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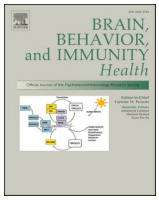

Comparison of cerebrospinal fluid biomarkers in patients with severe COVID-19 neurological outcomes and Alzheimer's disease

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ABSTRACT

Background: COVID-19 induces acute and long-term neurological symptoms. Links between COVID-19 neurological disturbance and Alzheimer's disease (AD) have been hypothesized because neuroinflammation plays a significant role in both diseases. However, it is unknown if COVID-19 patients with neurological disturbance present molecular alterations related to AD pathology. A better understanding of possible molecular links between COVID-19-induced neurological disease and AD would lead to improved patient follow-up and late-onset disease prevention. Here, we analyze early AD biomarkers in a Brazilian cohort of COVID-19 patients with neurological symptoms. We compared COVID-19 patients' neuroinflammatory and AD biomarker levels to controls, amnestic mild cognitive impairment (aMCI), and AD.

Methods: We analyzed cerebrospinal (CSF) biomarkers of neuroinflammation (interleukin-6 (IL6)), amyloid-beta (Aβ) proteinopathy (Aβ42/40), phosphorylated Tau (pTau181), and the neurodegeneration-associated biomarker total Tau in controls (n = 36), COVID-19 patients presenting neurological alterations (n = 35), aMCI (n = 19), and AD patients (n = 20). Comparisons were corrected by possible sex, age, and comorbidities confounding effects. CSF biomarkers were correlated with systemic and neuro-inflammation markers.

Results: We found that severe COVID-19 patients presented higher CSF Tau than controls, comparable to alterations observed in AD patients. However, we did not find changes in CSF Aβ42/40, pTau-181/Aβ42, or Tau/Aβ42 ratios. Severe COVID-19 patients presented higher Tau, Tau/Aβ42, and pTau181/Aβ42 than mild patients. In COVID-19 patients, CSF pro-inflammatory cytokine IL6 and AD biomarkers correlated with systemic inflammatory index (SII).

Conclusions: Collectively, our findings reveal that CSF tau levels are comparably elevated in COVID-19 neurological patients and AD, suggesting ongoing neurodegeneration in COVID-19 neurological disease, but no biomarker alterations related to AD pathology. Furthermore, CNS AD-related biomarker levels in COVID-19 patients change in association with disease severity and systemic inflammation. Considering that inflammation may persist post-COVID, our findings urge the assessment of possible AD-related biomarker changes in COVID-19 survivors with lingering symptoms.

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1. Introduction

COVID-19 frequently induces acute neurological symptoms, including headaches, encephalopathy, and cerebrovascular disease (Chou et al., 2021; Helms et al., 2020a, 2020b; Mao et al., 2020; Romero-Sánchez et al., 2020). Survivors may experience lingering symptoms, including cognitive deficits and mood alterations (Mazza et al., 2021; Sudo et al., 2024; Taquet et al., 2021a, 2021b, 2022; Woo et al., 2020). Although SARS-CoV-2's material is inconsistently found in the central nervous system (CNS) of infected patients, neurological symptoms are accompanied by several neuropathological changes, which include neuroinflammation (CNS cytokine upregulation, glial activation, and immune cell infiltration), neuroimaging abnormalities, and brain vascular damage (Barros-Aragão et al., 2024; Crunfli et al., 2022; Edén et al., 2022; Espíndola et al., 2020a; Espíndola et al., 2021; Thakur et al., 2021; Yang et al., 2021). We recently showed, in a cohort of hospitalized COVID-19 patients with acute/subacute neurological symptoms, that the levels of cerebrospinal fluid (CSF) pro-inflammatory cytokine interleukin-6 (IL6) elevate in association with COVID-19 severity and pronounced neuroimaging alterations (Barros-Aragão et al., 2024). In COVID-19 survivors, we showed that persistent systemic inflammation is associated with neuroimaging abnormalities and memory deficits up to one year post-COVID (Sudo et al., 2024). Altogether, available data supports that inflammation is a main driver of COVID-19-induced neurological disease.

