

# The Sociodemographic and Clinical Profile of Post COVID Patients with Neurological Manifestations Attending a Tertiary Care Centre

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## ABSTRACT

COVID-19 has spread worldwide in the past 3 years since first being recognized in Wuhan in central China in December 2019. The virus inflicts damage to the respiratory system causing hypoxia, causes endothelitis, incites cytokine storm, and antibody production. Binding of the virus to ACE-2 both in the blood-brain barrier and in the meninges leads to encephalitis or myelitis, leading to sequelae post infection, comprising the post COVID syndrome.

This study aimed to determine the sociodemographic and clinical profile of post COVID patients with neurological manifestations attending a tertiary care centre.

A hospital-based descriptive study was done among 261 post COVID patients who attended the post COVID OPD, General Medicine and Neurology OPD and corresponding wards in Govt. T D Medical College, Alappuzha during a period of 1 year. Samples were selected by consecutive sampling method. Data were collected using a structured proforma after taking history and clinically examining the patients seeking new onset or worsening neurological symptoms and signs.

It was noted that among a total of 261 subjects with neurological manifestations post COVID, the most common neurological presenting complaints were tremor (50.6%). This was followed by sleep disturbance (39.5%), neurocognitive decay (30.3%) and anosmia (29.9%).

New onset neurological manifestations are seen in post COVID patients in the form of tremor,

sleep disturbances, neurocognitive decline and anosmia, among less common but significant other presentations like stroke and GBS.

**Keywords:** COVID, post COVID syndrome, neurological manifestations, post COVID neuropathy

## INTRODUCTION

In December 2019, numerous unexplained pneumonia cases occurred in Wuhan, China, and rapidly spread to other parts of China, then to Europe, North America, and Asia. This outbreak was confirmed to be caused by a novel coronavirus (CoV).<sup>[1]</sup> The novel CoV was reported to have symptoms resembling that of severe acute respiratory syndrome CoV (SARS-CoV) in 2003.<sup>[2]</sup> Both shared the same receptor, angiotensin-converting enzyme 2 (ACE2).<sup>[3]</sup> Therefore, this virus was named SARS-CoV-2, and in February 2020, the World Health Organization (WHO) named the disease coronavirus disease 2019 (COVID-19).

Coronaviruses can cause multiple systemic infections or injuries in various animals.<sup>[4]</sup> The CoVs can adapt quickly and cross the species barrier, such as with SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV), causing epidemics or pandemics. Infection in humans often leads to severe clinical symptoms and high mortality.<sup>[5]</sup> As for COVID-19, several studies have described typical clinical manifestations including fever, cough,

diarrhea, and fatigue. Coronavirus disease 2019 also has characteristic laboratory findings and lung computed tomography (CT) abnormalities.<sup>[6]</sup>

There is now ample evidence indicating neurological manifestations occur in patients with COVID-19. Similarly, the other coronaviruses (CoV) epidemics; severe acute respiratory syndrome (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV) have been associated with neurological complications.<sup>[7]</sup> CoV neurotropism, direct invasion of the virus to the central nervous system (CNS) and post infection neurological complications were suggested as the cause of these presentations.<sup>[8]</sup> The damage seems to be caused by severe inflammatory responses, thrombotic microangiopathy, venous thromboembolism, and oxygen deprivation.<sup>[9]</sup>

Organ damage has been documented to persist in the lungs, the heart, the brain, the kidneys and the joints, even in some people who had only mild symptoms. The slow pace of recovery readily explains the duration of what has come to be called the “Post-COVID syndrome.”<sup>[10]</sup>

The persisting symptoms which resembled chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), lasted in some for about 20 months. The persisting illness following COVID-19 also is said to resemble CFS/ME.<sup>[11]</sup>

Certain individuals who have been infected with SARS-CoV-2 can experience long-term effects from their infection, known as post-COVID conditions (PCC) or long COVID.<sup>[12]</sup> Post-COVID conditions have been referred to by many names, including: Long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID.<sup>[12]</sup> CDC’s definition of Post-COVID-19 Conditions (PCC), conceptually first described by CDC in November 2020 and first labeled PCC in February 2021 forms a basis for the definition. Long COVID remains to be a colloquial term while PCC and PASC are

two scientific practical terms. The secondary and tertiary effects of COVID 19 can be included under the umbrella of PCC. The direct and indirect consequences of SARS-CoV-2 on human health is referred to PASC.<sup>[13]</sup>

