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Frequency and burden of neurological manifestations upon hospital presentation in COVID-19 patients: 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 and outcomes in the Brazilian population.

Methods: This study is part of the Brazilian COVID-19 Registry, a multicentric cohort, including data from 37 hospitals. For the present analysis, patients were grouped according to the presence of reported symptoms (i.e., headache; anosmia and ageusia; syncope and dizziness) vs. clinically-diagnosed neurological manifestations (clinically-defined neurological syndrome: neurological signs or diagnoses captured by clinical evaluation) and matched with patients without neurological manifestations by age, sex, number of comorbidities, hospital of admission, and whether or not patients had underlying neurological disease.

Results: From 6,635 hospitalized patients with COVID-19, 30.8% presented reported neurological manifestations, 10.3% were diagnosed with a neurological syndrome and 60.1% did not show any neurological manifestations. In patients with reported symptoms, the most common ones were headache (20.7%), ageusia (11.1%) and anosmia (8.0%). In patients with neurological syndromes, acute encephalopathy was the most common diagnosis (9.7%). In the matched analysis, patients with neurological syndromes presented more cases of septic shock (17.0 vs. 13.0%, $p = 0.045$), intensive care unit admission (45.3 vs. 38.9%, $p = 0.023$), and mortality (38.7 vs. 32.6%, $p = 0.026$; and 39.2 vs. 30.3%, $p < 0.001$) when compared to controls.

Conclusion: COVID-19 in-hospital patients with clinically defined neurological syndromes presented a higher incidence of septic shock, ICU admission and death when compared to controls.

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1. 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 [1]. 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 [2,3]. Also, previous studies have associated the presence of neurological comorbidities, such as epilepsy and dementia, to a poorer COVID-19 prognosis [4,5].

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 [6]. Both peripheral and central nervous systems may be affected, with a wide range of symptoms, signs and syndromes [6–8]. Importantly, the presence of neurological signs and/or syndromes, such as delirium and coma, has been associated with up to five times higher risk of in-hospital death, but this finding has not been consistent across studies [9,10]. General alterations in the patient's mental status during COVID-19 have been associated with in-hospital mortality [11]. Meanwhile, the presence of mild neurological symptoms, such as anosmia and ageusia, have been associated with a better disease prognosis [9–12]. Headache, for instance, is frequently associated with a lower duration of COVID-19 symptoms and low risk of in-hospital mortality [13–15]. Additionally, some manifestations are related to persistent disability, potentially associated with long-term care needs and high health, social, and economic costs [16]. 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.

2. Methods

2.1. Study design and subjects

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [17]. This was an urgent public health research study in response to a Public Health Emergency of International Concern. Methods were performed in accordance with guidelines and regulations [17].

Patients were selected from the Brazilian COVID-19 Registry, a retrospective 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 [18]. 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 adult patients (aged 18 or older) with confirmed COVID-19 diagnosis through real time polymerase-chain reaction (RT-PCR) or serologic testing (symptoms and positive test; diagnosis based only on typical clinical symptoms was not accepted), according to World Health Organization guidance, who were hospitalized in one of the participating centers from March 1st to September 30th, 2020, during the first wave of the COVID-19 pandemic in Brazil [19]. Patients who developed their first COVID-19 symptoms while hospitalized for other conditions, or those who were admitted on mechanical ventilation, unable to perform the complete neurological exam and collection of clinical history were not included in this analysis.

2.2. Data collection

Study data were collected by trained hospital staff using Research Electronic Data Capture (REDCap) tools [20], hosted at the Telehealth Center, University Hospital, Universidade Federal de Minas Gerais [21]. Medical records were reviewed by trained health professionals or interns, 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 presentation, and upon ICU admission (if admission was required); laboratory, imaging, electrocardiographic data; inpatient medications, treatment and outcomes. A detailed data management plan (DMP) was developed and provided to all participating centers (Supplementary File 1).

Stages of disease severity were defined based on WHO classification, as follows:

i. Critical COVID-19: presence of acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation or vasopressor therapy.

ii. Severe COVID-19: any of: (i) oxygen saturation < 90% on room air; (ii) signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute), in addition to the signs of pneumonia.

iii. Non-severe COVID-19: absence of any criteria for severe or critical COVID-19.

