

# Frequency and burden of neurological manifestations in hospitalized patients with COVID-19: findings from a large Brazilian cohort

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## **Abstract**

## **Background**

Scientific data regarding the prevalence of COVID-19 neurological manifestations and prognosis in Latin America countries is still lacking. Therefore, the study aims to understand neurological manifestations of SARS-CoV 2 infection in the Brazilian population and its association with patient outcomes, such as in-hospital mortality.

## **Methods**

This study is part of the Brazilian COVID-19 Registry, a multicentric COVID-19 cohort, including data from 37 Brazilian hospitals. For the analysis, patients were grouped according to the presence of self-reported vs. clinically-diagnosed neurological manifestations and matched with patients without neurological manifestations by age, sex, number of comorbidities, hospital, and whether or not patients had neurological underlying disease.

## **Results**

From 7,232 hospitalized patients with COVID-19, 27.8% presented self-reported neurological manifestations, 9.9% were diagnosed with a clinically-defined neurological syndrome and 1.2% did not show any neurological symptoms. In patients with self-reported symptoms, the most common ones were headache (19.3%), ageusia (10.4%) and anosmia (7.4%). Meanwhile, in the group with clinically-defined neurological syndromes, acute encephalopathy was the most common diagnosis (10.5%), followed by coma (0.6%) and seizures (0.4%). Men and younger patients were more likely to self-report neurological symptoms, while women and older patients were more likely to develop a neurological syndrome. Patients with clinically-defined neurological syndromes presented a higher prevalence of comorbidities, as well as lower oxygen saturation and blood pressure at hospital admission. In the paired analysis, it was observed that patients with clinically-defined neurological syndromes were more likely to require ICU admission (46.9 vs. 37.9%), mechanical ventilation (33.4 vs. 28.2%), to develop acute heart failure (5.1 vs. 3.0%, p=0.037) and to die (40.7 vs. 32.3%, p<0.001) when compared to controls.

## **Conclusion**

Neurological manifestations are an important cause of morbidity in COVID-19 patients. More specifically, patients with clinically defined neurological syndromes presented a poorer prognosis for the disease when compared to matched controls.

## **Introduction**

The coronavirus disease 19 (COVID-19) pandemic has affected millions of people worldwide. Clinical signs of upper respiratory tract infection such as nasal congestion and cough, alongside systemic symptoms like fatigue and fever usually precede lung involvement.<sup>1</sup> Besides the severity of respiratory symptoms, risk factors associated with worse clinical outcomes include, older age, male sex, baseline comorbidities (e.g. diabetes mellitus, chronic kidney disease, cerebrovascular disease, hypertension and obesity), and abnormal laboratory biomarkers.<sup>2,3</sup>

COVID-19 can also evolve with cardiac, renal, ophthalmologic, skin, and other manifestations. Several reports have described a series of neurological manifestations associated with COVID-19.<sup>4</sup> Both peripheral and central nervous systems may be affected, with a wide range of symptoms, signs and syndromes.<sup>4,5,6</sup> Importantly, the presence of neurological signs and/or syndromes has shown to be associated with five times higher risk of in-hospital death in a large cohort, even when adjusting for site, age, sex, race, and ethnicity, but this finding has not been consistent across studies.<sup>7,8</sup> Additionally, some manifestations are related to persistent disability, potentially associated with long-term care needs and high health, social, and economic costs.<sup>9</sup> Despite

the epidemiological and clinical relevance of the matter, data on the prevalence of those manifestations and their prognosis in Latin American patients is still lacking

Therefore, this study aimed: (i) to characterize the spectrum of neurological manifestations among Brazilian patients hospitalized with COVID-19; and (ii) to investigate the potential association between neurological manifestations and clinical outcomes, specifically in-hospital mortality.

## Methods

### Study design and subjects

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.<sup>10</sup> This was an urgent public health research study in response to a Public Health Emergency of International Concern.

Patients were selected from the Brazilian COVID-19 Registry, a prospective multicenter cohort project with 37 participant hospitals in 17 cities from five Brazilian states (Minas Gerais, Pernambuco, Rio Grande do Sul, Santa Catarina, São Paulo). Details of the cohort were published elsewhere.<sup>11</sup> The study was approved by the National Commission for Research Ethics (CAAE 30350820.5.1001.0008). Individual informed consent was waived by the National Commission for Research Ethics owing to the pandemic situation and the use of deidentified data, based on medical chart review only.