Given that systemic and neuro-inflammation have been associated with multiple neuropsychiatric and neurodegenerative conditions, these findings raise concerns that COVID-19 could trigger or accelerate ongoing molecular alterations that would lead to late-onset neurological poor outcomes, including increased risk for Alzheimer's disease (AD) (De Felice et al., 2020; Lyra e Silva et al., 2022). Accordingly, COVID-19 has been shown to induce cognitive morbidity, even in mild patients, increase the risk of dementia up to two years of follow-up, and accelerate cognitive decline in patients with dementia (Fernández-de-Las-Peñas et al., 2022; Merla et al., 2023; Taquet et al., 2022). Conversely, dementia, including AD, is a risk factor for COVID-19 severity and mortality (Tahira et al., 2021). Additionally, the Apoε 4 allele poses a genetic predisposition for both severe COVID-19 and AD (Kuo et al., 2020). These findings suggest a possible two-way link between the two diseases, where COVID-19 could increase the risk for clinical AD, and having AD (at a pre-clinical or clinical stage) could increase the risk of developing severe/neurological disease when infected by SARS-CoV-2, urging research on possible molecular links between the two diseases.

AD neuropathological changes (ADNPC) include amyloidopathy, tauopathy, neuroinflammation, and neurodegeneration that develop several years before detectable clinical symptoms (Jack Jr et al., 2024; Sperling et al., 2011). The earliest detectable stage of the disease is marked by changes in biomarkers for amyloid-beta (Aβ) proteinopathy and phosphorylated Tau (pTau), which are also termed core 1 AD biomarkers (Jack Jr et al., 2024). Currently, these changes may be detected by elevated cerebrospinal fluid (CSF) pTau181/Aβ42 and t-Tau/Aβ42 and decreased Aβ42/40 ratios, elevated plasma pTau217, or a positive amyloid positron emission tomography (PET) scan (Jack Jr et al., 2024). A growing body of research places neuroinflammation as a possible main contributor to ADNPC, and alterations in inflammatory biomarkers are associated with worse disease prognosis (Jack Jr et al., 2024; Kinney et al., 2018; Lyra e Silva et al., 2022).

COVID-19 patients who develop encephalopathy present higher plasma biomarkers of neurodegeneration, inflammation, and pTau181 than those who do not (Frontera et al., 2022). COVID-19 patients also present deregulated inflammatory and neurodegeneration plasma biomarkers at higher instances than AD patients (Frontera et al., 2022). Compared to controls, COVID-19 patients present altered biomarkers of amyloid processing in association with neuroinflammation (Ziff et al., 2022). The SARS-CoV-2 spike protein interferes with amyloid processing *in vitro* and promotes amyloid deposits and neuroinflammation in AD mice (Ma et al., 2022). These findings strengthen the molecular associations between COVID-19 neurological disease and AD. However, available data is insufficient to understand if COVID-19 patients with neurological disturbance present molecular alterations related to early ADNPC, or the extent of it, as previous reports did not evaluate all core AD biomarkers in COVID-19 patients or compared to controls and AD patients. A better understanding of possible molecular links between COVID-19-induced neurological disease and AD is necessary for improved patient follow-up and the development of preventive strategies for possible late-onset diseases.

Thus, in this study, we aim to evaluate CSF biomarkers associated with early ADNPC (core 1 biomarkers (Jack Jr et al., 2024) also known as the Amyloid, Tau, Neurodegeneration (ATN) framework (Jack et al., 2018)) in a Brazilian cohort of COVID-19 patients with neurological symptoms. Since the interpretation of ADNPC biomarker levels is limited by the lack of established cut-offs for diverse populations with different age ranges, we compared biomarker levels from COVID-19 patients to Brazilian cognitively unimpaired controls, amnestic mild cognitive impairment (aMCI), and AD patients. We further explored links between systemic disease, inflammation, and CNS biomarker levels. To the best of our knowledge, this is the first report that included all AD core CSF biomarkers in COVID-19 neurological patients and compared side-by-side with controls, aMCI, and AD patients. Additionally, reports from low- and middle-income countries (LMIC) are underrepresented in COVID-19 and AD biomarkers studies, adding relevance to this study.