2.3. Neurological manifestations

Neurological manifestations were assessed upon hospital presentation, i.e., when the patient sought care at the emergency department and had his/her first clinical assessment. They were categorized as: (1) 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) [9]. The controls were enrolled COVID-19 patients with no neurological manifestations/syndromes (for more details see Statistical analysis section).

2.4. Primary and secondary outcomes

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included hospital stay, admission and time to the intensive care unit (ICU), mechanical ventilation, acute kidney injury (AKI), septic shock, nosocomial infection, dialysis, acute heart failure, vascular thrombosis and laboratory parameters.

2.5. 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 Wilcoxon-Mann-Whitney or Kruskal-Wallis tests were used for continuous variables. Missing data were not imputed.

First, we compared clinical features and laboratory findings at hospital presentation among patients with reported symptoms, clinically-defined neurological syndrome and no neurological manifestations using the whole sample (unmatched). Bonferroni correction was undertaken for multiple testing, by dividing the critical p -value (0.05) by the number of comparisons.

When analyzing for primary and secondary outcomes, as categorizing patients according to the presence of neurological manifestations would lead to groups with different distribution of age, sex and number of comorbidities, treating hospital and presence of underlying neurological disease, and given the fact that these variables may be prognostic factors in COVID-19, a propensity score analysis through nearest neighbor matching (within 0.25 standard deviations of the logit of the propensity score, on a scale from 0 to 1.00) was used to control for confounding, by balancing those variables across the groups. Propensity score model was estimated by a logistic regression model, using the MatchIt package in R software. There were six different matchings:

i. Patient with at least one clinically-defined neurological syndrome, were matched with patients with no clinically-defined neurological syndrome, taking into account sex, age, number of comorbidities, admitting hospital, and past history of neurological disease;

ii. Patient with at least one clinically-defined neurological syndrome, were matched with patients with no clinically-defined neurological syndrome, taking into account sex, age, number of comorbidities, and admitting hospital, without taking into account past history of neurological disease;

iii. Patient with any neurological manifestation (clinically-defined neurological syndrome or reported neurological symptom) were matched with patients with no neurological manifestation, taking into account 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;

iv. Patient with any neurological manifestation (clinically-defined neurological syndrome or reported neurological symptom) were matched with patients with no neurological manifestation, taking into account 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), and admitting hospital, without taking into account past history of neurological disease;

v. Patient with a reported neurological symptom (and no clinically-defined neurological syndrome) were matched with patients with no neurological manifestation, taking into account 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;

vi. Patient with a reported neurological symptom (and no clinically-defined neurological syndrome) were matched with patients with no neurological manifestation, taking into account 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, without taking into account past history of neurological disease.

A prespecified sample size was not calculated. All patients who had the inclusion criteria and no excluding factors were included. All statistical analysis was performed with R software (version 4.0.2).

3. Results

This study involved 6635 patients (Fig. 1). The median age was 60.0 (47.0–72.0) years, 54.3% were men, and COVID-19 confirmation was through RT-PCR in 96.7% of them. Neurological manifestations were present in 39.9% of the patients, of which 30.8% were subjects with reported neurological manifestations, and 10.3% were subjects with clinically-defined neurological syndrome.

Headache was the most common reported neurological symptom (20.7%), followed by ageusia (11.1%) and anosmia (8.0%). Regarding clinically-defined neurological syndromes, acute encephalopathy was the most commonly diagnosed, affecting 9.7% of patients. Other neurological syndromes were much less frequent (Table 1).

Table S1 shows clinical features and laboratory findings stratified by each category of neurological manifestations for the original sample, and Table S2 shows the *p*-value for each comparison, with Bonferroni correction. When comparing patients with a clinically-defined neurological syndrome to those with reported neurological symptoms and those with no neurological symptoms, the first group was older and had a higher prevalence of all comorbidities assessed, except for obesity, which was lower than the other groups. They also had higher frequency of inotropes requirement, lower SF ratio, lower hemoglobin, higher leucocytes count, lactate, C-reactive protein, urea, creatinine and sodium at hospital presentation, as well as a higher frequency of several and critical diseases, when compared to both groups (Tables S1 and S2). When comparing patients with a reported neurological manifestation with those with no manifestations, the first group had a lower frequency to all assessed comorbidities, except for obesity.