The cohort study included consecutive patients with confirmed COVID-19 diagnosis according to World Health Organization guidance who were hospitalized in one of the participating centers from March to September 2020.<sup>12</sup>

For the present study, patients aged 18 or older were selected and categorized according to the presence or not of neurological manifestations upon hospital presentation, as defined below. Patients who developed first COVID-19 symptoms while hospitalized for other conditions were not included in this analysis.

### Data collection

Study data were collected by trained hospital staff using Research Electronic Data Capture (REDCap) tools.<sup>13</sup> Medical records were reviewed to collect data on patients' demographic and clinical characteristics, including age, sex, pre-existing medical conditions and home medications; COVID-19 symptoms at hospital presentation; clinical assessment upon hospital admission, third and fifth admission days; laboratory, imaging, electrocardiographic data; inpatient medications, treatment and outcomes. Definitions were previously published elsewhere.<sup>11</sup>

### Neurological manifestations

Neurological manifestations were assessed upon hospital presentation. They were categorized into (1) self-reported symptoms (*i.e.*, headache; anosmia and ageusia; syncope and dizziness) and (2) clinically-defined neurological syndrome: neurological signs or diagnoses captured by clinical evaluation (*i.e.*, acute encephalopathy; stroke; coma; seizure and/or status epilepticus; aphasia; abnormal brainstem reflexes; involuntary movements; motor and sensory deficits), as proposed by Chou et al. (2021).<sup>7</sup>

### Statistical analysis

Categorical data were presented as absolute numbers and proportions, and continuous variables were expressed as medians and interquartile ranges. Fisher Exact test was used to compare the distribution of categorical variables, and the Wilcoxon-Mann-Whitney or Kruskal-Wallis test for continuous variables. In the case of statistically significant results in Kruskal-Wallis test, we conducted Dunn's test with Bonferroni correction to determine which groups are different.

As categorizing patients according to the presence of neurological manifestations would lead to groups with different age distribution and given that age is a prognostic factor in COVID-19, propensity score analysis through nearest neighbor matching (within 0.25 standard deviations of the logit of the propensity score, on a scale from 0-1.00) was performed to specifically

investigate the impact of neurological manifestations. Propensity score model was estimated by a logistic regression model using the MatchIt package in R software.

The analysis was conducted in four different subsamples: i) Any neurological manifestation, sex, age, number of comorbidities (hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation or flutter, cirrhosis, chronic obstructive pulmonary disease, cancer, and previous stroke), admitting hospital, and past history of neurological disease ; ii) Any neurological manifestation, sex, age, number of comorbidities and admitting hospital; iii) Any clinically-defined neurological syndrome, sex, age, number of comorbidities, admitting hospital, and past history of neurological disease; iv) Any clinically-defined neurological syndrome, sex, age, number of comorbidities and admitting hospital, without taking into account past history of neurological disease.

Results were considered statistically significant if the two-tailed p-value was lower than 0.05. All statistical analysis was performed with R software (version 4.0.2).

## Ethics

The study was approved by the National Commission for Research Ethics (CAAE 30350820.5.1001.0008). Individual informed consent was waived by the National Commission for Research Ethics owing to the pandemic situation and the use of deidentified data, based on medical chart review only.

## Results

This study involved 7,232 patients hospitalized with COVID-19 in Brazil. The median age was 60.0 (47.0-72.0) years and 53.8% were male. Neurological manifestations were present in 38.2% of the patients, being 27.8% exclusively with self-reported neurological manifestations and 9.9% with exclusively clinically-defined neurological syndrome. Less than 2% (1.2%) of the patients presented both self-reported symptoms and clinically-defined neurological syndrome.

Headache was the most common self-reported neurological symptom (19.3%), followed by ageusia (10.4%) and anosmia (7.4%). Regarding clinically-defined neurological syndromes, acute encephalopathy was the most commonly diagnosed, affecting 10.5% of patients. Other neurological syndromes were much less frequent (Table 1).

