

# The manifestations of the impact of COVID-19 on the nervous system

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## ABSTRACT

This study aims to summarize and report on the frequency of neurological manifestations observed in patients hospitalized with coronavirus disease (COVID-19) in 2020 and 2022 from a multidisciplinary medical center in Tashkent, Uzbekistan.

**Keywords:** COVID-19, Neurological manifestations, Neurological complications, Neyro-Covid, Covid-Neyro, Cerebrovascular complications, Peripheral nervous system, Cognitive impairments, Cavernous sinus thrombosis, Comorbidities, Retrospective analysis, Statistical analysis

## Methods

We retrospectively analyzed data from 120 patients with COVID-19 who were evaluated by neurological services from March 1, 2020, to July 30, 2020. Patients were divided into 2 groups based on the timing of neurological manifestations: the «Neyro-Covid» group, who had neurological manifestations at the initial examination, and the «Covid-Neyro» group, whose neurological symptoms developed more than 24 hours after hospitalization. We analyzed age and gender data, comorbidities, disease severity, neurological symptoms, and diagnoses of both groups. Statistical analysis was conducted to compare the two groups.

## Observed results

- A total of 120 patients were included in the analysis (46.7% female and 53.3% male).
- The «Covid-Neyro» group had a high percentage of cerebrovascular complications (most commonly TCS), peripheral nervous system (PNS) involvement, and cognitive impairments.
- The «Neyro-Covid» group most commonly had cerebrovascular complications (most frequently II and TIA), seizures, and hypoxic-ischemic brain injury.
- Cavernous sinus thrombosis in the Covid-Neyro group was present in 75%, compared to 25% in the Neyro-Covid group ( $p = 0.05$ ) (detailed characteristics of this group of patients subject to our next publication).
- The prevalence of altered mental status and headache was relatively similar in both groups, while peripheral and cranial polyneuropathy was more common in the «Covid-Neyro» group ( $p = 0.51$ ;  $p = 0.12$  respectively).
- Neurological manifestations of COVID-19 directly depended on the timing of hospitalization and subsequent inclusion of patients in two different groups: «Neyro-Covid» or «Covid-Neyro».
- Despite similar comorbidities and age-gender distribution, patients in the «Covid-Neyro» group (with relatively late development of neurological symptoms after hospitalization) had a more severe course of the disease (consistent with the opinions of other authors).

## 1. INTRODUCTION

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, first emerged in Wuhan, China, and has since spread globally to affect over 215 countries. The disease presents with a range of symptoms, including fever, cough, fatigue, and respiratory distress, with severe complications such as respiratory failure observed in a minority of cases. Neurological manifestations have also been documented in various populations worldwide. This study focuses on exploring the neurological complications of COVID-19 in patients treated at our central clinic in Tashkent, Uzbekistan, where we provide diverse emergency care.

## 2. Methods

### 2.1.1 Study Design and Patient Population.

This was a series of retrospective observations conducted at a multidisciplinary medical center located in the city center of Tashkent, Uzbekistan. The study was approved by the Local Institutional Review Board. We reviewed the medical records of each patient with confirmed COVID-19 through real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis of nasopharyngeal swabs. A total of 250 hospitalized patients with a diagnosis of COVID-19 were included. These cases encompassed patients who were admitted to the intensive care unit, intensive therapy unit, or general ward or underwent formal neurological consultation for neurological complaints.

### 2.1.2 Data collection

The extraction and analysis of data from electronic medical records (EMRs) have provided invaluable insights into the demographics, clinical presentations, and outcomes of patients affected by COVID-19. Across multiple studies, researchers have meticulously gathered information on various parameters such as age, gender, race, pre-existing comorbidities, vital signs upon admission, laboratory test results, and radiological findings.

Classification of COVID-19 severity has been standardized, typically encompassing categories ranging from mild to critical, based on established diagnostic and treatment guidelines. This stratification aids in better understanding the spectrum of disease presentation and guiding appropriate clinical management strategies.