3.1. Matched analysis

3.1.1. Patients with any neurological manifestation vs. patients with no neurological manifestation (Table 2)

When comparing patients with any neurological manifestations to matched controls, there was no significant difference in the incidence of acute kidney injury, acute heart failure, septic shock, nosocomial infection, dialysis, acute heart failure and/or vascular thrombosis, as well as need for invasive mechanical ventilation support, intensive care unit admission and mortality.

3.1.2. Patients with a reported neurological symptom (and no clinically-defined neurological syndrome) vs. patients with no neurological manifestation (Table 3)

Mortality was lower in patients with reported neurological symptoms when compared to controls, in both comparisons (taking and not taking account underlying neurological diseases to select matched controls). When underlying neurological diseases (previously diagnosed neurological comorbidities) were taken into account to select matched controls, they also had a lower incidence of need for invasive mechanical ventilation support.

Table 1
Neurologic manifestations at hospital presentation in the study population (*n* = 6635).

Characteristics	Patients n (%)
Any neurological manifestation	2645 (39.86%)
Reported neurological symptoms	2042 (30.8%)
Headache	1371 (20.7%)
Ageusia	739 (11.1%)
Anosmia	529 (8.0%)
Syncope or dizziness	91 (1.4%)
Neurological diagnoses captured by clinical evaluation	679 (10.3)
Acute encephalopathy	645 (9.7%)
Coma	34 (0.5%)
Seizures	25 (0.5%)
Stroke	14 (0.2%)
Peripheral neuropathy	3 (0.04%)

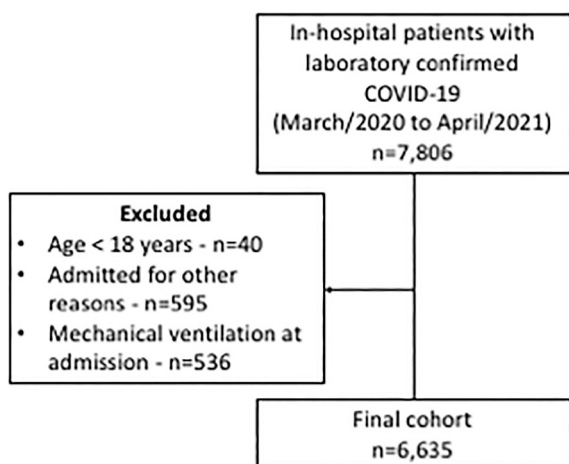


Fig. 1. Flowchart of COVID-19 patients included in the study.

Table 2

Clinical outcomes when comparing patients with any neurological manifestation with paired controls, taking or not account underlying neurological diseases.

Characteristics	Taking into account underlying neurological disease			Without taking into account underlying neurological disease		
	Cases	Controls*	p-value	Cases	Controls**	p-value
	n = 2564***	n = 2564		n = 2587***	n = 2587	
Age (years)	59.0 (46.0, 72.0)	60.0 (47.0, 71.0)	0.715	59.0 (46.0, 73.0)	60.0 (47.0, 71.0)	0.770
Men	1328 (51.8%)	1300 (50.7%)	0.451	1318 (50.9%)	1300 (50.3%)	0.636
Hospital stay	7.0 (4.0, 13.0)	8.0 (4.0, 13.0)	0.016	7.0 (4.0, 13.0)	8.0 (4.0, 13.0)	0.013
ICU	834 (32.6%)	875 (34.2%)	0.252	836 (32.4%)	890 (34.5%)	0.118
Mechanical ventilation	556 (22.2%)	596 (23.7%)	0.204	558 (22.0%)	581 (23.0%)	0.445
AKI	498 (23.2%)	551 (25.0%)	0.175	504 (23.2%)	551 (24.8%)	0.208
Septic shock	260 (10.1%)	269 (10.5%)	0.717	261 (10.1%)	266 (10.3%)	0.854
Nosocomial infection	232 (9.1%)	226 (8.8%)	0.803	233 (9.0%)	215 (8.3%)	0.401
Dialysis	206 (8.1%)	225 (8.8%)	0.372	207 (8.0%)	230 (8.9%)	0.269
Acute heart failure	64 (2.5%)	62 (2.4%)	0.926	64 (2.5%)	60 (2.3%)	0.785
Vascular thrombosis	103 (4.0%)	118 (4.6%)	0.337	103 (4.0%)	129 (5.0%)	0.093
Death	428 (16.7%)	437 (17.1%)	0.785	434 (16.8%)	890 (34.5%)	0.911

Numbers are presented as median (IQR) or n (%).