**Table 1**  
**Neurologic manifestations in the study population (n=7,232)**

<b>Characteristics</b>	<b>Patients n (%)</b>
Any neurological manifestation	2,809 (38.8%)
Neurological sign or diagnoses captured by clinical evaluation	802 (11.1%)
Acute encephalopathy	762 (10.5%)
Stroke	17 (0.2%)
Coma	41 (0.6%)
Seizures	29 (0.4%)
Peripheral neuropathy	3 (0.04%)
Self-reported neurological symptoms	2,092 (28.9%)
Anosmia	538 (7.4%)
Ageusia	749 (10.4%)
Headache	1,398 (19.3%)
Syncope or dizziness	99 (1.4%)

When comparing sociodemographic and clinical characteristics in groups with clinically-defined or self-reported neurological manifestations versus no neurological manifestations, differences emerged (Table 2). Men and younger patients were more likely to present self-reported neurological manifestations, while women and older patients had clinically-defined neurological syndromes. Patients with clinically-defined neurological syndromes had a higher prevalence of hypertension, coronary artery disease, heart failure, atrial fibrillation flutter, chronic obstructive pulmonary disease, cerebrovascular disease, epilepsy and dementia when compared to patients with self-reported neurological symptoms and no neurological symptoms. All of those comorbidities, except for coronary artery disease and epilepsy, were found to be significantly lower in the group with self-reported symptoms when compared to patients with no neurological manifestations.

Regarding clinical findings upon hospital admission, the median peripheral oxygen saturation/inspiratory oxygen fraction (SF) ratio and systolic blood pressure median were significantly lower among the clinically-defined neurological syndrome group when compared to patients with no neurological manifestations and the ones with self-reported neurological symptoms. A higher frequency of Glasgow score below 15 was more common in patients with clinically defined neurological syndrome (81.4%) than the other ones (Table 2). Patients with clinically-defined neurological symptoms had lower median hemoglobin level, as well as higher median white blood cell count, lactate, C-reactive protein, urea, creatinine and sodium levels (Table 2).

Table 2

Demographic and clinical features of patients presenting with self-reported neurological symptoms, with clinically-defined neurological syndromes and without neurological manifestations.

Characteristics	No neurological manifestation (n=4,423)	Self-reported neurological symptoms (n=2,092)	Clinically-defined neurological syndrome* (n=802)	p-value**
Age (years)	61.0 (48.0, 72.0)	54.0 (43.0, 65.0)	77.0 (65.0, 84.0)	<0.001
Men	2,467 (55.8%)	1,066 (51.0%)	396 (49.4%)	<0.001
<b>Past medical history</b>				
Hypertension	2,402 (54.3%)	1,012 (48.4%)	503 (62.7%)	<0.001
Coronary artery disease	254 (5.7%)	92 (4.4%)	66 (8.2%)	<0.001
Heart failure	304 (6.9%)	86 (4.1%)	95 (11.8%)	<0.001
Atrial fibrillation or flutter	165 (3.7%)	40 (1.9%)	51 (6.4%)	<0.001
COPD	298 (6.7%)	63 (3.0%)	83 (10.3%)	<0.001
Diabetes mellitus	1,302 (29.4%)	506 (24.2%)	252 (31.4%)	<0.001
Obesity (BMI>30kg/m <sup>2</sup> )	724 (16.4%)	425 (20.3%)	69 (8.6%)	<0.001
Cirrhosis	37 (0.8%)	7 (0.3%)	9 (1.1%)	0.031
Cancer	334 (7.6%)	67 (3.2%)	77 (9.6%)	<0.001
Cerebrovascular disease	157 (3.5%)	35 (1.7%)	118 (14.7%)	<0.001
Epilepsy	45 (1.0%)	17 (0.8%)	39 (4.9%)	<0.001
Dementia	53 (1.2%)	5 (0.2%)	110 (13.7%)	<0.001
<b>Clinical assessment at admission</b>				
SF ratio	433.3 (339.3, 457.1)	438.1 (350.0, 457.1)	353.6 (272.2, 442.9)	<0.001
Respiratory rate (irpm)	20.0 (18.0, 24.0)	20.0 (18.0, 24.0)	21.0 (18.0, 24.0)	0.028
Heart rate (bpm)	88.0 (78.0, 100.0)	88.0 (78.0, 100.0)	87.0 (76.0, 98.0)	0.053
Glasgow < 15	0 (0.0%)	60 (2.9%)	653 (81.4%)	<0.001
Systolic blood pressure				<0.001
≥ 90 (mm Hg)	4,179 (98.6%)	1,971 (98.9%)	726 (95.5%)	
< 90 (mm Hg)	57 (1.3%)	19 (1.0%)	27 (3.6%)	
Inotrope requirement	1 (0.0%)	2 (0.1%)	7 (0.9%)	
<b>Laboratory parameters</b>				
Hemoglobin (g/L)	13.1 (11.8, 14.4)	13.5 (12.5, 14.6)	12.3 (10.8, 13.7)	<0.001
Data is presented as frequency (%) or median (IQR)				
* In case patients had a clinically-defined neurological syndrome and a self-reported symptom, they were analyzed in the clinically-defined neurological syndrome group.				
** P-values for each comparison among individual groups are shown in Table S1.				