Of particular interest is the evaluation of neurological manifestations in COVID-19 patients. Detailed scrutiny of neurological symptoms and signs, whether present upon initial assessment or developing after hospital admission, has been a focal point. This distinction between 'Neuro first' and 'COVID first' presentations sheds light on the temporal relationship between COVID-19 infection and neurological involvement.

Furthermore, the integration of advanced electronic data capture tools such as REDCap or MedPlus has streamlined data management processes, facilitating comprehensive analysis and interpretation of study findings.

Collaborative efforts involving physicians, scientists, and medical treatment groups have contributed to a robust understanding of the epidemiological, clinical, and therapeutic aspects of COVID-19. This multidisciplinary approach ensures thorough examination of various facets of the disease, from its onset to hospital admission, clinical course, and outcomes.

Additionally, comprehensive literature searches have been conducted to encompass a broad spectrum of research findings, ensuring a comprehensive understanding of the clinical features and outcomes associated with SARS-CoV-2 infection.

### 2.1.3 Statistical Analysis

Statistical analyses were conducted to discern differences between groups and to assess the relationship between individual variables and predetermined clinical categories. For comparisons between cohort groups, we employed Student's t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test for dichotomous variables. These analyses were conducted using SPSS statistical software (version 21, Chicago, IL, USA). Statistical significance was determined at  $p < 0.05$  for all comparisons.

## 3. RESULTS

This analysis included 120 patients with confirmed COVID-19. At the time of data collection, 250 patients with COVID-19 were hospitalized, with a prevalence of neurological symptoms of 48%.

The total number of patients (n) was 120 (male - 64 (53.3%), female - 56(46.7%)).

- Neyro-Covid: 57 patients (47.5%) (male - 31, female - 26)

- Covid-Neyro: 63 patients (52.5%) (male - 33, female - 30)

Age: The mean age of patients was  $58.5 \pm 12.5$  years: in the Neyro-Covid group, it was  $60.3 \pm 10.2$ ; in the Covid-Neyro group, it was  $52.7 \pm 16.4$ .

**Table 1.** Age and Gender Distribution, Comorbidities, and Severity of COVID-19

	Overall	Neyro-Covid	Covid-Neyro	P-value
	n=120	n=57 (47,5%)	n=63 (52,5%)	
Age	58,5 ± 12,5	60,3± 10,2	52,7± 16,4	0,12
Comorbidities:	n(%)	n (%)	n (%)	
Arterial hypertension	65(54,2)	30(46,2)	35(53,8)	0,37
Diabetes mellitus	65 (54,2)	32(49,2)	33(50,7)	0,23
Hyperlipidemia	52(43,3)	38(73,1)	14(26,9)	0,31
Obesity (BMI>30)	48(40,0)	18(37,5)	30(62,5)	0,20
Chronic bronchopulmonary diseases	48(40,0)	25(52,1)	23(47,9)	0,27
Ischemic heart disease (IHD)	42(35,0)	27(64,3)	15(35,7)	0,25
Smoking and other harmful habits	38(31,7)	21(55,3)	17(44,7)	0,27
Chronic kidney disease	32(26,7)	16(50,0)	16(50,0)	0,26
No comorbidities	8(6,7)	3(37,5)	5(62,5)	
Percentage of severe/critical cases	65%	52,3%	75,5%	0,019
Intubation (percentage of intubated patients)	60%	35,5%	71,3%	0,022

When studying 120 patients with comorbidities, the following results were obtained (Table 1): Hypertension was present in 65 patients – 54.2% (35 of them – 53.8% in the Covid-Neyro group, 30 of them – 46.2% in the Neyro-Covid group); Diabetes mellitus in 65 patients – 54.2% (32 of them – 49.2% in the Neyro-Covid group, 33 of them – 50.7% in the Covid-Neyro group); Hyperlipidemia in 52 patients – 43.3% (14 of them – 26.9% in the Covid-Neyro group, 38 of them – 73.1% in the Neyro-Covid group); Obesity (BMI > 30) in 48 patients – 40.0% (18 of them – 37.5% in the Neyro-Covid group, 30 patients – 62.5% in the Covid-Neyro group), Chronic bronchopulmonary diseases in 48 patients – 40.0% (23 of them – 47.9% in the Covid-Neyro group, 25 of them – 52.1% in the Neyro-Covid group).

