ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 12, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

CLINICAL PROFILE OF NEUROLOGICAL MANIFESTATIONS OF COVID-19 DURING HOSPITAL STAY: A CROSS-SECTIONAL STUDY

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Received: 08 October 2024, Revised and Accepted: 21 November 2024

ABSTRACT

Objective: Since its emergence, coronavirus disease-19 (COVID-19), caused by syndrome coronavirus type 2 (SARS-CoV-2), has shown diverse neurological manifestations, including central nervous system (CNS) complications such as strokes, encephalitis, and delirium. In addition, peripheral nervous system conditions such as Guillain–Barré syndrome, and musculoskeletal issues such as myalgia and rhabdomyolysis are also reported in cases of COVID-19. These are linked to direct viral invasion, hypercoagulability, and immune-mediated injury. Our study during the pandemic systematically evaluated these neurological impacts to understand and address long-term morbidity.

Methods: This cross-sectional observational study at a dedicated COVID-19 center in Mumbai evaluated 200 SARS-CoV-2-positive patients for neurological manifestations. Patients were categorized into "Neuro first" and "COVID first" groups based on symptom onset. Comprehensive neurological assessments, laboratory tests, and imaging were conducted. Data were analyzed using SPSS with statistical tests to compare groups, and logistic regression identified factors linked to neurological involvement.

Results: Out of 200 COVID-19 patients, neurological manifestations were seen in 47.5%, with significantly higher proportions in severe cases (Stage IIB/III). Common findings included asymptomatic elevated creatine phosphokinase (CPK) (29.4%), headache (18.9%), stroke (15.8%), dysgeusia (14.7%), and anosmia (10.5%). Neurological involvement was 11.6 times higher in severe cases and significantly associated with lower PaO_2 and elevated CPK levels. Severe CNS complications, such as large vessel occlusion strokes and encephalitis, were exclusive to higher disease severity. Mortality was 7.5% overall, with no significant difference between those with and without neurological symptoms.

Conclusion: Neurological manifestations such as stroke, headache, and dysgeusia were common in COVID-19 patients. There was a significant correlation between neurological manifestations and disease severity as well as elevated CPK levels.

Keywords: COVID-19, Neurological manifestations, Delirium, Stroke.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i12.53450. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has spread worldwide. COVID-19 was declared as a pandemic by World Health Organization (WHO) on March 11, 2020 [1]. The most commonly reported symptoms of COVID-19 include fever, cough, dyspnea, myalgia, fatigue, sputum production, sore throat, diarrhea, and headache, with a majority of the population having a mild or uncomplicated course. Other serious complications, including respiratory failure, septic shock, and/or multi-organ involvement, are seen in increasing numbers [2].

Neurotropism is one common feature of previously described pathogenic coronavirus types such as severe acute respiratory syndrome coronavirus (2002) and Middle East respiratory syndrome coronavirus (2012) [3]. It has been suggested that SARS-CoV-2 could reach the CNS via circulation or upper nasal transcribial routes. Endothelium, glial cells, and neurons have been reported to express angiotensin-converting enzyme receptor 2, which makes them a potential target of SARS-CoV-2 since the virus enters the cells through this receptor [4].

There is a diverse range of neurological manifestations associated with COVID-19, which can be broadly classified into central nervous system (CNS), peripheral nervous system (PNS), and musculoskeletal complications. CNS manifestations include cerebrovascular events such as ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis [5]. The other uncommon neurological manifestations include inflammatory conditions such as acute disseminated encephalomyelitis and meningoencephalitis. Delirium and agitation have also been frequently observed in critically ill patients, particularly in the setting of hypoxia or systemic inflammation [6]. PNS involvement includes Guillain–Barré syndrome and its variants, with features such as areflexic paralysis and sensory deficits. Myalgias and rhabdomyolysis have been reported as musculoskeletal complications often correlated with elevated creatine kinase (CK) levels. [7] The pathophysiology behind these manifestations is complex and may involve direct viral invasion, hypercoagulability, immune-mediated injury, and cytokine storm [8]. This evolving spectrum of neurological involvement underscores the need for vigilant clinical evaluation and timely intervention to mitigate long-term morbidity [9].

In our study, during the pandemic, we have systematically evaluated and investigated the patients for evidence of this new emergent virus and its associated neurological manifestations.