2. Methods

COVID-19 Cohort. We analyzed clinical data and cerebrospinal fluid (CSF) samples from a well-characterized retrospective cohort of COVID-19 hospitalized patients presenting neurological symptoms at D'Or São Luiz Network Hospitals in Rio de Janeiro, Brazil, between April and November 2020 (Barros-Aragão et al., 2024). Inclusion criteria were (1) patients hospitalized with confirmed COVID-19 and (2) clinical indication for cerebrospinal fluid sampling. Exclusion criteria were: (1) COVID-19 tested negative; (2) CSF collected out of hospitalization period; (3) Confirmed infection by another pathogen; (4) Unable to retrieve medical history; (5) Patient under 18 years old. Confirmation of COVID-19 was achieved by detecting genetic material from SARS-CoV-2 through RT-qPCR assays (Allpex, 2019 n-CoV assay #RP10252W) in nasopharyngeal or nasal swabs, or by the detection of anti-SARS-CoV-2 IgG/IgM antibodies in blood. The study protocol and all amendments were approved by the National Commission for Research Ethics (CONEP) from the Brazilian Ministry of Health and the Committee for Research Ethics of D'Or Institute of Research and Education (IDOR), CAAE #29496920.8.0000.5262; CAAE #41576620.7.0000.5249.

Clinical data. We extracted medical history and comorbidities reported by patients or relatives at hospital admission anamnesis, clinical characteristics at hospital admission, in-hospital symptoms, complications, medication used, and laboratory results from the patient's medical records following an approved clinical research form (CRF) (International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and World Health Organization (WHO), 2020a) and clinical characterization protocol (CCP) (International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and World Health Organization (WHO), 2020b) from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and World Health Organization (WHO). An independent data review board had access to unblinded clinical, laboratory, and imaging data. COVID-19 severity classification followed the "Ordinal Scale for Clinical Improvement" proposed by a special committee of the WHO (World Health Organization, 2020). Mild cases encompassed hospitalized patients who did not require oxygen therapy or received oxygen through masks or nasal cannulas. Severe cases included hospitalized patients

who either died or needed one of the following treatments: non-invasive ventilation, high-flow oxygen, intubation, mechanical ventilation, or without additional organ support.

An experienced neurologist reviewed patients' clinical and neuroimaging data to define a major neurological feature. Encephalitis was described as presenting altered mental status for longer than one day and at least two of the following: a) seizures not attributable to a pre-existing condition; b) new-onset focal neurologic finding; c) CSF white blood cell (WBC) count above five cells/mm^3; d) acute neuroimaging alteration compatible with encephalitis; e) electroencephalography compatible with encephalitis, or f) fever (above 38 °C) proximal (within 3-days) of symptom start (Venkatesan et al., 2013).

Pre-pandemic cognitively healthy control, amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD) cohort. COVID-19 patients' CSF molecular biomarkers levels were compared with a pre-pandemic prospective and longitudinal aged cohort (Lourenco et al., 2021) (study protocol and amends were approved by the CONEP from the Brazilian Ministry of Health and the Committee for Research Ethics of IDOR, CAAE #47163715.0.0000.5249 and # 43007915.5.0000.5249). Inclusion criteria were 50 years old or above and eight years of scholarly or above. Participants were evaluated in a battery of cognitive and psychological tests which based their diagnosis as described below. We extracted medical history and comorbidities reported by patients or relatives at anamnesis. For comparison with COVID-19 groups, we included participants diagnosed as cognitively healthy control, aMCI, or AD who collected CSF samples.

Cognitive and behavioral assessments. The cognitive evaluation was performed by neuropsychologists using validated versions of tests. Normative data for the Brazilian population, according to age and schooling, was applied to define impairment cases in each task. The Mini-Mental State Examination (MMSE) was adopted to measure global cognitive performance (Brucki et al., 2003; Folstein et al., 1975). Episodic memory was assessed using the Rey-Auditory Verbal Learning test (RAVLT) (de Paula et al., 2012). The Trail-Making Test evaluated visual tracking/cognitive speed (TMT part A) and cognitive flexibility (TMT part B) (Campanholo et al., 2014). Working memory was measured using the Backwards Digit Span test (Zimmermann et al., 2015). The following scales were applied: the Geriatric Depression Scale (Castelo et al., 2010) and the Geriatric Anxiety Inventory (Massena et al., 2015).