Cases: patients with any neurological manifestation upon hospital presentation; controls: matched patients who did not have any neurological manifestation upon hospital presentation.

AKI: acute kidney injury. ICU: intensive care unit.

* Matched by age, gender, number of comorbidities, hospital and underlying neurological disease.

** Matched by age, gender, number of comorbidities and hospital.

Table 3

Clinical outcomes when comparing patients with reported neurological symptoms with paired controls, taking or not account underlying neurological diseases.

Characteristics	Taking into account underlying neurological disease			Without taking into account underlying neurological disease		
	Cases	Controls*	p-value	Cases	Controls**	p-value
	n = 1933***	n = 1933		n = 1933***	n = 1933	
Age (years)	54.0 (43.0, 65.0)	53.0 (41.0, 65.0)	0.265	54.0 (43.0, 65.0)	54.0 (41.0, 65.0)	0.467
Men	996 (51.5%)	1022 (52.9%)	0.421	1001 (51.8%)	1030 (53.3%)	0.367
Hospital stay	7.0 (4.0, 11.0)	7.0 (4.0, 12.0)	0.012	6.0 (4.0, 11.0)	7.0 (4.0, 12.0)	0.021
ICU	546 (28.3%)	610 (31.6%)	0.028	547 (28.3%)	590 (30.6%)	0.141
Mechanical ventilation	359 (18.9%)	387 (20.3%)	0.299	359 (18.9%)	387 (20.4%)	0.274
AKI	312 (19.5%)	321 (19.6%)	0.980	312 (19.5%)	336 (20.5%)	0.515
Septic shock	150 (7.8%)	159 (8.2%)	0.635	149 (7.7%)	171 (8.8%)	0.220
Nosocomial infection	162 (8.4%)	152 (7.9%)	0.596	162 (8.4%)	152 (7.9%)	0.596
Dialysis	139 (7.2%)	129 (6.7%)	0.566	139 (7.2%)	130 (6.7%)	0.613
Acute heart failure	28 (1.4%)	29 (1.5%)	>0.999	28 (1.4%)	35 (1.8%)	0.446
Vascular thrombosis	82 (4.2%)	94 (4.9%)	0.396	82 (4.2%)	94 (4.9%)	0.396
Death	177 (9.2%)	229 (11.9%)	0.008	177 (9.2%)	234 (12.1%)	0.004

Numbers are presented as median (IQR) or n (%).

Cases: patients with any neurological manifestation upon hospital presentation; controls: matched patients who did not have any neurological manifestation upon hospital presentation.

AKI: acute kidney injury. ICU: intensive care unit.

* Matched by age, gender, number of comorbidities, hospital and underlying neurological disease.

** Matched by age, gender, number of comorbidities and hospital.

*** The total number of patients with reported neurological symptoms is 1966, but in propensity score analysis we opt not to force the model to find a pair that does not meet all the pre-specified requirements, to avoid comparing to a sample that is not similar enough. That is also the reason for the different numbers when taking account or not underlying neurological disease.

3.1.3. Patients with clinically-defined neurological syndrome vs. patients with no clinically-defined neurological syndrome (Table 4)

Patients presenting with clinically-defined neurological syndromes had higher mortality when compared to controls, in both comparisons (taking and not taking into account underlying neurological diseases to select matched controls). In the comparison which took into account underlying neurological diseases, they also had a higher frequency of ICU admission (45.3% vs. 38.9%, $p = 0.02$). When underlying neurological diseases were not taken into account, they had a higher frequency of septic shock (17.0 vs. 13.0, $p = 0.045$).