Fatigue, shortness of breath and cognitive dysfunction are some of the common symptoms of long COVID. However, over 200 varied symptoms have been reported which could have an adverse impact on the quality of living. Several studies have inferred that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID. The exact numbers of those living with the condition are uncertain but it is believed to be more than 17 million people across the WHO European Region. This takes into consideration the people who may have experienced it during the first two years of the pandemic (2020/21).<sup>[14]</sup>

According to many reports and studies, the newly emerging SARS-CoV-2 virus that causes COVID-19 is associated with neurological complications. These complications could impact both the central and peripheral nervous systems. The neurological manifestations could be non-specific such as headache, altered mental status, and myalgia or more specific diseases and syndromes which require immediate medical attention.<sup>[15]</sup>

In our setting, there has been an increase in the number of patients presenting with various complaints encompassing multiple systems, including the nervous system, several weeks after being tested positive for COVID-19. In the light of the present, I intend to explore the sociodemographic and clinical profile of such ‘post COVID’ patients with neurological manifestations attending Govt. TD Medical College, Alappuzha.

#### **OBJECTIVE:**

To study the sociodemographic and clinical profile of post COVID patients with neurological manifestations attending a tertiary care centre.

## MATERIALS & METHODS

A hospital-based descriptive study was done among 261 post COVID patients who attended the post COVID OPD, General Medicine and Neurology OPD, and among the admitted patients in the wards of General Medicine and Neurology departments of Government TD Medical College Alappuzha during a period of 1 year. Samples were selected by consecutive sampling method.

**Sample size:** As per the reference study [1] the prevalence of headache as neurological manifestation was found to be 28%. Using the formula for sample size calculation  $4PQ/D^2$ ,  $P=28$   $Q=72$   $d=20\%$  of Prevalence, Substituting the value of prevalence in the above equation we get a sample size of 261.

### Inclusion Criteria:

1. Patients diagnosed as COVID-19 with oro-nasopharyngeal swab for covid 19 by RTPCR or Rapid antigen test or TRUNAAT who has given written informed consent for the study attending General Medicine OPD, Neuromedicine OPD, or Post Covid Clinic or is admitted in General Medicine or Neuromedicine ward in Govt.TD Medical College, Alappuzha.
2. Age 18 years old and above
3. Patients presenting after at least 4 weeks since first tested positive for COVID-19

### Exclusion Criteria:

1. Pregnant adults
2. Patients with pre-existing documented neurological disease (cerebrovascular accidents, neurodegenerative conditions, neuroinfections, immune related neurological illness, neurological malignancies and muscle diseases)
3. Terminally ill patients (Malignancy/End stage renal disease/Decompensated liver disease)

Patients were categorized as mild, moderate, severe according to the WHO guidelines

## STATISTICAL ANALYSIS

All data were entered in an Excel spreadsheet and analysed with the help of OpenEpi and SPSS V.16 Software. Qualitative data was summarized in percentages and proportions. Quantitative variables were summarized in mean with standard deviation.

## RESULTS

This was a hospital-based descriptive study with a sample size of 261.

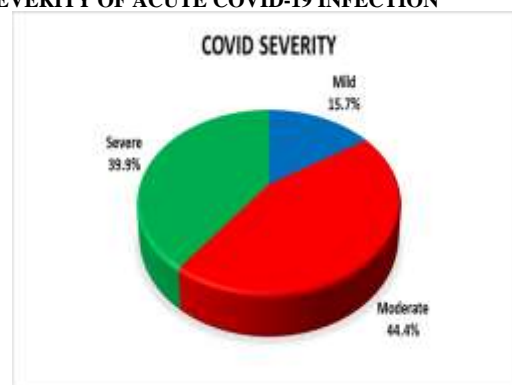
### 1.SOCIODEMOGRAPHIC PROFILE

Among a total of 261 patients 45.2% belonged to age group of more than 65 years, 33.4% were between 45 and 65 years of age and only 21.4 % were between 18 and 45 years of age.

Among them, 56.3% were women and 43.7% were men. The majority of patients (34.5%) were manual laborers and 12.3% were of a professional community. Subjects engaged in office work amounted to 15.7%. Subjects categorized as retired personnel constituted 12.3% of the study population.

