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Neurological manifestations by sex and age group in COVID-19 inhospital patients

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ABSTRACT

Introduction: Neurological manifestations have been associated with a poorer prognosis in COVID-19. However, data regarding their incidence according to sex and age groups is still lacking.

Abbreviations: ACE2, Angiotensin-converting enzyme 2; AD, Alzheimers disease; BMI, Body mass index; CI, Confidence interval; CNS, Central nervous system; COPD, Chronic obstructive pulmonary disease; IQR, Interquartile range; OR, Odds ratio.

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Neurological manifestations
Age
Sex
Delirium

Methods: This retrospective multicentric cohort collected data from 39 Brazilian hospitals from 17 cities, from adult COVID-19 admitted from March 2020 to January 2022. Neurological manifestations presented at hospital admission were assessed according to incidence by sex and age group.
Results: From 13,603 COVID-19 patients, median age was 60 years old and 53.0% were men. Women were more likely to present with headaches (22.4% vs. 17.7%, $p < 0.001$; OR 1.36, 95% confidence interval [CI] 1.22–1.52) than men and also presented a lower risk of having seizures (OR 0.43, 95% CI 0.20–0.94). Although delirium was more frequent in women (6.6% vs. 5.7%, $p = 0.020$), sex was not associated with delirium in the multivariable logistc regresssion analysis. Delirium, syncope and coma increased with age (1.5% [18–39 years] vs. 22.4% [80 years or over], $p < 0.001$, OR 1.07, 95% CI 1.06–1.07; 0.7% vs. 1.7%, $p = 0.002$, OR 1.01, 95% CI 1.00–1.02; 0.2% vs. 1.3% $p < 0.001$, OR 1.04, 95% CI 1.02–1.06), while, headache (26.5% vs. 7.1%, OR 0.98, 95% CI 0.98–0.99), anosmia (11.4% vs. 3.3%, OR 0.99, 95% CI] 0.98–0.99 and ageusia (13.1% vs. 3.5%, OR 0.99, CI 0.98–0.99) decreased ($p < 0.001$ for all).
Conclusion: Older COVID-19 patients were more likely to present delirium, syncope and coma, while the incidence of anosmia, ageusia and headaches decreased with age. Women were more likely to present headache, and less likely to present seizures.

1. Introduction

Neurological manifestations have been frequently associated with COVID-19 [1]. Symptoms may differ among patients, including symptoms and signs of both peripheral and central nervous system (CNS) dysfunction [1–3]. Such neurological manifestations, especially clinically-defined neurological syndromes (e.g. delirium), have been associated with a poorer COVID-19 prognosis, even when controlling for age, sex and number of medical comorbidities [4,5].

Previous studies have shown that age and sex are important prognostic factors in COVID-19 patients. Children and young adults are not as prone to severe forms of COVID-19 compared to older adults [6–9]. Elderly patients are more likely to progress to severe disease and mortality due to age-related immunosenescence and comorbidities [10–12]. The reasons for sex differences are believed to be related to distinct immune response profiles [13] and gender inequalities, including socioeconomic status and occupational exposure [14–16]. Age and sex-related differences in the efficiency of the immune response may influence disease presentation and outcomes [17].

In this context, there is a dearth of data regarding incidence of neurological manifestations in COVID-19 patients according to sex and age groups [18], especially in Latin America. Therefore, our aim was to fill this gap in knowledge, assessing a large database of Brazilian patients.

2. Methods

This study is part of a multicentric cohort, Brazilian COVID Registry Project, which collected data from 39 Brazilian hospitals from 17 Brazilian cities, described in detail elsewhere [19]. It was approved by the National Commission for Research Ethics (CAAE 30350820.5.1001.0008). Due to the worldwide concern on the pandemic and the urgency for studies of COVID-19 and to the fact that data was collected solely by review of medical records, individual informed consent was waived by the National Commission for Research Ethics.