Characteristics	No neurological manifestation (n=4,423)	Self-reported neurological symptoms (n=2,092)	Clinically-defined neurological syndrome* (n=802)	p-value**
White blood cells (10 <sup>9</sup> /L)	6.98 (5.09, 9.56)	6.48 (4.92, 8.60)	7.60 (5.54, 11.09)	<0.001
Platelet count (10 <sup>9</sup> /L)	198.0 (153.0, 261.0)	198.0 (155.3, 255.0)	194.0 (147.0, 257.5)	0.381
Lactate (mmol/L)	1.4 (1.1, 1.9)	1.4 (1.0, 1.8)	1.5 (1.1, 2.1)	<0.001
C-reactive protein (mg/L)	75.4 (34.8, 143.0)	63.8 (29.1, 120.0)	82.5 (40.1, 164.9)	<0.001
Urea (mg/dL)	36.0 (26.0, 52.0)	31.0 (23.0, 42.0)	53.0 (35.3, 83.3)	<0.001
Creatinine (mg/dL)	1.0 (0.8, 1.2)	0.9 (0.7, 1.1)	1.1 (0.8, 1.6)	<0.001
Sodium (mmol/L)	137.0 (134.5, 140.0)	137.8 (135.0, 140.0)	138.4 (135.3, 141.0)	<0.001

Data is presented as frequency (%) or median (IQR)

\* In case patients had a clinically-defined neurological syndrome and a self-reported symptom, they were analyzed in the clinically-defined neurological syndrome group.

\*\* P-values for each comparison among individual groups are shown in Table S1.

Patients presenting with clinically-defined neurological syndromes were more likely to require ICU admission (46.9 vs. 37.9%, p<0.001) and mechanical ventilation (33.4 vs. 28.2%, p=0.027), to develop acute heart failure (5.1 vs. 3.0%, p=0.037) and to die (40.7 vs. 32.3%, p<0.001) compared to controls. When underlying neurological diseases were not taken into account, a difference in ICU requirement (45.9 vs 40.8%, p=0.041) and death (41.5 vs. 30.5%, p <0.001) was still observed, and patients with clinically-defined neurological syndromes were more likely to develop septic shock (19.3 vs. 14.8%, p=0.016), but there was no significant difference in mechanical ventilation requirement and acute heart failure (Table 3).

When comparing patients with clinical manifestations overall (self-reported or clinically-defined) to matched controls, there was no difference in mechanical ventilation or intensive care unit requirement, and no difference in the proportion of patients who died (Table S2).

Table 3

Clinical outcomes when comparing patients with clinically-defined neurological syndromes with paired controls, taking or not account underlying neurological diseases