### 2.CLINICAL PROFILE

FIGURE 1. DISTRIBUTION OF POST COVID PATIENTS WITH NEUROLOGICAL MANIFESTATIONS BASED ON SEVERITY OF ACUTE COVID-19 INFECTION



**TABLE 1. DISTRIBUTION OF POST COVID NEUROLOGICAL MANIFESTATIONS**

Presenting complaints	Frequency	Percent
DYSGEUSIA	64	24.5
ANOSMIA	78	29.9
SLEEP DISTURBANCE	103	39.5
TREMOR	132	50.6
HEADACHE	60	23
CRANIAL NEUROPATHY	5	1.9
PERIPHERAL NEUROPATHY	48	18.4
ATAXIA	4	1.5
NEUROPSYCHIATRIC SYMPTOMS	6	2.3
MENINGITIS	3	1.1
GBS	3	1.1
ENCEPHALITIS	1	0.4
ISCHEMIC STROKE	34	13
IC BLEED	16	6.1
SEIZURE	33	12.6
NEUROCOGNITIVE DECLINE	79	30.3

**TABLE 2. PERCENTAGE DISTRIBUTION OF THE SAMPLE BASED ON ASSOCIATED OTHER SYSTEM INVOLVEMENT**

Other system involvement	Frequency	Percent
Respiratory	63	24.1
Cardiovascular	45	17.2
Rheumatological	42	16.9

**TABLE 3. PERCENTAGE DISTRIBUTION OF THE SAMPLE WITH HYPERTENSION, DIABETES MELLITUS AND DYSLIPIDEMIA**

COMORBIDITY	Frequency	Percent
Diabetes Mellitus	114	44
Hypertension	58	21.9
Dyslipidemia	89	34.1
Total	261	100

### 3.LABORATORY PROFILE

**TABLE 4. DISTRIBUTION OF POST COVID PATIENTS WITH NEUROLOGICAL MANIFESTATIONS ACCORDING TO SERUM FERRITIN**

FERRITIN	Frequency	Percent
<300	89	34.1
≥300	172	65.9
Total	261	100

**TABLE 5. DISTRIBUTION OF THE SAMPLE BASED ON D-DIMER MEASUREMENT**

D-DIMER	Frequency	Percent
≤1000	164	62.8
>1000	97	37.2
Total	261	100

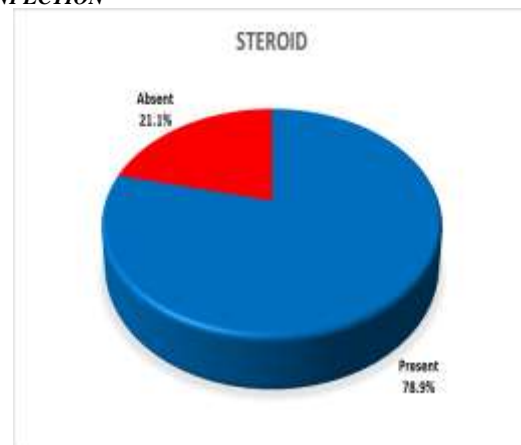
As for imaging studies, 81.6% did not undergo an MRI study, 8% had a normal study while 6.2% had evidence of brain infarction, 2.7% showed IC bleed. However only 1.1% had meningitis and only 0.4% had encephalitis on MRI. As for CT brain, 77.4% had a normal study, 7.3% had evidence of brain infarction, 3.4% showed hemorrhage whereas 65.9 % had not underwent a CT brain.

### 4.TREATMENT PROFILE

It was observed that 33.7% of the subjects did not require oxygen inhalation while 29.9 % required oxygen by mask and 16.5% required HFNC. About 19.9% required NIPPV.

Among 261 patients 42.1% had received Remdesivir while 33.7% had received Favipiravir. However, 52.5% had not received any antiviral drugs

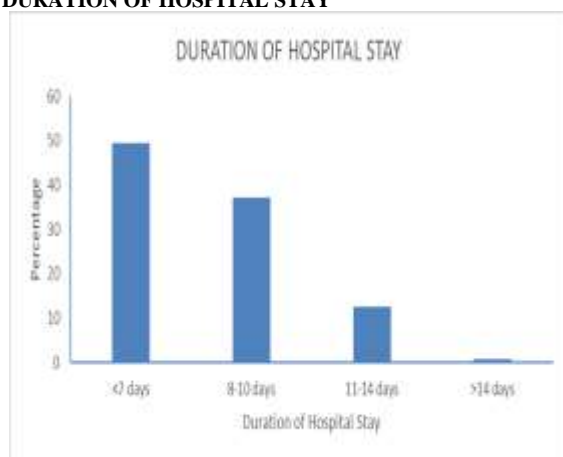
**FIGURE 3. DISTRIBUTION OF POST COVID PATIENTS WITH NEUROLOGICAL MANIFESTATIONS BASED ON ADMINISTRATION OF STEROIDS DURING ACUTE INFECTION**