Diagnosis. Dementia was diagnosed according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for Major Neurocognitive Disorder (American Psychiatric Association, 2013) as presenting a cognitive concern from the individual, a knowledgeable informant, or the clinician; evidence of substantial impairment in at least one cognitive domain, demonstrated by neuropsychological assessment; and significant functional difficulties, evidenced by clinical interview. The DSM-5 criteria for Mild Neurocognitive Disorder (American Psychiatric Association, 2013) based Amnestic Mild Cognitive Impairment (aMCI) diagnosis as presenting a cognitive concern of the individual, a knowledgeable informant, or the clinician; evidence of mild impairment in memory (accompanied or not by impairments in other cognitive domains), demonstrated by neuropsychological assessment; and overall preserved functional abilities, as evidenced by clinical interview. A probable AD etiology was indicated by the presence of all the following (American Psychiatric Association, 2013): prominent impairment in memory tasks; insidious onset and gradual progression of symptoms; symptoms not consistent with cerebrovascular disease, psychiatric disorders, *delirium*, traumatic brain injury, normal pressure hydrocephalus (NPH), reversible dementias, neuroinfectious diseases or other neurodegenerative conditions, according to clinical assessment, laboratory exams (complete blood count, VDRL, thyroid function tests, vitamin B-12, and folate level tests) and brain MRI examination by board-certified radiologists.

Charlson Commorbidity Index (CCI). CCI weighted score for each patient was calculated as originally described by Charlson et al., with the exception that dementia was excluded from the scoring system as it is already computed as a diagnosis in statistical analyses (Charlson et al., 1987). We thus weighed 18 comorbidities with a total maximum scoring of 36.

CSF collection and analysis. For all groups, CSF was immediately processed for routine laboratory analysis after lumbar puncture, including cell counts, total protein, glucose, lactate, microbiological analysis, and the opening pressure estimation. Fourteen COVID-19 CSF samples were investigated for the presence of SARS-CoV-2 and other pathogens using the Biomanguinhos (E + P1) RT-qPCR kit (ANVISA Registry 0925388202- FIOCRUZ, Brazil), XGEN Master COVID-19 (ANVISA Registry 80502070088 - Mobius Brazil), XGEN Viral Meningitis Panel (ANVISA Registry 80502070037 - Mobius, Brazil) or FilmArray Meningitis/Encephalitis Panel (ANVISA Registry 10158120699 - bioMérieux, Brazil). The remaining cell-free CSF supernatants were stored in polypropylene tubes and immediately frozen at −80 °C until used for molecular analysis.

CSF molecular biomarkers quantification. Before assays, CSF samples were thawed and kept on ice. Samples were tested undiluted. IL6 levels were measured using a *Human IL6 Quantikine ELISA kit* (*R and D Systems,* USA, Cat# D6050, RRID: AB_2928038). Before analysis, samples were diluted (1:2) in a solution provided by the kit (RD6F). CSF Alzheimer's disease (AD)-related biomarkers were quantified using validated ELISA kits for *in vitro* AD diagnosis (*EuroImmun Diagnóstico Médico Laboratorial*, Brazil) following the standard procedures indicated by the manufacturers, including sample dilution indications and internal high and low concentration quality controls (Brazilian Health Regulatory Agency (ANVISA) registry #10338930156 - Aβ40 EuroImmun #EQ 6511-9601-L; ANVISA #10338930142 - Aβ42 EuroImmun EQ 6521-9601-L; ANVISA #10338930157 - Tau EuroImmun #EQ 6531-9601-L; and ANVISA #81148560067 - pTau181 EuroImmun #EQ 6591-9601-L). Samples, quality controls, and calibrators were run duplicates for all targets following manufacturers' indications. Participants from the control group were included in experimental batches to ensure that inter-assay variability would not differentially impact control or experimental groups and bias analyses. Standard curves were calculated using a 4 (IL6) or 5-parameter logistic regression model, and undetermined levels were expressed as 0 pg/mL. Two COVID-19 patients (#20 and #25) samples exceeded the total tau standard curve and were defined as the highest value (1321 pg/mL).