Clinically-defined neurological syndromes										
Characteristic	Taking into account underlying neurological disease				Without taking into account underlying neurological disease					
	Cases		Controls*		p-value	Cases		Controls**		p-value
	N = 765 <sup>1</sup>	Non missing cases	N = 765 <sup>1</sup>	Non missing cases		N = 801 <sup>1</sup>	Non missing cases	N = 801 <sup>1</sup>	Non missing cases	
Age (years)	76.0 (65.0, 84.0)	765	75.0 (65.0, 84.0)	765	0.606	77.0 (65.0, 84.0)	801	76.0 (66.0, 83.0)	801	0.368
Men	379 (49.5%)	765	391 (51.1%)	765	0.604	396 (49.4%)	801	404 (50.4%)	801	0.689
Hospital stay	10.0 (5.0, 17.0)	763	9.0 (5.0, 15.0)	765	<b>0.031</b>	10.0 (5.0, 17.0)	799	9.0 (5.0, 16.0)	800	0.195
ICU	357 (46.9%)	761	288 (37.9%)	759	<b>&lt;0.001</b>	365 (45.9%)	796	325 (40.8%)	797	<b>0.041</b>
Time from admission to ICU	0.0 (0.0, 2.0)		1.0 (0.0, 4.0)		<b>&lt;0.001</b>	0.0 (0.0, 2.0)		1.0 (0.0, 4.0)		<b>&lt;0.001</b>
Mechanical ventilation	247 (33.4%)	739	207 (28.2%)	734	<b>0.027</b>	254 (32.8%)	774	242 (31.1%)	779	0.459
AKI	231 (34.8%)	664	242 (37.2%)	651	0.368	238 (34.1%)	697	252 (36.1%)	699	0.456
Dialysis	86 (11.3%)	761	99 (13.1%)	758	0.294	87 (10.9%)	796	98 (12.3%)	798	0.400
Septic shock	147 (19.3%)	763	116 (15.2%)	765	<b>0.034</b>	154 (19.3%)	799	118 (14.8%)	800	<b>0.016</b>
Vascular thrombosis	22 (2.9%)	763	32 (4.2%)	765	0.169	24 (3.0%)	799	36 (4.5%)	800	0.115
Acute heart failure	39 (5.1%)	763	23 (3.0%)	765	<b>0.037</b>	41 (5.1%)	799	29 (3.6%)	800	0.141
Nosocomial infection	102 (13.4%)	763	81 (10.6%)	765	0.094	109 (13.6%)	799	102 (12.8%)	800	0.598
Death	310 (40.7%)	761	245 (32.3%)	759	<b>&lt;0.001</b>	330 (41.5%)	796	243 (30.5%)	797	<b>&lt;0.001</b>
Cases: patients with clinically-defined neurological syndromes upon hospital presentation; controls: matched patients who did not have any clinically-defined neurological syndrome upon hospital presentation.										
AKI: acute kidney injury; ICU: intensive care unit.										
* Paired by age, gender, number of comorbidities, center and underlying neurological disease										
**Paired by age, gender, number of comorbidities and center										

## Discussion

To the best of our knowledge, this is the first cohort study to systematically investigate COVID-19-related acute neurological manifestations and their impact in a representative sample of hospitalized patients from Brazil/Latin America. Previous Brazilian and Latin American studies have reported cross-sectional case-series, usually focusing on specific neurological manifestations and investigating pathophysiological processes instead of assessing the whole picture and the prognostic impact.<sup>14,15,16</sup> Our results showed that approximately 40% of the patients admitted to a hospital due to COVID-19 presented self-reported or clinically-diagnosed neurological symptoms and/or syndromes upon hospital presentation. More importantly, presence of clinically-defined neurological symptoms was associated with worse clinical outcomes, including the need for ICU admission, ventilatory support and death.

The incidence of COVID-19, as well as its complications and mortality rates differ substantially depending on the region/country. These differences seem to be related to various factors, including political decisions regarding social distancing, organization of health care delivery, and epidemiological characteristics of the affected population (*e.g.*, age composition, comorbidities).<sup>17</sup> The COVID-19 pandemic has exerted a particularly devastating impact on Brazil that has exhibited the second highest COVID-19 related mortality number.<sup>18</sup> Therefore, an in-depth analysis of clinical manifestations and factors associated with worse prognosis among Brazilians is of utmost importance.

Previous studies comprising case series and/or cohorts using different definitions and clinical samples led to very diverse incidence estimates of COVID-related neurological manifestations. To provide more reliable and/or generalizable information on the incidence, type, and outcomes of neurological manifestations among patients a recent systematic review analyzed 350 studies, involving 145,721 patients.<sup>8</sup> When considered only the subanalysis of hospitalized patients, the observed incidence of ageusia in our study was inside the confidence interval (10.4 vs. 13% [95%CI 8 to 19%]), but it was slightly lower than expected for anosmia (7.4 vs. 11% [95%CI 8 to 15%]); while the frequency of headache was higher than the authors observed in the pooled analysis (19.3 vs. 11% [95%CI 10 to 12%]).

It has been hypothesized that patients with severe COVID-19 might not be able to provide a clear history regarding smell or taste impairment.<sup>8</sup> This could have impacted our results, especially when taking into account that the overall mortality previously observed in our cohort (22.0%) was observed to be higher than what was observed in other countries.<sup>11</sup> Ageusia and anosmia have been regarded as independent positive prognostic factors of a less severe COVID-19 infection.<sup>19,20</sup> In the aforementioned meta-analysis, patients with severe COVID-19 were less likely than those with mild disease to have decreased smell (OR 0.44, 95% CI 0.28–0.68) and taste (OR 0.62, 95% CI 0.42–0.91).<sup>8</sup>

The frequency of headache was much higher in an European multicenter study (44%), but the study was limited for having included not only hospitalized patients, but also medical doctors and nurses with COVID-19 who worked in the participant hospitals and volunteered.<sup>21</sup> Those who volunteered might have had more symptoms than the other patients. Our frequency of dizziness was much lower than this study and the meta-analysis as well (1.4% vs. 7% [95%CI 6 to 9%]).<sup>8</sup> Altogether, our findings and these studies support that self-reported neurological symptoms are relatively frequent during COVID-19, but the numbers vary significantly depending on the sample studied and the severity of the presentation.