METHODS

A cross-sectional, noninterventional, observational study was conducted at Topiwala National Medical College and B.Y.L Nair Hospital-A tertiary care center in Mumbai. Our hospital was converted to dedicated COVID center for stage II and stage III (WHO staging of severity of COVID infection) [10] severity patients. The study was conducted in the Department of Neurology for 3 weeks. Two hundred

consecutive adult patients admitted to COVID wards of Nair Hospital were detected as SARS-CoV-2 positive by polymerase chain reaction (PCR). The real-time reverse-transcription polymerase chain reaction assay using a SARS-CoV-2 102 nucleic acid was done from oral and nasopharyngeal samples in all patients. Informed consent was obtained verbally or telephonically; if the patient was incapable of giving consent, physical informed. Patients/relatives not consenting and patients with pre-existing neurological illness were excluded. All patients in the study, vital signs were obtained. COVID-positive patients examined by investigator/faculty/resident for acute recent neurological involvement suggested in the questionnaire –headache, loss of taste/smell, weakness, giddiness, vertigo, hemiplegia, altered sensorium, and new-onset seizures. The investigator, faculty, and residents were in full personal protective equipment and followed strict Indian Council of Medical Research guidelines to prevent the transmission of infections. Laboratory tests, including complete blood cell count with differential, liver and renal function assessment, C-reactive protein, ferritin level, CK, D-Dimer, and lactate dehydrogenase were done. Brain CT, electroencephalography, nerve conduction study, and CSF analysis investigations were performed according to the neurological symptoms in need. High-resolution thorax computed tomography (HRCT) and laboratory findings (Interleukin-6 [IL-6], D-dimer, and CK) of all patients were evaluated.

Our study group with neurologic manifestations categorized into nonspecific symptoms (headache, dizziness, and myalgia), neuropsychiatric disorders (insomnia, depression, anxiety, and psychosis), CNS disorders (direct viral infection, disorders of consciousness, seizures, and stroke), PNS disorders (cranial neuropathies, anosmia/dysgeusia, and peripheral neuropathy), myopathy, and demyelinating events. The severity of COVID-19 was defined by the WHO guidelines for community-acquired pneumonia into stages I, IIA, IIB, and III based on the severity of respiratory involvement [10]. Patients were then categorized into two groups: "Neuro first," with neurological manifestations on initial assessment, and "COVID first," who developed neurological symptoms >24 h after COVID-19 infection.

The data were analyzed using SPSS version 23.0 version. $p<0.05$ was considered statistically significant. Descriptive statistics were expressed as means and proportions. Comparisons between groups with and without neurological manifestations were made using Chi-square or Fisher's exact tests for categorical variables and independent t-tests for normally distributed continuous variables (e.g., hemoglobin, leukocyte count, mean corpuscular volume (MCV), platelet count, PaO_2). Nonnormally distributed variables (e.g., ferritin, D-dimer, IL-6, Creatine phosphokinase [CPK]) were analyzed using the Mann–Whitney *U* test for two groups and the Kruskal–Wallis test for more than two groups. Multivariate logistic regression was performed to identify factors associated with neurological manifestations, with results expressed as odds ratios.

RESULTS

A total of 200 consecutive patients were admitted to the hospital with confirmed SARS-CoV-2 infection by reverse transcription PCR positive swab from April 2021 for consecutive weeks. Most common affected age group was found to be between 51 and 60 years (23.5%) and 61–70 years (22.5%). Individuals <30 years old were least commonly affected (7%). The gender distribution showed there was a significant male preponderance with an M: F ratio of 1:0.492. Majority of individuals (44.5%) had no comorbidities. Diabetes was the most common comorbidity, observed in 72 cases (36.0%), followed by hypertension, which was reported in 63 cases (31.5%). Other less frequently reported conditions included chronic kidney disease in 12 cases (6.0%), ischemic heart disease or cardiovascular disease in 11 cases (5.5%), neurological diseases in 8 cases (4.0%), alcoholic or chronic liver disease in 3 cases (1.5%), and other conditions in 5 cases (2.5%) (Table 1).

Means and standard deviations of hemoglobin, MCV, total leukocyte count, platelet count, and PaO_2 were 12.00±1.88 g/dL, 84.96±8.59 fL, 8590.10±3925.26 cells/mm^3, 215.21±90.46 ×10^9/L, and 84.65±12.89 mmHg, respectively (Table 2).