Blood laboratory Data. Blood tests closest to CSF sampling were retrieved. All COVID-19 had a blood examination proximal to CSF analysis (median 0 days interval, interquartile range (IQR) 0-1). We were also able to retrieve blood analysis from 15 AD, 15 aMCI, and 26 controls (median 9 days interval, IQR 0-19.5). Two AD patients, three aMCI, and ten controls did not have blood test results or results were more than two months apart from CSF sampling and were excluded from further analysis. Systemic inflammatory index (SII) was calculated by multiplying neutrophils and platelet counts and dividing them by lymphocyte counts (Mazza et al., 2021).

Statistical Analysis. Statistical analyses were performed using Prism Software, v 9 or 10 (GraphPad, USA), or Matlab R2019b (Mathworks, USA). The level of statistical significance was set at 5 %. Missing or unavailable data were not included in the statistical analysis. Categorical variables are analyzed using Fisher's exact or Chi-squared tests, followed by post-hoc Chi-Squared pairwise comparison. Continuous variables were checked for normal distribution using the D'Agostino & Pearson normality test. Non-parametric data were analyzed using the Mann-Whitney test, Kruskal-Wallis test followed by Dunn's multiple comparisons test, or Spearman correlation. The false-discovery rate (FDR) method was used to account for multiple Spearman correlations. Parametric data was analyzed using a *t*-test or one-way ANOVA followed by Tukey's comparison test. For CNS and systemic biomarker comparisons, the possible confounding effects of age (months), sex, and comorbidities (CCI) were adjusted using multiple linear regression (MLR) analyses. The CCI was used for comorbidity weighing in the

model because this index correlates both with COVID-19 severity and with AD-related CSF biomarkers in non-demented patients (Lund et al., 2024; Zenuni et al., 2021). When necessary and indicated, biomarker levels were analyzed after Log or Box-Cox transformation. Low multicollinearity was verified by a Variance Inflation Factor (VIF) lower than four. The normality of residuals was checked using the D'Agostino-Pearson Omnibus (K2) and Shapiro-Wilk (W) tests. Of note, because of the large number of zero values in control, aMCI, and AD groups for CSF IL6 concentration, the distribution of residuals from the MLR failed the normality test even after the data Box-Cox transformation. Given the retrospective design, sample sizes for each comparison were restricted to sample availability and are provided in Suppl. Table 4. The achieved power for each comparison was calculated a posteriori (Suppl. Table 4) using G*Power software Version 3.1.9.6 (Heinrich Heine Universität Düsseldorf, Germany).

3. Results

3.1. Clinical presentation of COVID-19 hospitalized patients with neurological symptoms

We retrospectively analyzed data from a well-characterized cohort of COVID-19 hospitalized patients with important neurological symptoms (Barros-Aragão et al., 2024). In this cohort, thirty-five patients were sequentially included from 11 hospitals in Brazil (Fig. 1), 17 with mild disease and 18 with severe disease or death. Patients' ages ranged from 26 to 87 years old (mean 55.6), with 12 females (34.3 %) (See Table 1). Severe/dead patients were older, more frequently of male sex, presented more comorbidities, and had a longer hospitalization period (Table 1). Seven patients (20 %) presented neurological comorbidity (Table 1), including stroke (2), demyelinating disease (1), and migraine (3). No patients, patient's relatives, or medical team reported a previous diagnosis of dementia or cognitive impairment. All patients underwent lumbar puncture for CSF analysis as clinically indicated (Table 1). Neurological features were diverse, and some patients presented more than one important neurological symptom or complication (Table 1). One patient with meningoencephalitis had his case previously described elsewhere in detail (Freitas et al., 2021). Concomitant to neurological symptoms, inflammatory and coagulopathy blood laboratory biomarkers were altered both in mild and severe cases, although more prominently in severe cases (Table 2). Systemic inflammation (SII) was higher in severe cases after adjusting for age, sex, and comorbidities and correlated with COVID-19 severity score (Fig. 2a and 4a). As we reported previously (Barros-Aragão et al., 2024), CSF IL6, a biomarker of neuroinflammation, was also higher in severe compared to mild COVID-19 patients even after adjusting for age, sex, and comorbidities (Fig. 2b).