4. 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. It is also the first study that associates, in a large sample, the presence of reported neurological symptoms, such as anosmia and ageusia to a better COVID-19 prognosis. 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 [22–24]. Our results showed that approximately 40% of the patients admitted to a hospital due to COVID-19 presented reported or clinically-diagnosed neurological symptoms and/or syndromes upon hospital presentation. More importantly, the presence of clinically-defined neurological symptoms was associated with worse clinical outcomes, including the

Table 4

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

Characteristics	Taking into account underlying neurological disease			Without taking into account underlying neurological disease		
	Cases	Controls*	p-value	Cases	Controls**	p-value
	n = 648***	n = 648		n = 672***	n = 672	
Age (years)	78.0 (66.8, 84.0)	77.0 (66.0, 84.0)	0.785	78.0 (67.0, 85.0)	77.0 (66.0, 85.0)	0.719
Men	325 (50.2%)	322 (49.7%)	0.912	333 (49.6%)	350 (52.1%)	0.383
Hospital stay	10.0 (5.0, 16.0)	9.0 (5.0, 16.0)	0.498	9.5 (5.0, 16.0)	9.0 (5.0, 15.0)	0.249
ICU	292(45.3%)	251 (38.9%)	0.023	295 (44.2%)	264 (39.6%)	0.101
Mechanical ventilation	203 (32.4%)	180 (28.4%)	0.135	204 (31.4%)	191 (29.2%)	0.437
AKI	188 (33.2%)	206 (36.0%)	0.341	193 (32.9%)	208 (35.4%)	0.389
Septic shock	111 (17.2%)	93 (14.4%)	0.191	114 (17.0%)	87 (13.0%)	0.045
Nosocomial infection	72 (11.1%)	66 (10.2%)	0.646	73 (10.9%)	78 (11.6%)	0.737
Dialysis	68 (10.6%)	74 (11.5%)	0.656	69 (10.3%)	78 (11.1%)	0.472
Acute heart failure	33 (5.1%)	21 (3.2%)	0.125	34 (5.1%)	25 (3.7%)	0.284
Vascular thrombosis	22 (3.4%)	37 (5.7%)	0.063	22 (3.3%)	28 (4.2%)	0.474
Death	249 (38.7%)	210 (32.6%)	0.026	262 (39.2%)	202 (30.3%)	<0.001

Numbers are presented as median (IQR) or n (%).

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.

* Matched by age, gender, number of comorbidities, hospital and underlying neurological disease.

** Matched by age, gender, number of comorbidities and hospital.

*** The total number of patients with clinically-defined neurological syndromes is 679, but in propensity score analysis we opt not to force the model to find a pair that does not meet all the pre-specified requirements, to avoid comparing to a sample that is not similar enough. That is also the reason for the different numbers when taking account or not underlying neurological disease.

need for ICU admission, septic shock and death.

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, which is currently the largest meta-analysis on the topic [8]. When considering only the subanalysis of hospitalized patients, the observed incidence of ageusia and anosmia in our study was inside the confidence interval (10.4 vs. 13% [95% CI 8 to 19%], and 7.4 vs. 11% [95% CI 8 to 15%], respectively); while the frequency of headache was higher than the authors observed in the pooled analysis (19.3 vs. 11% [95%CI 10 to 12%]) [8].

It has been hypothesized that patients with severe COVID-19 might not be able to provide a clear history regarding smell or taste impairment [8]. 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 [18]. Ageusia and anosmia have been regarded as independent positive prognostic factors of a less severe COVID-19 infection [25,26]. 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) [8].

The incidence of headache in the aforementioned meta-analysis was 13% (95% CI 12%–15%, 202 studies) [8], lower than what we observed in our cohort (20.7%). Interestingly, a subgroup analysis has shown that the pooled prevalence of headache was higher from April to September 2020 (16%–22%) compared to January–March 2020 (8%–14%). In Brazil, the first COVID-19 case was at the end of February, and there were only a few cases included in this cohort in March, as it can be seen in a previous publication by our group [18]. We hypothesize that this may explain the difference in incidence when compared to the point estimate.

Acute encephalopathy was the most common clinically-defined neurological syndrome (9.7%) in our study, similar to the one reported in the aforementioned systematic review [8]. 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 severe COVID-19 and mortality, up to one year of hospitalization [10,27]. 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 [28].

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 [7] and observed a higher prevalence of neurological manifestations overall. The presence of clinically-defined syndromes, but not reported symptoms, were associated with worse outcomes, i.e. increased risk of in-hospital mortality, 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 [7]. 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 presentation, 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 [28].