The following comorbidities were less frequently identified: ischemic heart disease (IHD) in 42 patients – 35.0% (27 of them – 60% in the Neyro-Covid group, 15 – 35.7% in the Covid-Neyro group); smoking and other harmful habits in 38 patients – 31.7% (21 of them – 55.3% in the Neyro-Covid group, 17 of them – 44.7% in the Covid-Neyro group); chronic kidney disease in 32 patients – 26.7% (16 each – 50.0% in both groups); The remaining 8 patients had no identified comorbidities.

The «Covid-Neyro» group had more severe/critical cases compared to the «Neyro-Covid» group (75.5% vs. 52.3%, p 0.019) and were more likely to require intubation and mechanical ventilation (71.3% vs. 35.5%, p 0.022).

In the cohort of 120 patients, numerous neurological manifestations were observed (Table 2). It should be noted that some patients had more than one neurological manifestation. Cerebrovascular events were the most common, occurring in 33.3% (n = 42) of patients, including ischemic stroke (IS) in 26.2% (n = 11), intracerebral hemorrhage (ICH) in 12% (n = 5), non-aneurysmal subarachnoid hemorrhage (SAH) in 7.1% (n = 3), transient ischemic attack (TIA) in 7.1% (n = 3), Cavernous sinus thrombosis (CST) in 47.6% (n = 20). The second most frequently observed symptom was altered mental status (23.3% or n = 28). Cases of peripheral polyneuropathy were common, particularly signs of dysautonomia, which occurred in 15% (n = 18) of patients, followed by muscle damage with elevated CK levels in 33.3% (n = 6), and there were also cases of cranial polyneuropathy at 10.8% (n = 13).

**Table 2.** Observed Neurological Manifestations:

Groups	Overall	Neyro-Covid	Covid-Neyro	'p	
	n=120	n=57 (47,5%)	n=63(52,5%)		
Cerebrovascular complications:	42(33,3)	22(52,4)	20(47,6)	0,36	
Among the m:	Ischemic stroke	11(26,2)	6 (54,5)	5 (45,5)	0,61
	Intracerebral hemorrhage	5(12)	2 (40)	3(60)	0,60
	Subarchnoid hemorrhage	3(7,1)	1 (33,3)	2 (66,7)	0,83
	Transient ischemic attack	3(7,1)	2 (66,7)	1(33,3)	0,83
	Cavernous sinus thrombosis	20 (47,6)	5 (25)	15 (75)	0,06
Changes in mental status	28(23,3)	16(57,1)	12(42,9)	0,13	

Peripheral polyneuropathy	18(15)	5(27,8)	13(72,2)	0,51
Headache	15(12,5)	7(46,7)	8(53,3)	0,35
Cranial polyneuropathy	13(10,8)	5(38,5)	8(61,5)	0,11
Seizures	12(10)	7(58,3)	5(41,7)	0,46
Cognitive impairments	10(8,3)	3(30)	7(70)	0,25
Hypoxic-ischemic brain injury	10(8,3)	6(60)	4(40)	0,04
Posterior reversible encephalopathy syndrome(PRES)	7(5,8)	2(28,6)	5(71,4)	0,21

Headache occurred in 12.5% (n=15) of patients, followed by seizures in 10% of patients (n=12), cognitive impairments, and hypoxic-ischemic brain injury (HIBI) each occurring in 8.3% (n=10) of patients. Posterior reversible encephalopathy syndrome (PRES) was observed in 7 patients (5.8%). In the «Covid-Neyro» group, there were 5 cases of PRES, while in the «Neyro-Covid» group, there were 2 cases.