On studying the clinical profile of the study participants, 105 patients (52.5%) had 25–50% CT severity chest involvement, <25% involvement seen in 44 patients and more than 50% involvement in 50 patients. There was no statistically significant relation between the severity of HRCT thorax and neurological manifestation (Table 3).

Neurological manifestations were present in 47.5% of patients, with majority (42.1%) were having the onset of manifestations more than 1 week after COVID symptoms and 25.2 % presented with neurological manifestations 1 week before COVID symptoms. The common neurological manifestations were asymptomatic elevated CPK (29.4%) followed by headache (18.9%), dysgeusia (14.7%), anosmia (10.5%), myalgia (9.4%) and stroke (15.8%). Similarly, the neurological manifestations were significantly higher in those with PaO2 <90 mmHg compared to those with higher oxygen saturation groups of 90–94 mm Hg (32.5%) and ≥94 (41.8%) ($p<0.05$) (Table 4).

The proportions of those with neurological manifestations were significantly higher in stage IIB/III (84.4.6%) compared to stage IIA (36.8%). The association with the severity of the COVID disease was statistically significant ($p<0.05$). Factors such as age, gender, comorbidities were not significantly associated with the neurological manifestations, and the proportions of deaths did not vary significantly with the presence or absence of neurological manifestations ($p>0.05$) (Table 5).

Table 1: Sociodemographic profile of the study subjects

Particulars	n (%)
Age-group in years (n=200)	
≤30	14 (7.0)
31–40	26 (13.0)
41–50	35 (17.5)
51–60	47 (23.5)
61–70	45 (22.5)
>70	33 (16.5)
Gender (n=200)	
Males	134 (67.0)
Females	66 (33.0)
Comorbidities[§]	
No Comorbidities	89 (44.5)
Diabetes	72 (36.0)
Hypertension	63 (31.5)
Chronic kidney disease	12 (6.0)
Ischemic heart disease/cardiovascular disease	11 (5.5)
Neurological diseases[•]	08 (4.0)
Alcoholic/chronic liver disease	03 (1.5)
Others[¥]	05 (2.5)

[§]n>200 as there are multiple coexisting comorbidities in some of the patients, [•]includes parkinson's/ cerebrovascular accident/ Seizures/ myaesthenia gravis; [¥]includes Hepatitis B/ Obesity/ hypothyroid/ pancytopenia/ BCELL-ALL

Table 2: Average laboratory parameters of the study subjects

Laboratory parameters	Mean±standard deviation
Hemoglobin (g/dL)	12.00±1.88
Mean corpuscular volume (fL)	84.96±8.59
Total Leukocyte Count (cells/mm^3)	8590.10±3925.26
Platelet count (×10^9/L)	215.21±90.46
Serum ferritin (ng/mL)[¥]	656 (430.00– 963.25)
D-dimer (ng/mL)[¥]	280.00 (120.00–650.0)
PaO_2 (mmHg)	84.65±12.89
Creatine phosphokinase (µg/L)[¥]	57.50 (37.00–89.00)
Interleukin-6 (pg/mL)[¥]	2280 (747.50–4595.00)

[¥]-Median with inter-quartile range

The mean and standard deviation of hemoglobin and total leucocyte count was higher and those of MCV, platelet count, and PaO_2 were lower among those with neurological manifestations compared to those without neurological manifestations, but there was no significant difference in hemoglobin, total leukocyte count, MCV, platelet count and PaO_2 between those with or without neurological manifestations (p>0.05) (Table 6).

The median values of CPK were significantly higher (77 µg/L) in those with neurological manifestations compared to those with no neurological manifestations (53 µg/L) (p<0.05). (Table 7). The CPK levels were relatively higher in stage III; however, it lacks statistical significance (p>0.05) (Table 8).

The odds of severity of COVID-19 with the occurrence of neurological manifestations was 11.61, indicating that the occurrence of neurological manifestation is 11.6 times higher among those with higher severity of stage IIB and III compared to stage IIA (p<0.05). Similarly, the odds of occurrence of neurological manifestations was 1.02 times higher with unit rise in CPK levels (p<0.05) (Table 9).