The pathogenesis of neurological manifestations is still under investigation, and it seems to involve different mechanisms for distinct signs or symptoms [9,16]. 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 encephalopathy have increased serum levels of

pro-inflammatory molecules, such as interleukins 6 and 8. Furthermore, critically ill patients with COVID-19 commonly develop delirium, which can be a prodromal symptom of hypoxia secondary to severe respiratory failure, microvascular disease, and/or inflammatory brain changes, with significantly higher microglial activation in the hippocampus [12,29–35]. In contrast, patients with headache (but no encephalopathy) did not display increased levels of inflammatory cytokines [23].

In a recent meta-analysis assessing the impact of neurological manifestations on COVID-related mortality, involving 21 studies, the authors observed a higher mortality among patients with any neurological manifestations than the one observed for the ones with neurological manifestations in the current analysis (18.3% vs. 27% [95% CI 19%–35%]) [10]. Some of the studies included in the meta-analysis only assessed clinically-defined neurological syndromes, which could explain the higher mortality rate. In our study, when assessing patients with any neurological manifestations at hospital presentation when compared to matched controls, there were no significant differences in the assessed outcomes. For the comparison of patients with clinically defined neurological syndromes with matched controls, our findings were in line and expanded the results of the meta-analysis, with higher frequency of septic shock, ICU admission, and mortality, regardless of previous history of neurological diseases. 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.

Surprisingly, patients with reported neurological symptoms had a lower mortality than matched controls. A recent meta-analysis of 45 articles including 42,120 COVID-19 patients from 17 different countries has shown that severely ill COVID-19 patients have a lesser chance of experiencing anosmia than non-severely ill patients (odds ratio 0.527 [95% CI 0.373–0.744; $p < 0.001$]) [29]. There is also evidence of an independent association between anosmia and lower mortality (OR: 0.180, 95% CI: 0.069–0.472) and ICU admission (OR: 0.438, 95% CI: 0.229–0.838, $p = 0.013$) [12,36]. Previous publications have shown differences in inflammatory response in patients with anosmia, including significantly lower serum IL-6 and fibrinogen levels, as well as higher leukocyte and CD8-lymphocyte counts [37].

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. Also, it is the first study that evaluates the prevalence of neurological manifestations of COVID-19 in the Brazilian population, corroborating with findings from studies from different regions while also bringing the association between milder neurological symptoms (such as anosmia and ageusia) and better disease prognosis. However, the present study also has limitations that must be acknowledged. Even though the classification of neurological manifestation was based on the one used in ENERGY study, which included three large multicentric neurological cohorts [9] the categorization has methodological limitations. We opted to use the same classification to enable comparisons of the frequencies of the different categories in that study with our results. Additionally, we did not assess the impact of the neurological manifestations across ethnicities. Brazil is a highly miscigenic country, and there is evidence of worse prognosis among *Pardo* and Black populations [38]. That is an important topic for future studies. Second, the study is subjected to the drawbacks inherent to data retrospectively obtained from medical record reviews. To minimize that, the research staff was extensively trained and the data was subject to periodic auditing to ensure data quality. Another limitation 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 reported neurological symptoms or clinically defined neurological syndromes before intubation), which unable full neurological exam and collection of clinical history. 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 reported neurological symptoms could not be determined, and relevant information (e.g. neuroimaging results) was not available in all sites, during admission. Furthermore, participant hospitals were not randomly selected, and they are not necessarily representative of the whole healthcare system in Brazil. Finally, SARS-CoV-2 is susceptible to genetic modifications, which result in the development of multiple variants [39]. These may have different profiles regarding neurological symptoms, therefore our data can not be fully extrapolated to other waves.

5. 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.

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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. MSM had full access to all the data in the study and had responsibility for the decision to submit for publication.

Data sharing statement

Since data was obtained through patients' records, 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, LEFR, LFIA, FA, LK, ASMC, MCAN, HD, KPMPM, LBM, CTCAS, NRO, PKZ, MHGJ, MOSSL, RLOA, 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.

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

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

Final approval of the version to be published: all authors.

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.

Declaration of Competing Interest

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Appendix A. Supplementary data

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