**TABLE 6. DISTRIBUTION OF THE SAMPLE BASED ON ICU ADMISSION DURING ACUTE ILLNESS**

ICU ADMISSION	Frequency	Percent
Present	83	31.8
Absent	178	68.2
Total	261	100

FIGURE 4. DISTRIBUTION OF THE SAMPLE BASED ON DURATION OF HOSPITAL STAY



## DISCUSSION

This was a hospital based, descriptive study with a study population of 261 subjects. A total of 261 post COVID patients who had attended Govt. T.D. Medical College, Alappuzha, Kerala in India, were enrolled in our study after considering the inclusion and exclusion criteria.

Among the study subjects, 45.2% belonged to age group of more than 65 years, 33.4% were between 45 and 65 years of age and only 21.4 % were between 18 and 45 years of age. A literature review conducted by Adekunle Sanyaolu, Chuku Okorie et al had also observed that older population are more prone to develop COVID related complications<sup>[5]</sup>.

This study observed that 56.3% of the study subjects were women and 43.7% were men, in line with the prospective study conducted by Francesca Bai, Daniele Tomasoni et al who observed that the female gender is more associated with post COVID manifestations<sup>[3]</sup>.

Amongst the 261 subjects, the majority (34.5%) were manual laborers whereas only 11.1% constituted the retired population. The subjects engaged in office work amounted to 15.7% while professional job holders constituted 12.3% of the study population.

149 subjects (44%) were diabetic, 107 (21.9%) were hypertensive and 132 (34.1%) were dyslipidemic. Okorie et.,al had observed that patients with COVID -19

disease who have concomitant illnesses like hypertension or diabetes mellitus, have more chance of developing complications<sup>[5]</sup>. Subjects were categorized based on the category of acute COVID 19. Most (44.4%) of the subjects gave a history of having suffered from a moderate infection while 39.9% and 15.7% had severe and mild infection respectively. A study conducted by Janet D Pierce, Qihua Shen et al revealed that post COVID manifestations can occur in any patients who are recovering or recovered from COVID 19 irrespective of their category of illness.<sup>[4]</sup>

It was observed that 33.7% of the subjects did not require oxygen inhalation while 29.9 % required oxygen by mask and 16.5% required HFNC. Only 19.9% required mechanical ventilation (NIPPV). But this observation was not completely in concurrence with Ramadan et., al who observed that prolonged COVID-19-mediated hypoxia could cause serious complications and can lead to lasting neurological symptoms.

It was also observed that 42.1% had received Remdesivir while 33.7% had received favipiravir. However, 24.2% had not received any antiviral drugs. There have not been studies implicating antiviral use during acute covid 19 disease with post covid manifestations. According to our study, 78.9% of the subjects had received steroids while 21.1% had not.

Regarding the duration of hospital stay our study showed that 49.4% of the study subjects had been hospitalized for less than a week, 37.2% for 8 to 10 days, 12.6% for 11 to 14 days and 0.8% for more than 2 weeks. Among the 261 subjects only 31.8% required ICU care.

## CLINICAL PRESENTATION

During our study we found that the most common neurological presenting complaints were tremor (50.6%), sleep disturbance (39.5%), neurocognitive decay (30.3%) and anosmia (29.9%). Other complaints included dysgeusia (24.5%), headache (23%), peripheral neuropathy (18.4%),

ischemic stroke (13%) and seizure (12.6%). Less common symptoms include cranial neuropathy (1.9%), ataxia (1.5%), neuropsychiatric symptoms (2.3%), meningitis (1.1%), encephalitis (0.4%) and intra cerebral bleed (6.1%). It was also observed that among the 261 study subjects 24.1% had associated respiratory symptoms, 17.2% had associated cardiovascular manifestations and 16.9% had concomitant rheumatological manifestations.