3.2. COVID-19 patients display altered neuroinflammatory and neurodegeneration biomarkers in association with systemic inflammation and disease severity

We next compared biomarkers for inflammation (SII), neuroinflammation (IL6), and early (core 1) AD biomarkers (Jack Jr et al., 2024) in mild and severe COVID-19 patients with neurological symptoms to a pre-pandemic Brazilian cohort of cognitively healthy controls (n = 36), aMCI (n = 19), and AD (n = 20) patients (Fig. 1). aMCI and AD patients presented global cognitive decline and impairments in memory and executive functioning tests compared to controls (Suppl. Table 1). CSF routine laboratory analysis did not differ between controls, aMCI, and AD groups. However, COVID-19 patients presented higher opening pressures, red blood cells (RBC) count, and glucose levels than all other groups (Suppl. Table 2). Since AD is age-associated, COVID-19 groups included participants younger than other groups, particularly those with mild disease (Suppl. Fig. 2a). Groups also differ in sexes and cardiovascular and metabolic diseases proportions (Suppl. Fig. 2b and Suppl. Table 3). Therefore, inflammatory and AD biomarkers comparisons were adjusted for the possible age, sex, and comorbidities effects. Sample sizes and achieved power for each comparison are provided in Suppl. Table 4.

As a result, COVID-19 patients (mild and severe) presented higher biomarker levels of systemic (SII) and CNS (CSF IL6) inflammation than controls, aMCI, AD (Fig. 2). In COVID-19 patients, but not controls, CSF IL6 varied independently from COVID-19 symptoms' duration or possible blood contamination, as accounted for RBC traces (Fig. 4a and Suppl. Figs. 2 and 3). As expected, AD patients present lower CSF Aβ42 and Aβ42/40 ratio and higher total Tau, pTau181, Tau/Aβ42, and pTau181/Aβ42 levels compared to controls (Fig. 3). aMCI patients also showed lower CSF Aβ42/40 and higher Tau/Aβ42 ratios than controls (Fig. 3b and f). Severe COVID-19 patients present higher CSF Tau levels than controls, comparable to AD (Fig. 3c). Further, compared to mild disease, severe COVID-19 presented higher Tau, Tau/Aβ42, and pTau181/Aβ42 CSF levels (Fig. 3c–e, f).

Four severe COVID-19 patients stood out with higher levels of CSF Tau/Aβ42 (Fig. 2f). All of them were male, and only one died from the disease (83 years old, presented with multiple ischemic strokes and myopathy). Two of them had older ages (65 years old) and were diagnosed with meningoencephalitis and encephalopathy. The last was middle-aged (53 years old) and presented with stroke and encephalopathy.

Beyond the association with disease severity, we found positive correlations between CSF IL6 and multiple early AD biomarkers and systemic inflammation (SII) in COVID-19 patients (Fig. 4, Suppl. Fig. 2). These associations of CNS biomarkers and SII were not present in controls, aMCI, or AD patients (Suppl. Figs. 3–5). We also explored the

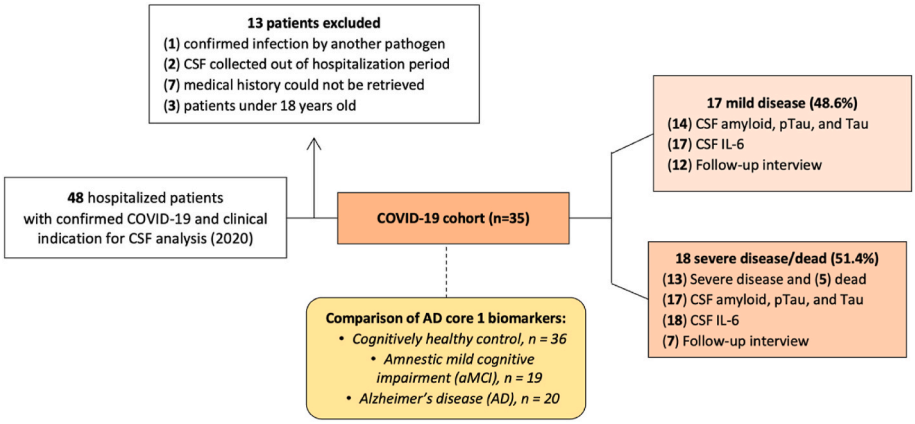

Fig. 1. Study enrolment and analysis. (AD) Alzheimer's disease; (aMCI) amnestic mild cognitive impairment; (CSF) Cerebrospinal fluid; (IL6) Interleukin-6; (pTau) phosphorylated Tau.