The onset of neurological manifestations was not associated with the severity of COVID-19 (p>0.05). All the subjects with higher severity of stage IIB and III disease-45 patients, 38 patients (82.2%) had severe CNS neurological manifestations such as stroke due to large vessel occlusion, i.e., anterior and posterior circulatory stroke, hyperactive/hypoactive encephalopathy and encephalitis compared to those with lower severity of COVID-19, i.e., stage IIA (p<0.05) compared to stage IIA. All the subjects with higher severity of stage IIB/III disease had other neurological manifestations 84.4% compared to 36.7% in stage IIA (Table 10).

Out of 200 COVID patients, 185 were discharged (92.5%) and 15 patients succumbed (7.5%).Out of 95 patients affected with neurological manifestations, 86 patients (95%) were discharged, and 9 patients had death (9.4%). Proportion of death did not very significantly with the presence or absence of neurological manifestations (p>0.05).

Table 3: Clinical profile of the study participants

Particulars	Categories	Number (%)
X-Ray Chest Involvement+HRCT	>75%+6	06 (3.0)
CORAD Score (n=200)	50–75%+6	43 (21.5)
	50–75%+5	01 (0.5)
	25–50%+6	105 (52.5)
	25%+6	41 (20.5)
	25%+5	02 (1.0)
	25%+4	02 (1.0)
Current status (n=200)	Stage IIA	51 (25.5)
	Stage IIB	127 (63.5)
	Stage III	22 (11.0)
Outcome (n=200)	Discharged	185 (92.5)
	Expired	15 (07.5)
Neurological manifestations (n=200)	Present	95 (47.5)
	Absent	105 (52.5)
Onset of manifestation (n=95)	More than 1	41 (20.5)
	week<1 week	27 (13.5)
	Simultaneously	33 (16.5)
	Not known	04 (02.0)

DISCUSSION

A total of 22 patients (11%) had severe COVID stage III, 127 had stage IIB (63.5%), and 51 (25.5%) stage IIA severity of infection. Of these 200 COVID positive patients, 95 (47.5%) have neurological manifestations. Meppiel *et al*. conducted a study of 222 patients based on the severity of COVID-19 infection [11]. There were 55 (24.8%) mild, 65(29.3%) Moderate and 46(20.7%), severe and 56 (25.2%) critical patients reported in this study. Similarly, Romero-Sánchez *et al*. studied had a total of 329 (39.1%) had severe COVID-19, 77 (9.16%) were admitted to the intensive care unit (ICU), and 197 (23.4%) died during the course of their hospital admission. Neurologic complications were considered to be the fundamental cause of patient death in 8 cases (4.1% of total deaths) [12]. Our results were consistent with Romero-Sánchez *et al*. study [12].

The mean age of the patients in our study was 55.03±14.92 years and it ranged between 15 years and 84 years. Majority of patients were in the age group of >50 years (62.5%). Males (67.0%) outnumbered females (33.0%). Garg *et al*. studied Neurological Symptoms as Initial Manifestation of COVID-19 [13]. In this study, the mean age of the study group (n=391) was 49.07±15.74 years. Males constituted 61%

Table 4: Classification of neurological manifestations due to COVID-19 by type and site

Type/location	Manifestations		n (%)
Nonspecific symptoms	Headache (n=95)		18 (18.9)
	Vertigo (n=95)		04 (4.2)
CNS and cranial nerve	Encephalopathy, encephalitis, and impaired consciousness	Hyperactive encephalopathy (n=95)	07 (7.4)
		Hypoactive encephalopathy (n=95)	01 (1.1)
		Encephalitis (n=95)	04 (4.2)
	Cerebra vascular accident	Anterior circulation stroke (n=95)	10 (10.5)
		Posterior circulation stroke (n=95)	05 (4.2)
		Stroke - large vessel Occlusion (n=95)	15 (15.8)
		Cerebral venous sinus thrombosis (n=95)	06 (6.3)
	Seizure/status epilepticus (acute demyelination)	Acute seizure (n=95)	01 (1.1)
		Encephalomyeloradiculitis (n=95)	01 (1.1)
		Post viral demyelinating disease (n=95)	01 (1.1)
	Myelopathy	Transvers myelitis (n=95)	02 (2.1)
	Cranial nerve neuropathy	Cranial nerve palsy (n=95)	01 (1.1)
		Anosmia (n=95)	10 (10.5)
		Dysguesia (n=95)	14 (14.7)
	Others	Ataxia (n=95)	03 (3.1)
		Acute Onset Extrapyramidal Signs (n=95)	01 (1.1)
		Locked-in state (n=95)	01 (1.1)
PNS	Guillian–barre syndrome (n=95)		07 (7.4)
	Critical illness polyneuropathy (n=95)		03 (3.1)
Musculoskeletal	Myalgia (n=95)		09 (9.4)
	Myasthenia gravis (n=95)		01 (1.1)
	Asymptomatic elevated CPK (n=95)		28 (29.4)

