while it was normal for all 66 (100%) patients in COVID negative group (Table 2).

More number of COVID positive patients required analgesics (39.13%), steroids (68.12%), antibiotics (28.99%), oxygen (26.09%), vitamins (55.07%) and antiplatelets (17.39%) than the COVID negative group (analgesics (27.27%), steroids (19.7%), antibiotics (4.55%), oxygen (10.61%), vitamins (37.88%), antiplatelets (18.18%). There was no statistically significant difference in treatment with analgesics, anticoagulants, and antiplatelets between the groups (p-value>0.05) except for steroids, antibiotics, oxygen, and vitamins (p-value<0.05) (Table 3).

**TABLE 1.** Comparison of baseline parameter between study group (N=135)

| Parameter | Study group | | P value |
|---|---|---|---|
| | Group I (post COVID + COVID +ve) (N=69) | Group II (COVID -ve) (N=66) | |
| Age in years | 51.71 ± 15.9 | 46.33 ± 18.17 | 0.069* |
| **Gender** | | | |
| Male | 37 (53.62%) | 45 (68.18%) | 0.083† |
| Female | 32 (46.38%) | 21 (31.82%) | |
| **RT PCR** | | | |
| Positive | 66 (95.65%) | 0 (0%) | ‡ |
| Negative | 3 (4.35%) | 66 (100%) | |
| **Symptoms** | | | |
| Headache | 27 (39.13%) | 17 (25.76%) | ‡ |
| Seizure | 4 (5.8%) | 12 (18.18%) | |
| Ischemic Stroke | 11 (15.94%) | 12 (18.18%) | |
| Haemorrhagic Stroke | 4 (5.8%) | 1 (1.52%) | |
| Vestibulopathy | 5 (7.25%) | 3 (4.55%) | |
| Brain fog | 3 (4.35%) | 3 (4.55%) | |
| Cranial Neuropathy | 3 (4.35%) | 2 (3.03%) | |
| Peripheral Neuropathy | 3 (4.35%) | 0 (0%) | |
| GBS | 2 (2.9%) | 1 (1.52%) | |
| Neuromuscular disorder | 2 (2.9%) | 8 (12.12%) | |
| Encephalopathy | 3 (4.35%) | 3 (4.55%) | |
| Myelopathy | 0 (0%) | 3 (4.55%) | |
| Neuro Infection | 2 (2.9%) | 0 (0%) | |
| Movement Disorder | 1 (1.45%) | 0 (0%) | |
| **Onset** | | | |
| Primary Presentation Neurological | 25 (36.23%) | 66 (100%) | ‡ |
| Primary Presentation Non-Neurological | 44 (63.77%) | 0 (0%) | |

** - Independent sample t test, ‡ - No statistical test was applied - due to 0 subjects in the cells † Chi-square test*

**TABLE 2.** Comparison of investigations and imaging between study group (N=135)

| Parameter | Study group | | P value |
|---|---|---|---|
| | Group I (Post COVID + COVID +ve) (N=69) | Group II (COVID -ve) (N=66) | |
| **Investigations** | | | |
| CRP (<5mg/L) | 21.23 ± 16.58 | 2.53 ± 1.57 | <0.001* |
| Serum Ferritin (21. 8-274.66 ng/ml) | 405.25 ± 133.46 | 139.57 ± 87.8 | <0.001* |
| LDH (180-360 IU/L) **(N=125)** | 339.51 ± 106.18 | 284.48 ± 88.51 | 0.002* |
| D-dimer (0-0.5 mg/ml) (**N=123)** | 0.96 (0.64,2.45) | 0.32 (0.16,0.42) | <0.001§ |
| ESR(1-19 mm/hr) **(N=135)** | 25 (21,32) | 4 (2,11.25) | <0.001§ |
| IL-6 (0-7pg/ml) **(N=21)** | 8.6 (7.9,11.05) | 2.95 (2.13,6.55) | 0.004 § |
| **Imaging** | | | |
| CT brain | 20 (28.99%) | 10 (15.15%) | 0.053† |
| MRI brain | 43 (62.32%) | 54 (81.82%) | 0.012† |
| NCS | 8 (11.59%) | 5 (7.58%) | ‡ |
| EEG | 4 (5.8%) | 18 (27.27%) | ‡ |
| LP-CSF | 8 (11.59%) | 14 (21.21%) | ‡ |
| MRI spine | 1 (1.45%) | 1 (1.52%) | ‡ |
| **CT Chest** | | | |
| Mild | 56 (81.16%) | 0 (0%) | ‡ |
| Moderate | 12 (17.39%) | 0 (0%) | |
| Severe | 1 (1.45%) | 0 (0%) | |
| Normal | 0 (0%) | 66 (100%) | |

**-Independent sample t test, † Chi-square test, §-Mann Whitney U test, ‡-No statistical test was applied- due to 0 subjects in the cells*