Table 1
COVID-19 patients' clinical and neurological profile.

	All patients N = 35	Severe/Dead N = 18	Mild N = 17	Odds ratio [95 % Confidence Interval], (p-value)
Age [years], mean (SD)	55.6 (17.0)	61.8 (15.9)	49.1 (15.9)	**(0.024)**
Sex, male (%)	23 (65.7)	15 (83.3)	8 (47.1)	**5.5 [1.1 - 22], (0.035)**
Clinical history, No (%)				
Cardiovascular disease	16 (45.7)	12 (66.7)	4 (23.5)	**6.5 [1.5 - 28.8], (0.018)**
Obesity	5 (14.3)	1 (5.6)	4 (23.5)	0.2 [0.02 - 1.9], (0.177)
Other metabolic disorders	11 (37.1)	8 (44.4)	3 (17.6)	3.7 [0.82 - 15], (0.146)
Malignant neoplasm	4 (11.4)	3 (16.7)	1 (5.9)	3.2 [0.3 - 34.2], (0.603)
Chronic pulmonary disease	3 (8.6)	1 (5.6)	2 (11.8)	0.4 [0.04 - 5.4], (0.603)
Smoking	2 (5.7)	0 (0.0)	2 (11.8)	0.0 [-∞ - +∞], (0.229)
Chronic renal disease	4 (11.4)	3 (16.7)	1 (5.9)	3.2 [0.3 - 34.2], (0.603)
Neurological or neuropsychiatric disease	7 (20.0)	4 (22.2)	3 (17.6)	1.3 [0.3 - 7.1], (1.00)
Other comorbidities	15 (42.9)	8 (44.4)	7 (41.2)	1.1 [0.27 - 4.0] (1.00)
Charlson Comorbidity Index (CCI) > 0	20 (57.1)	15 (83.3)	5 (29.4)	**12.0 [2.3 - 48.4] (0.002)**
Hospital admission and hospitalization period				
Duration [days], median (IQR)	17 (7-46.5)	46.5 (30.2-67.7)	7.0 (3-11)	**(<0.0001)**
ICU stay [days], mean (SD)	25.2 (32.0)	48.5 (37.0)	6.9 (4.8)	**(0.008)**
Fever, N° (%)	22 (62.9)	11 (61.1)	11 (64.7)	0.86 [0.2 - 3.4], (1.00)
Sepsis, N° (%)	9 (25.7)	8 (44.4)	1 (5.9)	**12.8 [1.4 - 118.3], (0.018)**
Respiratory discomfort, N° (%)	18 (51.4)	12 (66.7)	6 (35.3)	3.7 [0.9 - 15], (0.094)
Pneumonia and other pulmonary complications, N° (%)	19 (54.3)	15 (83.3)	4 (23.5)	**16 [2.8 - 67], (0.0006)**
Cardiovascular complications, N° (%)	11 (31.4)	11 (61.1)	0 (0.0)	**∞ [5.1 - ∞], (0.0001)**
Thromboembolic complications, N° (%)	7 (20.0)	6 (33.3)	1 (5.9)	8.0 [0.93 - 97], (0.088)
Hepatic dysfunction, N° (%)	2 (5.7)	1 (5.6)	1 (5.9)	0.94 [0.05 - 19], (1.00)
Acute Renal Failure, N° (%)	9 (25.7)	9 (50.0)	0 (0.0)	**∞ [3.3 - ∞], (0.001)**
Clinical indication for cerebrospinal fluid (CSF) examination, N (%)				
Suspected encephalitis or other inflammatory disease from the CNS	27 (77.1)	12 (66.7)	15 (88.2)	0.27 [0.05 - 1.5], (0.23)
Seizures	4 (11.4)	4 (22.2)	0 (0.0)	∞ [0.9 - ∞], (0.10)
Paresis, facial paralysis, dysarthria, or suspected Guillain-Barré Syndrome (GBS)	6 (17.1)	3 (16.7)	3 (17.65)	0.93 [0.2 - 4.5], (1.00)
Altered level of consciousness	7 (20)	6 (33.3)	1 (5.9)	8.0 [0.9 - 96.6], (0.09)
Headache	3 (8.6)	0 (0.0)	3 (17.65)	0.0 [0.0-1.0], (0.10)
Suspected hydrocephalus/intracranial hypertension	1 (2.9)	0 (0.0)	1 (5.9)	0.0 [0.0 - 8.5], (0.49)
Main neurological finding or complaint, N (%)				
Undetermined	6 (17.1)	4 (22.2)	2 (11.8)	2.1 [0.4 - 12], (0.658)
Stroke	4 (11.4)	4 (22.2)	0 (0.0)	∞ [0.94 - ∞], (0.104)
Neuromuscular Syndromes	4 (11.4)	2 (11.1)	2 (11.8)	0.94 [0.13 - 6.6], (1.00)
Refractory epilepticus status	2 (5.7)	2 (11.1)	0 (0.0)	∞ [0.44 - ∞], (0.486)
Inflammatory disease from CNS	12 (34.3)	6 (33.3)	6 (35.3)	0.92 [0.25 - 3.4], (1.00)
Encephalopathy	7 (20.0)	5 (27.8)	2 (11.8)	2.9 [0.44 - 16], (0.402)
Headache	5 (14.3)	0 (0.0)	5 (29.4)	**0.0 [0.0 - 0.6], (0.019)**
Drugs during hospitalization, number of patients in use, No (%)				
Immunoglobulins	2 (5.7)	0 (0)	2 (11.8)	0.0 [-∞ - +∞], (0.229)
Corticosteroids	18 (51.4)	11 (61.1)	7 (41.2)	2.2 [0.6 - 8.7], (0.318)
Antibiotics	28 (80.0)	11 (61.1)	12 (70.6)	3.3 [0.6 - 20.2], (0.228)
Anticoagulants	24 (68.6)	13 (72.2)	11 (64.7)	1.4 [0.3 - 5.9], (0.725)
Antivirals	10 (28.6)	8 (44.4)	2 (11.8)	**6.00 [1.0-34.3], (0.06)**
Antipsychotics	2 (5.7)	1 (5.6)	1 (5.9)	0.9 [0.05 - 16.3], (1.00)
Antidepressants	1 (2.9)	1 (5.6)	0 (0)	∞ [-∞ - +∞], (1.00)
Anxiolytic	1 (2.9)	1 (5.6)	0 (0)	∞ [-∞ - +∞], (1.00)