(n=241) of total enrolled patients. 55.5% had existing comorbidities, with diabetes being the commonest (36.0%) followed by hypertension (31.5%). The proportion of those with neurological manifestations was significantly higher in stage IIA (52.3%) compared to the more severe stages, i.e., IIB and III (29.6%). The onset of neurological manifestations was not associated with the severity of COVID-19 (p>0.05) (Table 10). However, another study done by Mao *et al*. study found that neurological manifestations were common in severe cases as compared with non-severe cases (45.5% vs. 30.2%) [14].

In this study, common neurological manifestations were asymptomatic elevated CPK (29.4%) followed by headache (18.9%), dysguesia (14.7%), anosmia (10.5%), and myalgia (9.4%). Headache features -migraine breakthrough, nonsepecific headache of recent onset, aseptic meningitis and thunderclap headache. Karadas *et al*. study showed most common manifestation to be headache (26.7%), followed by muscle pain (15.1%), sleep disturbances (12.6%) and impaired consciousness (9.6%) [15]. Pinna *et al*. showed the most common neurological manifestations to be encephalopathy (n=30), cerebrovascular disease (n=20), cognitive impairment (n=13), seizures (n=13), hypoxic brain injury (n=7), dysgeusia (n=5) and extraocular movement abnormalities (n=5) [16].

Among those who had neurological manifestations due to cerebrovascular accidents, majority (15.8%) had stroke due to large vessel occlusion followed by cerebral venous sinus thrombosis (6.3%). In our study, the majority of CVA were due to large vessel stroke. However, all the subjects with higher severity of stage IIB and III disease significantly had severe neurological manifestations such as stroke due to large vessel occlusion compared to those with lower severity of COVID-19, i.e., stage IIA (p<0.05). Out of 15 large vessel stroke, 10 patients had anterior circulation stroke and five had posterior circulation stroke. One patient had cardioembolic stroke, three patients succumbed during the hospital stay. However, magnetic resonance imaging (MRI) imaging was the limitation in our study. These findings were Similar to the findings of the study conducted by Nannoni *et al*. [17].

Among the patients with anterior circulation stroke, six had after COVID symptoms and four patients before COVID symptoms. Among the patients with posterior circulation, three had before COVID symptoms and two had after symptoms. Seven (7.4%) patients had hyperactive encephalopathy, 1 (1.1%) had hypoactive encephalopathy and four (4.2%) had encephalitis. Pinna *et al*. cohort had higher percentages of altered mental status (60% vs. 14.8%), followed by headache (24% vs. 13%). Cerebrovascular complications were more common in their patient population (20% vs. 2.8%). However, all the subjects with higher severity of stage IIB and III disease had hyperactive encephalopathy and encephalitis compared to those with lower severity of COVID-19, i.e., stage IIA (p<0.05). Higher proportion of those with IIB and III (50.0%) have hypoactive encephalopathy compared to stage IIA (22.2%) (p>0.05). All patients in our study had mild-to-moderate confusion state with normal metabolic parameters. Three patients had associated sepsis.

Our findings were consistent with Romero-Sánchez *et al*., who reported that nervous system symptoms were significantly more common in severe cases as compared with non-severe cases (40 [45.5%] vs. 38 [30.2%], p<0.05) [12]. These symptoms included acute cerebrovascular disease and impaired consciousness [1]. Two patients had transverse myelitis (2.1%). 40-year-old male patient presented with paraplegia with bladder disturbance for the last 3 days. Similarly, Román *et al*. study showed cases of COVID-19-associated myelitis in a period of 10 months around the world. COVID-19-associated ATM was reported in 23 males (53%) and 20 females (47%) ranging in age from 21 to 73 years (mean age 49 years) excluding children [18].