Consecutive adult patients with laboratory confirmed diagnosis of COVID-19 [20], who were admitted to the participating hospitals from March 2020 to January 2022, were enrolled in the study. Data on patient's demographic and clinical characteristics, laboratory findings and outcomes were collected through the revision of medical records by trained hospital staff using Research Electronic Data Capture (REDCap) tools [21]. Neurological manifestations caused by COVID-19 presented at hospital presentation systematically assessed in this study included stroke, delirium, coma, seizures, manifestations of the peripheral nervous system (e.g. hypo/anesthesia, dysesthesia, pain), anosmia, ageusia, headaches and syncope.

For data analysis, categorical data was expressed by proportions and absolute numbers, meanwhile continuous variables were presented as medians and interquartile ranges. To compare distribution of categorical and continuous variables, the Fisher Exact test and the Kruskal-Wallis tests were used, respectively. The analysis was conducted evaluating neurological manifestations by sex and age group: i) 18–39; ii) 40–59; iii) 60–79; iv) 80 years old or over.

To assess age and sex as predictors of each neurological manifestation, stepwise multivariate logistic regression analysis was performed. In addition to age and sex, other variables assessed at hospital admission which have shown to be prognostic predictors in a previous analysis were also included as covariates [22]. For the analysis of self-reported symptoms (ageusia, anosmia, headache), patients with coma, delirium and dementia were not included in the models given the possibility of reporting bias.

All statistical analyses were performed using the R software (version 4.0.2), and its packages data.table, tidyverse, gtsummary and gt. A *p*-value below 0.05 was considered as statistically significant.

3. Results

The current study included 13,603 COVID-19 patients (median age 60 years old, interquartile range [IQR] 47–71, 53.0% were men). Hypertension (53.0%) was the most common medical comorbidity, followed by diabetes (27.1%) and obesity (17.8%) (Table 1).

When comparing demographic data regarding both sexes, it was observed that women were slightly older than men (median age of 61 vs. 58 years old). Also, the prevalence of hypertension, heart failure, asthma, diabetes, psychiatric conditions, obesity and dementia were higher in women, meanwhile coronary artery disease, cirrhosis and chronic kidney disease were more prevalent in men (Table 1).

When stratifying groups according to sex, women had a higher frequency of delirium (6.6% vs. 5.7%, $p = 0.020$) and headache (22.4% vs. 17.7%, $p < 0.001$) when compared to men (Table 2). However, sex was not associated with delirium in the multivariable logistc regresssion analysis. Women had a higher risk of headaches (OR 1.36, 95% confidence interval [CI] 1.22–1.52), and lower risk of seizures (OR 0.43, 95% CI 0.20–0.94) (Table 3).

As shown on Table 4, incidence of delirium, syncope and coma increased with age; older age was associated with delirium and coma in the multivariable logistic regression analysis. Conversely, headache, anosmia and ageusia decreased with increased age, findings confirmed in the multivariate analysis. (Tables 3 and 4).

4. Discussion

The Brazilian COVID Registry Project is one of the largest cohorts of COVID-19 patients which assessed neurological manifestations in detail. We observed that older patients presented a higher incidence of neurological manifestations associated with worse prognosis, such as delirium and coma, when compared to other age groups. Conversely,

Table 1
Demographic and clinical characteristics according to sex in the Brazilian COVID Registry Project, 2020–2022 (n = 13,603).

Characteristics	Overall[a] (n = 13,603)	Men[a] (n = 7211)	Women[a] (n = 6392)	p-value[b] [c]
Age	60.0 (47.0, 71.0)	58.0 (46.0, 70.0)	61.0 (48.0, 73.0)	<0.001
Atrial flutter/ fibrillation	379 (2.8%)	197 (2.7%)	182 (2.8%)	0.722
Hypertension	7205 (53.0%)	3486 (48.3%)	3719 (58.2%)	<0.001
Coronary artery disease	683 (5.0%)	421 (5.8%)	262 (4.1%)	<0.001
Heart failure	745 (5.5%)	348 (4.8%)	397 (6.2%)	<0.001
Stroke	458 (3.4%)	226 (3.1%)	232 (3.6%)	0.121
Chagas disease	45 (0.3%)	21 (0.3%)	24 (0.4%)	0.481
Asthma	797 (5.9%)	256 (3.6%)	541(8.5%)	<0.001
COPD	697 (5.1%)	350 (4.9%)	347 (5.4%)	0.139
Pulmonary fibrosis	55 (0.4%)	26 (0.4%)	29 (0.5%)	0.472
Diabetes mellitus	3689 (27.1%)	1790 (24.8%)	1899 (29.7%)	<0.001
Obesity (BMI > 30 kg/m2)	2417 (17.8%)	1059 (14.7%)	1358 (21.2%)	<0.001
Cirrhosis	76 (0.6%)	50 (0.7%)	26 (0.4%)	0.034
Psychiatric diseases	1018 (7.5%)	354 (4.9%)	664 (10.4%)	<0.001
Chronic renal disease	674 (5.0%)	382 (5.3%)	292 (4.6%)	0.055
Dementia	298 (2.2%)	111 (1.5%)	187 (2.9%)	<0.001