Acute encephalopathy was the most common clinically-defined neurological syndrome (10.5%) in our study, similar to the one reported in the aforementioned systematic review.<sup>8</sup> This review showed that 1 in every 3 hospitalized older patients with COVID-19 had delirium compared to 5% of younger adults. In addition, acute encephalopathy has shown to be a risk factor for mortality after one year of hospitalization and for the development of dementia.<sup>8,22</sup> Actually, the World Health Organization has alerted clinicians about the importance of implementing measures to prevent acute encephalopathy or delirium, as well as its prompt identification and management.<sup>23</sup>

The Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID), and the European Academy of Neurology (EAN) Neuro-COVID Registry (ENERGY) worked together producing a joint report from four cohorts<sup>7</sup>, and observed a higher prevalence of neurological manifestations overall. The presence of clinically-defined syndromes, but not self-reported symptoms, were associated with worse outcomes, *i.e.* increased risk of in-hospital death, as observed in our study. It is worth

noticing that despite meaningful results and aiming at a global representativeness of COVID-19 neurological impact, both GCS-NeuroCOVID and ENERGY cohorts clearly had a skewed composition of developed countries in North America and Europe.<sup>7</sup> Additionally, in some of those cohorts only patients with neurological manifestations were eligible. Therefore, the overall incidence of neurological manifestations was overestimated.

The pooled prevalence of stroke in the aforementioned systematic review of neurological manifestations of COVID-19 was 2% (95% CI 1-2%, but with high heterogeneity,  $i^2 = 86\%$ ), a number ten times higher than the one observed in our cohort (0.2%). This might be partially explained by the fact that our cohort probably included more severe cases of COVID-19 leading to a higher mortality rate. Another hypothesis that could explain this difference is that in our study we analyzed neurological manifestations at hospital admission, meanwhile stroke may be presented during disease course. It is worth mentioning that the diagnosis of stroke can be overlooked in critically-ill patients, especially those requiring sedation for ventilation support.<sup>23</sup>

The pathogenesis of these neurological manifestations is still under investigation, and it seems to involve different mechanisms for distinct signs or symptoms.<sup>9</sup> Overall, while a direct role of CNS infection remains controversial, hypoxemia, hypovolemia, inflammatory and/or immune-mediated damage are very likely to play relevant roles. For example, patients with severe COVID-19 probably have delirium because of a 'cytokine storm', i.e. marked increase of circulating levels of pro-inflammatory cytokines, such as interleukins (IL-1 $\beta$ , IL-6, IL-10) and tumor necrosis factor (TNF- $\alpha$ ). TNF- $\alpha$  can cross the blood-brain barrier, activating microglia and astrocytes that secrete several mediators able to interfere in neuronal functioning.<sup>24,25,26</sup>

In a recent meta-analysis assessing the impact of neurological manifestations on COVID-related mortality and involving 21 studies, the authors observed a higher mortality in this group of patients compared to the mortality among patients with any neurological manifestations in the current analysis (18.3% vs. 27% [95% CI 19–35%]).<sup>8</sup> Some of the studies included in the meta-analysis only assessed clinically-defined neurological syndromes, what could explain the higher mortality rate. In our study, when assessing patients with any neurological manifestations when compared to matched controls, there were no significant differences in the assessed outcomes. Of note, relevant differences emerged when considering the group of patients with clinically-defined neurological syndromes. When comparing patients with clinically defined neurological syndromes with matched patients without neurological manifestations, we observed a higher incidence of ICU requirement, septic shock and mortality, regardless of past history of neurological diseases. Importantly, patients with neurological manifestations and a past history of neurological diseases had a higher frequency of mechanical ventilation requirement and acute heart failure compared to the matched controls. This novel information may be useful to clinicians and healthcare managers, alerting to the need of careful neurological follow-up of these patients who may need more intensive clinical care and possibly should be prioritized for an ICU bed.