Keshavarzi *et al*. reported that of 5872 people who were admitted to hospitals in Iran with COVID-19 during the study period, 45 came to the emergency room with seizures [19]. This makes seizure a presenting manifestation of COVID-19 in 0.8% of all patients with severe illness. Of these patients, 93% were 15 years of age and older. Four of the individuals presenting with seizures (9%) had a past history of epilepsy. Fifteen of these individuals (33%) had other chronic medical conditions (e.g., cancer, diabetes mellitus, heart disease, etc.).Three patients had critical illness polyneuropathy (3.1%), diagnosed after relevant electrophysiological, CSF studies, and blood investigations. Frithiof *et al*., after screening 122 patients, included 111 COVID-19 patients in their study. Out of these patients, 14 patients (group 2) developed ICUAW, of whom 11 patients were diagnosed with CIN/CIM (group 3), and three patients did not receive a diagnosis of neuromuscular disorder (one patient had normal MRI, one had cerebral infarctions, and one had acute necrotizing encephalopathy). Out of the surviving COVID-19 patients who remained intubated for >2 weeks, 8 patients (62%) developed ICUAW16. Three patients (3.1%) had pan-cerebellar ataxia, one had acute onset extrapyramidal syndrome (1.1%), and one presented with a locked-in state (1.1%) [20].

Table 5: Association of neurological parameters with different risk factors

Variables (n=200)	Neurological manifestations		χ^2 – Value (p-value)
	Yes	No	
Age			
≤55	47 (49.0)	49 (51.0)	0.16 (0.69)
>55	48 (46.2)	56 (53.8)	
Gender			
Males	68 (50.7)	66 (49.3)	1.72 (0.19)
Females	27 (40.9)	39 (59.1)	
Comorbidities			
Yes	52 (46.8)	59 (53.2)	0.04 (0.84)
No	43 (48.3)	46 (51.7)	
PaO_2 in mmHg			
<90	37 (84.1)	07 (15.9)	31.64 (<0.001)*
90–94	25 (32.5)	52 (67.5)	
≥94	33 (41.8)	46 (58.2)	
Severity			
Stage IIA	23 (45.1)	28 (54.9)	6.32 (0.04)*
Stage IIB	56 (44.1)	71 (55.9)	
Stage III	16 (72.7)	06 (27.3)	
Outcome			
Discharge	86 (46.5)	99 (53.5)	1.01 (0.31)
Death	09 (60.0)	06 (40.0)	

*Indicates statistically significant association

Table 6: Comparison of different laboratory parameters with neurological manifestations

Variables	Neurological manifestations (Mean±standard deviation)		t-value [95% confidence interval]	p-value
	Yes (n=95)	No (n=105)		
Haemoglobin (g/dL)	12.04±1.62	11.94±2.06	0.41 (−0.41–0.63)	0.68
Mean corpuscular volume (fL)	84.32±8.46	85.57±8.61	−1.03 (−3.63–1.14)	0.30
Total leukocyte count (cells/mm^3)	8795.58±4212.06	8359.05±3593.71	0.79 (−652.35–1525.14)	0.43
Platelet count (×10^9/L)	213.83±79.72	215.27±98.95	−0.11 (−26.66–23.79)	0.91
PaO_2 (mmHg)	84.59±14.33	84.70±11.52	−0.06 (−3.77–3.56)	0.95

Table 7: Comparison of important inflammatory markers -serum ferritin, d-dimer, interleukin-6 and creatine phosphokinase with neurological manifestations

Variables	Mean ranks of neurological manifestations		U-value	p-value
	Yes (n=95)	No (n=105)		
Serum ferritin (ng/mL)[¥]	105.32	96.14	4529.5	0.26
D-dimer (ng/mL)[¥]	101.03	100.02	4937.5	0.90
Interleukin-6 (pg/mL)[¥]	101.89	99.24	4855.0	0.75
Creatine phosphokinase (µg/L)[¥]	119.90	82.95	3144.5	<0.001*

[¥]-Mann-Whitney U test applied, *Significant

Table 8: Comparison of creatine phosphokinase with severity of COVID-19

Variable	Stage IIA	Stage IIB	Stage III	p-value
CPK (µg/L)	59 (9–1000)	54 (12–2000)	81.5 (22–1800)	0.21