[a] Statistics are presented as n (%).
[b] Statistical tests performed: chi-square test of independence; Fisher's exact test.
[c] COPD: chronic obstructive pulmonary disease; BMI: body mass index.

Table 2
Incidence of neurological manifestations according to sex in the Brazilian COVID Registry Project, 2020–2022 (n = 13,603).

Neurological manifestation	Overall[a] (N = 13,603) n(%)	Men[a] (N = 7211) n(%)	Women[a] (N = 6392) n(%)	p-value[b]
Headache	2705 (19.9%)	1275 (17.7%)	1430 (22.4%)	**<0.001**
Ageusia	1275 (9.4%)	643 (8.9%)	632 (9.9%)	0.056
Anosmia	1110 (8.2%)	561 (7.8%)	549 (8.6%)	0.091
Delirium	834 (6.1%)	409 (5.7%)	425 (6.6%)	**0.020**
Syncope	133 (1.0%)	69 (1.0%)	64 (1.0%)	0.861
Coma	68 (0.5%)	36 (0.5%)	32 (0.5%)	>0.999
Stroke	27 (0.2%)	16 (0.2%)	11 (0.2%)	0.647
Seizures	39 (0.3%)	26 (0.4%)	13 (0.2%)	0.121
Peripheral neuropathy	10 (0.1%)	8 (0.1%)	2 (0.0%)	0.116

[a] Statistics are presented as n (%)
[b] Statistical tests performed: chi-square test of independence; Fisher's exact test.

Table 3
Prediction models for each neurological manifestation, taking account clinical features obtained at hospital presentation.

Variable	OR (CI 95%)	p-value
Ageusia		
(Intercept)	0.636	0.102
Age	0.987 (0.982–0.992)	<0.001
Female sex	1.124 (0.978–1.292)	0.100
Urea	0.995 (0.992–0.998)	0.001
C-reactive protein	0.998 (0.997–0.999)	<0.001
Platelet count	0.999 (0.998–1.000)	0.002
Heart rate	0.996 (0.992–1.001)	0.112
Anosmia		
(Intercept)	0.460	0.004
Age	0.987 (0.982–0.992)	<0.001
Urea	0.997 (0.994–1.000)	0.035
C-reactive protein	0.999 (0.998–1.000)	0.020
Heart rate	0.994 (0.990–0.999)	0.016
Coma		
(Intercept)	0.002	<0.001
Age	1.039 (1.020–1.058)	<0.001
Mechanical ventilation	12.109 (5.411–27.098)	<0.001
Oxygen saturation	0.994 (0.991–0.996)	<0.001
Delirium		
(Intercept)	0.000	<0.001
Age	1.070 (1.064–1.077)	<0.001
Mechanical ventilation	0.000 (0.000)	0.957
Urea	1.006 (1.004–1.008)	<0.001
Oxygen saturation	0.999 (0.998–1.000)	0.020
Heart rate	1.012 (1.007–1.017)	<0.001
Headache		
(Intercept)	1.477	0.082
Age	0.981 (0.978–0.985)	<0.001
Female sex	1.363 (1.224–1.517)	<0.001
Urea	0.993 (0.990–0.995)	<0.001
Number of comorbidities	0.920 (0.871–0.971)	0.003
C-reactive protein	0.999 (0.998–1.000)	0.004
SF ratio	1.000 (1.000–1.001)	0.055
Platelets	0.999 (0.999–1.000)	0.027
Heart rate	0.998 (0.994–1.001)	0.147
Peripheral neuropathy		
(Intercept)	0.001	<0.001
Number of comorbidities	0.657 (0.338–1.275)	0.214
Seizure		
(Intercept)	0.008	<0.001
Female sex	0.433 (0.199–0.942)	0.035
C-reactive protein	0.991 (0.984–0.998)	0.009
Stroke		
(Intercept)	0.001	<0.001
Platelets	1.004 (1.001–1.007)	0.016
Syncope		
(Intercept)	0.005	0 < 0.001
Age	1.012 (1.000–1.025)	0.059
Number of comorbidities	1.157 (0.984–1.361)	0.078
C-reactive protein[a]	0.998 (0.995–1.000)	0.077