**TABLE 3.** Comparison of treatment between study group (N=135)

| Treatment | Study group | | P value |
|---|---|---|---|
| | Group I (Post COVID + COVID +ve) (N=69) | Group II (COVID -ve) (N=66) | |
| Analgesics | 27 (39.13%) | 18 (27.27%) | 0.144† |
| Anti-inflammatory | 10 (14.49%) | 0 (0%) | ‡ |
| Steroids | 47 (68.12%) | 13 (19.7%) | <0.001† |
| Antibiotics | 20 (28.99%) | 3 (4.55%) | <0.001† |
| Antivirals | 11 (15.94%) | 0 (0%) | ‡ |
| Immunomodulators | 1 (1.45%) | 0 (0%) | ‡ |
| Oxygen | 18 (26.09%) | 7 (10.61%) | 0.021† |
| Vitamins | 38 (55.07%) | 25 (37.88%) | 0.045† |
| Anticoagulants | 11 (15.94%) | 12 (18.18%) | 0.729† |
| Antiplatelet | 12 (17.39%) | 12 (18.18%) | 0.904† |
| AED | 6 (8.7%) | 12 (18.18%) | 0.105† |
| H1 agonist | 4 (5.8%) | 3 (4.55%) | 1.000* |
| IVIG | 2 (2.9%) | 1 (1.52%) | 1.000* |
| Anticholinesterase | 4 (5.8%) | 4 (6.06%) | 1.000* |
| Antiedema | 4 (5.8%) | 0 (0%) | ‡ |
| Dopa depletes | 1 (1.45%) | 0 (0%) | ‡ |

**-Fisher exact test, † Chi-square test, ‡No statistical test was applied- due to 0 subjects in the cells*

There was statistically no significant difference between study groups in comorbidity like diabetic mellitus, hypertension, CKD, and alcohol. There was a statistically significant difference between the two groups in comorbidity like dyslipidemia, IHD, and smoking. The difference in hospital mortality between the study groups was found to be significant with a p-value of 0.011, where the majority of 11 (15.94%) patients were in the COVID positive group. There was the minimum difference between study groups in length of stay in hospital (days), where it was statistically not significant (P> 0.05). The differ-

**TABLE 4.** Comparison of comorbidity and other parameter between study group (N=135)

| Parameter | Study group | | P value |
|---|---|---|---|
| | Group I (Post COVID + COVID +ve) (N=69) | Group II (COVID -ve) (N=66) | |
| **Comorbidities** | | | |
| Diabetic mellitus | 19 (27.54%) | 19 (28.79%) | 0.872† |
| Hypertension | 26 (37.68%) | 24 (36.36%) | 0.874† |
| Dyslipidaemia | 12 (17.39%) | 25 (37.88%) | 0.008† |
| IHD | 5 (7.25%) | 16 (24.24%) | 0.006† |
| CKD | 6 (8.7%) | 6 (9.09%) | 0.936† |
| Alcohol | 5 (7.25%) | 5 (7.58%) | 1.000* |
| Smoking | 19 (27.54%) | 2 (3.03%) | <0.001† |
| Others | 4 (5.8%) | 0 (0%) | ‡ |
| **In hospital Mortality** | 11 (15.94%) | 2 (3.03%) | 0.011† |
| **Length of stay in hospital (days) (N=132)** | 3 (1,11) | 4 (1,6) | 0.184§ |
| **MRS Score at admission (N=129)** | | | |
| No Symptoms at all | 16 (24.62%) | 16 (25%) | ‡ |
| No Significant Disability Despite Symptoms | 19 (29.23%) | 7 (10.94%) | |
| Slight Disability | 0 (0%) | 2 (3.13%) | |
| Moderate Disability | 4 (6.15%) | 12 (18.75%) | |
| Moderately Severe Disability | 17 (26.15%) | 25 (39.06%) | |
| Severe Disability | 9 (13.85%) | 2 (3.13%) | |
| **MRS score at discharge (N=125)** | | | |
| No Symptoms at all | 36 (59.02%) | 29 (45.31%) | <0.001† |
| No Significant Disability Despite Symptoms | 4 (6.56%) | 16 (25%) | |
| Slight Disability | 3 (4.92%) | 13 (20.31%) | |
| Moderate Disability | 8 (13.11%) | 5 (7.81%) | |
| Moderately Severe Disability | 10 (16.39%) | 1 (1.56%) | |

*‡ -No statistical test was applied- due to 0 subjects in the cells, † Chi-square test, *-Fisher exact test, §-Mann Whitney U test*

ence in mRS (Modified Rankin Score) score at discharge between the study groups was found to be significant with a p-value of <0.001 (Table 4).

Among the people with stroke and brain fog, there was a statistically significant difference between the two groups in length of hospital stay (p value <0.05). Among the people with encephalopathy, there was a difference between the two groups in length of hospital stay but not statistically reporting significance (p value <0.05) (Table 5).