The «Covid-Neyro» group had a high percentage of cerebrovascular complications (most frequently CST), peripheral nervous system (PNS) involvement, and cognitive impairments. The «Neyro-Covid» group more frequently experienced cerebrovascular complications (most frequently IS and TIA), seizures, and HIBI.

Cavernous sinus thrombosis (CST) was present in 15 patients (75%) in the Covid-Neyro group and 5 patients (25%) in the Neyro-Covid group (p=0.055). The prevalence of altered mental status and headache was relatively similar in both groups, while peripheral and cranial polyneuropathy were more common in the Covid-Neyro group (p=0.509; p=0.114, respectively).

Comparative analysis of vital signs at admission (Diagram 1) revealed that the Covid-Neyro group had a higher respiratory rate and lower oxygen saturation at admission (23 vs. 17, p=0.005 and 92 vs. 95, p=0.019, respectively). The Neyro-Covid group had a lower heart rate and higher systolic blood pressure (SBP) compared to the Covid-Neyro group, where the heart rate was higher and SBP was lower (92 vs. 88, p=0.141 and 85.9 vs. 97, p=0.001, respectively).

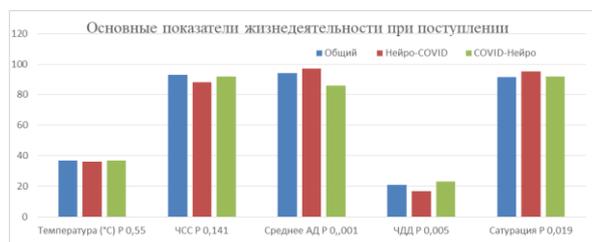


DIAGRAM 1:

Vital signs at admission.

- HR- Heart Rate;
- SBP- Systolic Blood Pressure;
- RR – respiratory rate;
- SpO<sub>2</sub> – oxygen saturation.

Laboratory parameters post-hospitalization are shown in Table 3. When comparing markers of inflammation and coagulation, including D-dimer, ferritin, CRP, as well as other laboratory data between the two groups, the following changes were noted: In the "Covid-Neyro" group, significantly higher levels of leucocytes (14.5-20.8 vs. 10.8-13.9, p=0.035), D-dimer (650.7-820.5 vs. 552.8-618.2, p=0.038), CRP (15.7-38.3 vs. 11.5-15.2, p=0.035), CK (35.8-52.4 vs. 25.4-38.5, p=0.041), and ferritin (1650.6-2154.3 vs. 807.5-1693.7, p=0.042) were observed.

Table 3. Table with laboratory data for the patient population..

	Overall	Covid-Neyro	Neyro-Covid	P-value*
The number of leucocytes (Average: 4-11*10 <sup>9</sup> /л)	10,8-21,5	14,5-20,8	10,8-13,9	0,04
The number of neutrophils (Average: 1,5-8 *10 <sup>9</sup> /л)	8,7-19,2	12,8-18,6	9,2-12,6	0,12
The number of lymphocytes (Average: 0,72-5,20 *10 <sup>9</sup> /л)	1,2-11,8	8,5-10,2	6,0-7,8	0,25
The number of Platelets	380,8-590,5	488,2-580,6	400,8-480,5	0,03

(Average: 150–399 *10 <sup>9</sup> /л)				
CK* (Average: 0-23 н/л)	22,5-55,2	35,8-52,4	25,4-38,5	0,04
Creatinine (Average: 50-130 мкмоль/л)	128,8-160,4	110,8-152,5	80,5-102,5	0,06
D-dimer (Average: <500 мг/л FEU)	525,7-824,8	650,7-820,5	552,8-618,2	0,04
CRP* (Average: от 0,3 до 10 мг/л)	10,8-40,7	15,7-38,3	11,5-15,2	0,04
Ferritin (Average: 12–410 нг/мл)	450,7-1824,4	1650,6-2154,3	807,5-1693,7	0,04

\*CRP (C-reactive protein), CK (creatinine kinase).