[a] OR: odds ratio; CI: confidence interval

younger patients were more likely to present mild neurological symptoms, such as anosmia, ageusia and headache. Women were more likely to present headache, and less likely to have seizures.

COVID-19 clinical presentations vary widely from asymptomatic cases and mild respiratory symptoms to severe pulmonary, neurological and cardiovascular manifestations [23]. When infecting the human body, SARS-CoV-2 binds to Angiotensin-Converting Enzyme 2 (ACE2) [24] receptors present in different cell types of the CNS [25]. These CNS cells expressing ACE2 receptors are mainly present in the posterior cortex, posterior cingulate cortex, medial temporal gyrus and the olfactory bulb [25]. Besides a potential direct effect of SARS-CoV-2 on neurons and glial cells, the elicited systemic inflammatory cascade can lead to neuroinflammation and, therefore, contribute to CNS dysfunction and related symptoms and signs [26–28] This unregulated inflammatory response is more common in elderly people, what justifies a higher incidence of symptoms related to a poorer prognosis and are more likely to present severe COVID-19 neurological presentation, including delirium and coma. This finding corroborated previous studies showing delirium as the most frequent neurological symptom in older adults with COVID-19 [29,30]. Delirium has even been described as an atypical presentation of COVID-19, particularly in frailty older adults and those with dementia [31].

Recent systematic reviews observed that anosmia was more common in less-severe cases of COVID-19, but information on anosmia and ageusia in older patients was still limited [32,33]. The current study addressed this gap showing that older patients are less likely to present anosmia. Studies with non-COVID-19 upper respiratory tract infections have already shown that women present a higher prevalence of anosmia than men. Nonetheless, the prevalence of anosmia in these respiratory infections was higher in older than younger patients [34]. In COVID-19, younger patients have a higher incidence of anosmia and ageusia. Since delirium is frequent in older patients with COVID-19, it is possible that these patients with delirium did not report anosmia and ageusia. The same trend of decreasing typical manifestations and increasing

Table 4
Incidence of neurological manifestations according to age group in the Brazilian COVID Registry Project, 2020–2022 (n = 13,603).

Manifestation	Age group (years-old)[a]				p-value[b]
	18–39 $N = 1840$ n(%)	40–59 $N = 4923$ n(%)	60–79 $N = 5277$ n(%)	80 or over $N = 1563$ n(%)	
Delirium	27 (1.5%)	107 (2.2%)	350 (6.6%)	350 (22.4%)	<0.001
Coma	4 (0.2%)	17 (0.3%)	26 (0.5%)	21 (1.3%)	<0.001
Seizure	6 (0.3%)	13 (0.3%)	15 (0.3%)	5 (0.3%)	0.924
Stroke	3 (0.2%)	7 (0.1%)	14 (0.3%)	3 (0.2%)	0.570
Anosmia	210 (11.4%)	473 (9.6%)	375 (7.1%)	52 (3.3%)	<0.001
Ageusia	241 (13.1%)	565 (11.5%)	414 (7.8%)	55 (3.5%)	<0.001
Peripheral neuropathy	2 (0.1%)	6 (0.1%)	1 (0.0%)	1 (0.1%)	0.153
Headache	487 (26.5%)	1271 (25.8%)	836 (15.8%)	111 (7.1%)	<0.001
Syncope	12 (0.7%)	36 (0.7%)	58 (1.1%)	27 (1.7%)	0.002

[a] Statistics are presented as n (%).
[b] Statistical tests performed: chi-square test of independence; Fisher's exact test.

frequency of delirium with age has been observed in other diseases, such as in viruses' and bacterial infections [33,35].