While this study has several strengths, including its sample size, careful characterization of neurological manifestations, control for multiple confounding variables, and representativeness of multiple Brazilian regions ensuring the diversity of the population studied, it has limitations that must be acknowledged. First, the study is subjected to the drawbacks inherent to data retrospectively obtained from medical record reviews. To minimise that, research staff was extensively trained and the data was subject to periodic auditing to ensure data quality. Another limitation in the analysis of prevalence of neurological manifestations is the fact that we had to exclude patients who were admitted on mechanical ventilation (for being attended first by the emergency medical service, or being transferred from another institution without any information about self-reported neurological symptoms or clinically defined neurological syndromes before intubation). Additionally, the pragmatic design of the study implies that it was not possible to control for interexaminer reliability in neurological examination and diagnosis. The severity of self-reported neurological symptoms could not be determined, and relevant information (e.g. neuroimaging results) was not available in all sites. Furthermore, participant hospitals were not randomly selected, and not necessarily representative of the whole healthcare system in Brazil.

## Conclusion

In conclusion, our findings in a large Brazilian cohort corroborate the emerging view that neurological manifestations represent a significant risk of morbidity in COVID-19 patients. More importantly, the development of clinically-defined neurological

syndromes have prognostic implications.

## Declarations

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### Role of the funder/sponsor

The sponsors had no role in study design; data collection, management, analysis, and interpretation; writing the manuscript; and deciding to submit it for publication. xx had full access to all the data in the study and had responsibility for the decision to submit for publication.

### Competing of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Data sharing statement

Data is available upon reasonable request.

### Transparency declaration

The lead authors (MSM and ALT) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

### Contributorship statement

Substantial contributions to the conception or design of the work: MSM, MCP, ALT.

Substantial contributions to the acquisition, analysis, or interpretation of data for the work: MSM, MCP, LFIA, FA, LK, ASMC, MCAN, HD, KPPMPM, LBM, CTCAS, NRO, PKZ, MHGJ, MOSSL, SCF, LSMM, TFO, MDS, BLF, CCRC, AOM, SMMG, SFA, GFN, DVS, KBR, TCO, AVS, LAN, MAF, VBS, CMR, JCA, ALBAS, ERFM, GPC, JDLB, DP, JMR, AFBB, PJLM, HRV, LCC, CRGM, GGV, ECP, JMC, MFG, ALTJ, RBSM.

Drafted the work: MSM, ALT, MCP, DNP, IGB, FA, LK.

Revised the manuscript critically for important intellectual content: all authors.

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Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: ALT, MSM, MCP.

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## Supplemental Tables

**Table S1. Comparison between groups and p-values**

Variable	Comparison	P-value	P-value reference
Age (years)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
Age (years)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
Age (years)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Men	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Men	Clinically-defined neurological syndrome - Self-reported neurological symptoms	0.447	0.017
Men	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Hypertension	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Hypertension	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Hypertension	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Coronary artery disease	Clinically-defined neurological syndrome - No neurological manifestation	0.007	0.017
Coronary artery disease	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Coronary artery disease	No neurological manifestation - Self-reported neurological symptoms	0.024	0.017
Heart failure	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Heart failure	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Heart failure	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Atrial fibrillation or flutter	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Atrial fibrillation or flutter	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Atrial fibrillation or flutter	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
COPD	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
COPD	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
COPD	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Diabetes mellitus	Clinically-defined neurological syndrome - No neurological manifestation	0.258	0.017
Diabetes mellitus	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Diabetes mellitus	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Obesity (BMI>30kg/m2)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017

Obesity (BMI>30kg/m2)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Obesity (BMI>30kg/m2)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Cirrhosis	Clinically-defined neurological syndrome - No neurological manifestation	0.426	0.017
Cirrhosis	Clinically-defined neurological syndrome - Self-reported neurological symptoms	0.02	0.017
Cirrhosis	No neurological manifestation - Self-reported neurological symptoms	0.021	0.017
Cancer	Clinically-defined neurological syndrome - No neurological manifestation	0.047	0.017
Cancer	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Cancer	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Cerebrovascular disease	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Cerebrovascular disease	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Cerebrovascular disease	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Epilepsy	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Epilepsy	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Epilepsy	No neurological manifestation - Self-reported neurological symptoms	0.427	0.017
Dementia	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Dementia	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Dementia	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
SF ratio	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
SF ratio	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
SF ratio	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Respiratory rate (irpm)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	0.023	0.05
Glasgow < 15	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Glasgow < 15	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017
Glasgow < 15	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.017
Systolic blood pressure	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.017
Systolic blood pressure	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.017