### **DISTRIBUTION OF POST COVID PATIENTS WITH NEUROLOGICAL MANIFESTATIONS BASED ON CONCOMITANT ALTERNATE POST COVID MANIFESTATIONS**

Among the 261 patients studied, 16.9% had post COVID rheumatological symptoms, 17.2 % had post COVID cardiovascular manifestations and 24.1% had lung manifestations. However, 33% did not have any significant post COVID manifestations. A systematic review was done by Muhammad Abdel-Gawad, Mariam S Zaghloul et.,al which showed that 35% to 90.5% of patients who have recovered from COVID -19 goes on to experience several clinical manifestations like fatigue, dyspnoea, neuropsychological disorders including pain and rheumatological manifestations<sup>[16]</sup>. S V Aswathy Raj, Abraham Jacob et.,al conducted a study to determine the clinical factors and associated risk factors of post COVID syndrome in the northern part of Kerala and the study revealed that most of the patients complained of dyspnoea (48%), fatigue (32%), and cough (25.6%). It was noticed that the respiratory system was commonly involved (61.2%)<sup>[17]</sup>.

### **LABORATORY PROFILE DURING ACUTE COVID**

#### **Acute phase reactants**

Among 261 subjects 65.9% had a ferritin value equal to or above 300 whereas only 34.1% had a value less than 300. A case control study by Gameil et.,al revealed persistent higher levels of inflammatory

markers such as ESR, CRP, D-dimer, and ferritin in COVID-19 survivors denoting residual systemic inflammatory response.<sup>[6]</sup>

#### **D-dimer**

It was observed that 37.2% of the subjects had a value equal to or above 1000 whereas only 62.8% had a value less than 1000, acute covid.<sup>[7]</sup>

#### **Neuroimaging**

Among 261 subjects, 89 underwent a CT Brain scan. 77.4% had a normal CT brain study, 7.3% had evidence of brain infarction, 3.4% showed hemorrhage.

48 MRI brain scans were done. 8% of all study subjects had a normal MRI study while 6.2% had evidence of brain infarction, 2.7% showed features of IC bleed. Only 1.1% had features of meningitis and only 0.4% had encephalitis on MRI. Mao et al has reported cerebral infarction and hemorrhages in covid patients.<sup>[1]</sup> There are several other reports of ADEM, aseptic meningitis in patients with covid 19, with residual symptoms persisting even after months.<sup>[8]</sup>

#### **LIMITATIONS OF THE STUDY**

The selection of samples was conducted using convenient sampling (non probability sampling) and this was a single centre based study. Only the short term outcomes were analysed using the study. Long term mortality and morbidity data could not be assessed.

Possibility of other viral infections were not considered during the course of the study. A consensus on how to distinguish post COVID neurological diseases from other causes and types of neuropathologies could not be arrived at. Several patients who had documented evidence of neurological diseases were excluded from the study as a result of which primary disease progression in post COVID patients could not be studied. Newer treatment modalities and their association with post COVID neurological manifestations could not be studied due to the timeline of the study.

## CONCLUSION

From the study the following conclusions were drawn. It was noted that among a total of 261 subjects with neurological manifestations post COVID, the most common neurological presenting complaints were tremor (50.6%). This was followed by sleep disturbance (39.5%), neurocognitive decay (30.3%) and anosmia (29.9%).

A 45.2% of subjects belonged to the age group of more than 65 years, 33.4% were between 45 and 65 years of age and only 21.4 % were between 18 and 45 years of age, women were more commonly (56.3%) affected than men (43.7%).

Most (44.4%) of the subjects gave a history of having suffered from a moderately severe infection of acute COVID 19 while 39.9% and 15.7% had severe and mild infection respectively. It was also observed that 33.7% of the subjects did not require oxygen inhalation while 29.9 % required oxygen by mask and 16.5% required HFNC. Only 19.9% required mechanical ventilation (NIPPV).

The study observed that among the 261 patients 149(44%) were diabetic, 107 (21.9%) were hypertensive and 132 (34.1%) were dyslipidemic.

16.9% subjects had coexisting post COVID rheumatological symptoms, 17.2 % had post COVID cardiovascular manifestations and 24.1% had lung manifestations. However, 33% did not have any other significant post COVID manifestations apart from neurological complications.

Also was noted the higher levels of acute phase reactants of the study subjects during the phase of their acute COVID 19 (like s. ferritin > 300 in 65.9%).

Neuroimaging revealed features of infarction and haemorrhage in a small proportion of subjects.

### Declaration by Authors

**Ethical Approval:** Approved

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**Conflict of Interest:** The authors declare no conflict of interest.

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