The increased incidence of headache in women might reflect a larger epidemiological and biological trend that women are more prone to headache disorders than men [36,37]. A previous outpatient clinic study also observed that headaches were more frequent COVID-19 symptoms in women, as well as olfactory and taste dysfunctions [38]. Although it is considered a mild symptom, post-COVID headaches can be persistent for over three months in up to 19% of cases, impacting directly in the quality of life of post-COVID-19 patients [39].

It is unclear why women had a higher frequency of delirium than men in the study sample. This is a puzzling finding, as male sex is a risk factor for severe COVID-19, and delirium has been associated with worse outcomes, representing a sign of brain/neurological dysfunction [40]. However, in the multivariate analysis, sex was not a predictor for delirium, indicating confounding factors. For instance, the prevalence of dementia was higher in women than men (2.9% vs. 1.5%; $p < 0.001$) and, as a consequence, of delirium [41]. Compelling evidence suggests that women have a greater lifetime risk of developing Alzheimer's disease (AD) or any dementia than men. At age 65, men and women have a lifetime risk of approximately 14% and 20%, respectively, to develop dementia [42,43]. Of note, there is a growing interest in the study of the contribution of social/cultural determinants of health, including social circumstances, environmental characteristics, and early-life exposures, to delirium risk. In this context, it would be tempting to speculate whether these social determinants played any role in the susceptibility of Brazilian women to delirium. However, the matter is still understudied [44,45], and even education level, an important risk factor for dementia, is not properly considered in the delirium literature [45].

The incidence of coma at hospital presentation was low (0.5%, and 1.3% in octogenarians). Results of a registry for neurologic manifestations of 971 patients from 19 countries from an earlier phase of the pandemic also reported that coma corresponded to 23.6% of these manifestations and had a high risk for a worse outcome [46]. As the previously cited study was meant to evaluate only neurological manifestation, a selection bias may have impacted results, since there is no other studies that found such high frequencies of coma in COVID-19 patients.

Overall, the present study allowed us to have a better understanding of neurological manifestations of COVID-19 according to age groups as well as differences of symptoms between the sexes. Even though this study has several strengths, such as its multicentric character, large sample size, it is the largest Brazilian cohort that evaluated COVID-19 neurological manifestations, and one of the largest cohorts which assessed neurological symptoms worldwide, it has limitations. First, as this was an observational study based on data collected from patient charts, there was no formal checklist for neurological signs or symptoms. However, both the Brazilian Ministry of Health COVID-19 Guidelines and the Guidelines from the Brazilian Society of Infectology, Brazilian Society of Pneumology and Brazilian Medical Association recommended global assessment of COVID-19 patients [47], including formal assessment of neurological manifestations. Moreover, there were several online lectures and training in each hospital, to improve and harmonize patient assessment and treatment. Still, we cannot guarantee that the attending physician followed these recommendations, including a standardized assessment of neurological signs and symptoms. Standardized definitions were used for data collectors, who collected data from the medical records [48]. Another limitation is the fact that the current study evaluated neurological manifestations at hospital presentation only, and symptoms emerging later during the hospitalization were not registered for the purpose of the present analysis. At last, it is possible that older people and those who presented more severe neurological symptoms, such as delirium and coma, were not able to report milder symptoms, such as anosmia and ageusia. However, even excluding patients with delirium, coma and dementia from the regression analysis of the self-reported symptoms, younger age was still associated with higher risk of those symptoms.

5. Conclusion

In conclusion, elderly COVID-19 patients presented a higher prevalence of delirium, syncope and coma when compared to younger patients, and older age increased risk of delirium and coma. Younger patients were more likely to present less severe symptoms, such as anosmia, ageusia and headaches. Additionally, women were more likely to present with headache.

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Credit author statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2022.100419.

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