Systolic blood pressure	No neurological manifestation - Self-reported neurological symptoms	0.148	0.017
Hemoglobin (g/L)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
Hemoglobin (g/L)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
Hemoglobin (g/L)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
White blood cells (10 <sup>9</sup> /L)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
White blood cells (10 <sup>9</sup> /L)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
White blood cells (10 <sup>9</sup> /L)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Lactate (mmol/L)	Clinically-defined neurological syndrome - No neurological manifestation	0.047	0.05
Lactate (mmol/L)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
C-reactive protein (mg/L)	Clinically-defined neurological syndrome - No neurological manifestation	0.014	0.05
C-reactive protein (mg/L)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
C-reactive protein (mg/L)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Urea (mg/dL)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
Urea (mg/dL)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
Urea (mg/dL)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Creatinine (mg/dL)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
Creatinine (mg/dL)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
Creatinine (mg/dL)	No neurological manifestation - Self-reported neurological symptoms	<0.001	0.05
Sodium (mmol/L)	Clinically-defined neurological syndrome - No neurological manifestation	<0.001	0.05
Sodium (mmol/L)	Clinically-defined neurological syndrome - Self-reported neurological symptoms	<0.001	0.05
Sodium (mmol/L)	No neurological manifestation - Self-reported neurological symptoms	0.001	0.05

**Table S2. Clinical outcomes when comparing patients with any neurological manifestations (clinically defined or self-reported) with paired controls, taking or not account underlying neurological diseases**

**Any neurological manifestation**

Characteristic	Taking into account underlying neurological disease					Without taking into account underlying neurological disease				
	Cases		Controls**		p-value	Cases		Controls*		p-value
	N = 2,741 <sup>1</sup>	Non missing cases	N = 2,741 <sup>1</sup>	Non missing cases		N = 2,762 <sup>1</sup>	Non missing cases	N = 2,762 <sup>1</sup>	Non missing cases	
Age (years)	59.0 (46.0, 73.0)	2,741	60.0 (47.0, 72.0)	2,741	0.681	59.0 (46.0, 73.0)	2,762	60.0 (47.0, 72.0)	2,762	0.639
Men	1,398 (51.0%)		1,426 (52.0%)		0.449	1,390 (50.3%)		1,402 (50.8%)		0.747
Hospital stay	7.0 (4.0, 13.0)	2,739	8.0 (5.0, 14.0)	2,740	<b>0.004</b>	7.0 (4.0, 13.0)	2,760	8.0 (4.0, 14.0)	2,761	<b>0.020</b>
ICU	906 (33.2%)	2,730	916 (33.5%)	2,736	0.818	914 (33.1%)	2,759	950 (34.5%)	2,757	0.296
Time from admission to ICU	1.0 (0.0, 3.0)		1.0 (0.0, 3.0)		<b>0.014</b>	1.0 (0.0, 3.0)		1.0 (0.0, 3.0)		0.237
Mechanical ventilation	606 (22.6%)	2,676	628 (23.6%)	2,666	0.430	611 (22.6%)	2,704	641 (23.7%)	2,703	0.330
AKI	551 (24.0%)	2,295	595 (25.6%)	2,326	0.216	557 (24.1%)	2,314	608 (25.6%)	2,371	0.213
Dialysis	226 (8.3%)	2,731	242 (8.8%)	2,735	0.449	227 (8.2%)	2,759	274 (9.9%)	2,757	<b>0.027</b>
Septic shock	299 (10.9%)	2,739	300 (10.9%)	2,740	0.969	299 (10.8%)	2,760	313 (11.3%)	2,761	0.552
Vascular thrombosis	106 (3.9%)	2,739	144 (5.3%)	2,740	<b>0.014</b>	105 (3.8%)	2,760	136 (4.9%)	2,761	<b>0.041</b>
Acute heart failure	69 (2.5%)	2,739	67 (2.4%)	2,740	0.860	68 (2.5%)	2,760	72 (2.6%)	2,761	0.734
Nosocomial infection	267 (9.7%)	2,739	223 (8.1%)	2,740	<b>0.037</b>	274 (9.9%)	2,760	260 (9.4%)	2,761	0.521
Death	490 (17.9%)	2,730	494 (18.1%)	2,736	0.918	504 (18.3%)	2,759	492 (17.8%)	2,757	0.684

\* Paired by age, gender, number of comorbidities, center and underlying neurological disease

\*\*Paired by age, gender, number of comorbidities and center