#### 4. DISCUSSION

In our comprehensive analysis of 120 COVID-19 patients at our multi-profile medical center, we uncovered a spectrum of neurological manifestations affecting both the central and peripheral nervous systems. Notably, the majority of our patients were elderly and presented with significant comorbidities, consistent with previous research indicating widespread organ involvement in this viral illness. Among the most prevalent neurological symptoms were cerebrovascular events, altered mental status, nerve involvement, headaches, seizures, and transient memory impairments.

To provide a nuanced understanding of disease progression and outcomes, we categorized our patient cohort into "Neyro-Covid" and "Covid-Neyro" groups. Despite similar baseline characteristics, the "Covid-Neyro" group exhibited a more severe clinical profile, characterized by abnormal vital signs, elevated inflammatory and coagulopathy markers, and a higher likelihood of requiring intensive care and intubation. This subgroup also showed a higher incidence of cerebrovascular complications, peripheral nerve involvement, and cognitive impairments, indicating a more profound systemic illness compared to the "Neyro-Covid" group.

Comparing our findings with those of Mao et al., we observed a higher prevalence of neurological manifestations in our patient population, likely influenced by the higher rates of hypertension and diabetes mellitus type 2 among our patients. Additionally, our cohort experienced a higher incidence of cerebrovascular complications and altered mental status, suggesting potential differences in disease severity and patient characteristics.

In contrast to a study in Strasbourg, France, which reported various neurological symptoms not specific to the underlying disease mechanism, our study identified more frequent cases of peripheral and cranial polyneuropathy. Notably, certain conditions reported in other studies, such as Guillain-Barré syndrome, were absent in our cohort.

The diverse pathogenesis of neurological symptoms in COVID-19 involves potential targeting of the brain by the SARS-CoV-2 virus through ACE2 expression in glial cells and neurons. This complex interplay may occur via multiple routes, including peripheral nerves, hematogenous spread, direct endothelial damage, or hypercoagulable states. Our study provides compelling evidence supporting these mechanisms, particularly with the observed cases of cavernous sinus thrombosis, which will be further detailed in our subsequent publication.

#### 5. CONCLUSION

Our study employs a meticulous retrospective methodology, meticulously selecting patients who underwent comprehensive neurological evaluations by specialists at our esteemed central clinic in Tashkent, Uzbekistan. This rigorous approach ensures a detailed understanding of the neurological implications within the context of COVID-19. By focusing exclusively on this subset of patients, we aim to capture the full spectrum of neurological manifestations associated with the disease, providing valuable insights into its prevalence, severity, and long-term outcomes.

In our forthcoming review, we will delve deeply into the long-term follow-up results, meticulously examining the persistence and evolution of delayed neurological symptoms beyond the acute phase of the illness. This comprehensive analysis will shed light on the potential long-term effects of COVID-19 on neurological health and function, informing future clinical management and interventions.

The diverse presentation of neurological manifestations throughout COVID-19 underscores the multifaceted nature of the disease and its impact on patients' overall well-being. Furthermore, the significant burden placed on healthcare systems by these neurological complications highlights the urgent need for tailored treatment approaches. Therefore, it is imperative to identify and implement timely and qualified pathogenetic treatments to mitigate disability and mortality associated with these manifestations.

Our study endeavors to contribute to the collective understanding of neurological complications in COVID-19, ultimately aiming to improve patient care and outcomes. Through meticulous research and analysis, we hope to pave the way for more effective strategies in managing and treating neurological manifestations of the disease.

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