Table 9: Multivariate analysis of significant variables with neurological manifestations of COVID-19

Parameter	p-value	Adjusted odds ratio	95% confidence interval
Severity of COVID-19 [Stage IIA versus IIB/III]	<0.001*	11.61	4.47–30.15
CPK (Neurological manifestations versus no neurological manifestations)	<0.001*	1.02	1.01–1.03

*indicates a statistical significance at $p<0.05$

Table 10: Association of different types of strokes with severity of COVID-19[¥]

Variables (n=95)	Severity		χ^2-value (p-value)
	Stage II A (n=155)	Stage II B/III (n=45)	
Overall neurological manifestations[*]			
Yes	56 (52.3)	08 (29.6)	31.78 (0.03)*
No	51 (47.7)	19 (70.4)	
Onset of neurological manifestations[#]			
Simultaneous	22 (71.0)	09 (29.0)	2.66 (0.26)
More than 1 week	23 (57.5)	17 (42.5)	
<1 week	12 (50.0)	12 (50.0)	
Stroke with large vessel occlusion			
Yes	0 (0.0)	15 (100.0)	<0.001*
No	155 (83.8)	30 (16.2)	
Stroke with anterior circulation			
Yes	0 (0.0)	10 (100.0)	<0.001*
No	155 (81.6)	35 (18.4)	
Stroke with posterior circulation			
Yes	0 (0.0)	05 (100.0)	<0.001*
No	155 (79.5)	40 (20.5)	
Hyperactive encephalopathy			
Yes	0 (0.0)	07 (100.0)	<0.001*
No	155 (80.3)	38 (19.7)	
Hypoactive encephalopathy			
Yes	01 (50.0)	01 (50.0)	0.4
No	154 (77.8)	44 (22.2)	
Encephalitis			
Yes	0 (0.0)	04 (100.0)	<0.001*
No	155 (79.1)	41 (20.9)	

[¥]-Fisher's exact test applied, [*]indicates significant statistical, association at P<0.05. Row % and chi-square test applied. # Column % and chi square test

Means and standard deviations of hemoglobin, MCV, total leucocyte count, platelet count, and PaO_2 were 12.00±1.88 g/dL, 84.96±8.59 fL, 8590.10±3925.26 cells/mm^3, 215.21±90.46 ×109/L, and 84.65±12.89 mmHg, respectively. Karadas *et al*. showed that D-dimer blood levels were detected to be significantly higher in patients with at least one neurological symptom than in patients without neurological symptoms (p<0.05) [15]. IL-6 level was found to be significantly higher in patients with headache than in those without headache (p<0.05). CK level was detected to be significantly higher in patients with muscle pain (p<0.05). After entering the variables (significant on univariate analysis) in the logistic regression model, we found that the severity of COVID-19 and CPK levels were significant predictors of neurological manifestations in COVID-19 (p<0.05). The odds of developing severe COVID-19 with the occurrence of neurological manifestations were 11.61, indicating that the occurrence of neurological manifestations was 11.6 times higher among those with higher severity of stage IIB and III compared to stage IIA (p<0.05). Similarly, the odds of occurrence of neurological manifestations were 1.02 times higher with a unit rise in CPK levels (p<0.05). To determine the disease course and outcome, we divided our cohort into the "Neuro first" and "COVID first" groups. However, no significant difference was seen in clinical features or demographic data. Pinna *et al*. showed that the "COVID first" group was sicker, had abnormal vital signs on admission, had elevated inflammatory and coagulopathy markers, and were more likely to require intubation and ICU care [16]. The "COVID first" group had more cases of altered mental status, hypoxic-ischemic injury, and seizures compared to the "Neuro first" group, which was not seen in our study.

Limitation of the study

Our limitations included the observational nature of the study without a control group and the absence of a dedicated MRI facility for COVID-19 patients. In addition, long-term follow-up and outcome data were unavailable; thus, delayed neurological symptoms could not be analyzed.

CONCLUSION

Neurological manifestations are common occurrence in patients with COVID-19, emphasizing the need for early neurological evaluation. These neurological manifestations were found to have a significant association with disease severity and elevated CPK levels. Common manifestations included stroke, headache, and dysgeusia. Severe cases showed higher chances of neurological complications and have a prognostic relevance in COVID-19 management.

CONFLICT OF INTEREST

None.

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