Neurological manifestations by sex and age group in COVID-19 in-hospital 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.

Keywords:
COVID-19

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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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 admission were assessed according to sex and age group. Inclusion criteria were consecutive adult patients with laboratory confirmed diagnosis of COVID-19.

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 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 logistic regression 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, 95% 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.

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

| Characteristics | Overall (n = 13,603) | Men (n = 7211) | Women (n = 6392) | p-value |
|-----------------|---------------------|--------------|-----------------|---------|
| Age             | 60.0 (47.0, 71.0)   | 58.0 (46.0, 70.0) | 61.0 (48.0, 73.0) | <0.001 |
| Airflow/         | 379 (2.8%)          | 197 (2.7%)   | 182 (2.8%)      | 0.722  |
| Fibrillation     | 2705 (53.0%)        | 1346 (28.3%) | 1379 (58.2%)    | <0.001 |
| Coronary artery  | 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         | 1899 (29.7%)    | <0.001 |
| Obesity (BMI > 30 kg/m2) | 1417 (10.0%) | 713 (10.0%) | 704 (11.0%) | <0.001 |
| Chronic obstructive pulmonary disease | 2705 (19.9%) | 1275 (17.7%) | 1430 (22.4%) | <0.001 |
| Psychiatric diseases | 507 (6.0%) | 409 (5.7%) | 198 (6.1%) | <0.001 |
| Chronic renal disease | 1018 (7.5%) | 354 (4.9%) | 664 (10.4%) | <0.001 |
| Dementia         | 298 (2.2%)          | 111 (1.5%)   | 187 (2.9%)      | <0.001 |

<sup>a</sup> Statistics are presented as n (%).
<sup>b</sup> Statistical tests performed: chi-square test of independence; Fisher’s exact test.
<sup>c</sup> 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 (N = 13,603) n(%) | Men (N = 7211) n(%) | Women (N = 6392) n(%) | p-value |
|---------------------------|---------------------------|---------------------|-----------------------|---------|
| Headache                  | 2705 (19.9%)              | 1275 (17.7%)        | 1430 (22.4%)          | <0.001 |
| Age                       | 1275 (9.4%)               | 643 (8.9%)          | 632 (9.9%)            | 0.056  |
| Anosmia                   | 1110 (8.2%)               | 561 (7.8%)          | 549 (8.6%)            | 0.091  |
| Ageusia                   | 834 (6.1%)                | 409 (5.7%)          | 425 (6.6%)            | 0.020  |
| Delirium                  | 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  |

<sup>a</sup> Statistics are presented as n (%).
<sup>b</sup> 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             | 0.636       | 0.102   |
| Female sex          | 0.987 (0.982-0.992) | <0.001 |
| Urea                | 1.124 (0.978-1.292) | 0.100   |
| C-reactive protein  | 0.995 (0.992-0.998) | 0.001   |
| Platelet count      | 0.999 (0.998-1.000) | 0.002   |
| Heart rate          | 0.996 (0.992-1.001) | 0.112   |
| Anosmia             | 0.460       | 0.004   |
| Female sex          | 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                | 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            | 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            | 1.477       | 0.082   |
| Number of comorbidities | 0.657 (0.338-1.275) | 0.214   |
| Seizure             | 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              | 0.001       | <0.001  |
| Platelets           | 0.999 (0.999-1.000) | 0.027   |
| Heart rate          | 0.998 (0.994-1.001) | 0.147   |

<sup>a</sup> OR: odds ratio; CI: confidence interval
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 under-studied [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 manifestations, 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

| Manifestation | Age group (years-old) | p-value<sup>b</sup> |
|---------------|-----------------------|---------------------|
|               | 18–39 | 40–59 | 60–79 | 80 or over |
| N = 1840 | n(%) | N = 4923 | n(%) | N = 5277 | n(%) | 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 (4.3%) | 473 (4.7%) | 375 (7.2%) | 52 (3.3%) | <0.001 |
| Ageusia | 241 (4.7%) | 565 (7.8%) | 414 (7.1%) | 55 (3.5%) | <0.001 |
| Peripheral neuropathy | 2 (0.1%) | 6 (0.1%) | 1 (0.0%) | 1 (0.1%) | 0.153 |
| Headache | 487 (9.2%) | 1271 (25.8%) | 836 (15.8%) | 11 (0.2%) | <0.001 |
| Syncope | 12 (0.7%) | 36 (0.7%) | 58 (1.1%) | 27 (1.7%) | 0.002 |

<sup>a</sup> Statistics are presented as n (%).
<sup>b</sup> Statistical tests performed: chi-square test of independence; Fisher’s exact test.
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