## DISCUSSION

In this study, out of 135 subjects, 69 were COVID-19 positive patients with neurological manifestations related to COVID-19. Headache was the common complaint followed by stroke. Patients with COVID-19 had significant differences in laboratory values, including acute-phase proteins and ESR. The in-hospital mortality rate was more in COVID-positive patients.

Headaches are the most common neurological symptom in both the groups in our study and were slightly higher in the COVID group (39.13%). Headache might be precipitated by hypoxia and decreased cerebral blood flow in COVID patients [14]. A recent case series by Gupta N et al. also reported headache as the major complaint along with fever, cough, sore throat, and breathlessness [15]. The prevalence varies in different reports but can affect

**TABLE 5.** Comparison of length of stay in hospital between the study groups

| Length of stay in hospital (days) | Study Group | | Mann Whitney U test (P value) |
|---|---|---|---|
| | Group I (Post COVID + COVID +ve) Median (IQR) | Group II (COVID -ve) Median (IQR) | |
| Among stroke cases (N=28) | 12 (11,13) | 8 (5,9) | <0.001 |
| Among brain fog cases (N=6) | 10 (10,11) | 5 (5,5) | 0.034 |
| Among encephalopathy cases (N=6) | 13 (12,14) | 5 (4,7) | 0.050 |

up to one-third of diagnosed patients. The pathophysiological connection of headache with COVID-19 is not much known, even though it is a well-described manifestation of meningitis, encephalitis, vasculitis, and intracranial hypertension [16,17].

Many studies have reported a significant increase in stroke rates in patients with COVID-19 [18–20]. However, in this study, the occurrence of stroke rate was almost similar in both groups. American Heart Association/American Stroke Association Stroke Council Leadership has stated that the different processes for stroke mechanisms in COVID-19 could include the release of pro-inflammatory cytokines with a direct effect on plaque rupture through local inflammation and activation of coagulation factors or cardioembolism from virus-related cardiac injury [20].

In the present study, d-dimer and the inflammatory indices such as C-reactive protein and erythrocyte sedimentation rate showed an increase in the COVID group. This marker profile is consistent with the findings in disseminated intravascular coagulation and may play an important role in the incidence of stroke and severity in COVID patients [21]. Abnormal coagulation parameters have also been shown to be associated with poor prognosis in patients with COVID-19 associated pneumonia [22].

There was a slight elevation in LDH in COVID patients in this study. Muscle enzymes like creatine kinase and lactate dehydrogenase (LDH) are seen to be highly elevated in symptomatic patients and confirm muscle membrane damage. The exact mechanism of muscle damage is not known. Possibilities include viral invasion of muscle through ACE-2 receptor tropism and immune-mediated damage of muscle fibers [8].

Treatments were different in both groups, with wider use of steroids followed by vitamins, analgesics, antibiotics, and oxygen therapy in the COVID-19 group, in this study. Similarly, in Mahammedi A et al. [23] the study, steroids were used by the majority of the COVID patients, while in a study by Benussi A et al., high-flow oxygenation was commonly used in the COVID-19 group [18].

Although significant differences were not observed for comorbid conditions between the groups, hypertension was the most common comorbid condition found in the COVID group, followed by diabetes and smoking habits in this study. Similar findings were observed in Benussi A et al. study [18] Studies by many authors on COVID-19 patients reported hypertension as the major comorbidity [23,24]. Modified Rankin Scores(mRS) at discharge were higher in the COVID group in the study by Benussi A et al. [18]. The in-hospital mortality rate was higher for the COVID group, similar to Benussi A et al. study [18].

## LIMITATIONS

Our study has several limitations. Only 69 patients with confirmed COVID-19 were included in the present analysis, and a large, multi-center study is warranted to verify the neurological manifestations of COVID-19. Some of the critically ill patients in our ICU were receiving intensive sedation because of invasive MV (mechanical ventilation), which may have resulted in underestimation of the incidence of neurological complications. All data were obtained from the electronic medical records; certain patients with neurologic symptoms might not be included if their neurologic manifestations were too mild.

## CONCLUSION

This study result showed a varied neurologic spectrum in COVID-19 patients, among which headache was the most common neurologic symptom. In the COVID-19 group, the length of hospital stay, inflammatory markers, morbidity, and mortality were found to be more. So during this COVID-19 pandemic, SARS-CoV-2 infection must be considered as a differential diagnosis for patients with neurologic manifestations to avoid misdiagnosis or delay in diagnosis and prevent transmission. Special attention should be given to the treatment modalities as it varies in COVID-19 patients.

**Ethical considerations**

The study was approved by the institutional review board and the ethics committee of the hospital and data confidentiality was maintained.

**Acknowledgments**

We acknowledge the technical support in data entry, analysis, and manuscript editing by “Evidencian Research Associates.”

*Conflict of interest:* none declared
*Financial support:* none declared

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