Categorical variables are expressed as the number of positive cases (N°) and percentage (%). Normal distributed continuous variables are expressed as mean and standard deviation (SD). Non-parametric continuous variables are expressed as the median and interquartile range (IQR). Fisher's exact test or *t*-test or Multiple linear regression (MLR) considering sex, age (months), and comorbidity (CCI) factors. Groups were compared for hospitalization days after Log transformation. Central nervous system (CNS) inflammatory diseases include meningitis, encephalitis, meningoencephalitis, encephalomyelitis, myelitis, vasculitis, and acute disseminated encephalomyelitis (ADEM). Neuromuscular syndromes include Guillain-Barré Syndrome (GBS), cranial neuropathy, peripheral facial paralysis, and myopathy.

effects of age, sex, and comorbidities in CSF IL-6 and AD-related biomarkers in COVID-19 patients (Fig. 4a, Suppl. Figs. 6 and 7). We found several correlations between AD biomarkers, but not CSF IL-6 or SII, and age in COVID-19 patients (Fig. 4a). Female COVID-19 patients were younger than male participants. In analyses corrected for age, comorbidities, and COVID-19 severity effects, we found no differences in inflammatory and AD-related biomarkers levels in male and female COVID-19 patients (Suppl. Fig. 6). Finally, comorbidities (CCI) were independently associated with age, CSF IL6, and CSF Tau in COVID-19 patients (Suppl. Fig. 7).

4. Discussion

Our results collectively link CNS neuroinflammation and AD-biomarkers levels to disease severity and systemic inflammation in COVID-19 neurological patients. Furthermore, this study shows that severe COVID-19 patients present similarly high Tau levels to AD but no other biomarker alteration specific to AD pathology in direct comparison to controls, aMCI, and AD patients.

We hypothesized that COVID-19 acute manifestations, including systemic hyper-inflammation, could induce molecular alterations related to neurodegeneration (De Felice et al., 2020; Lyra e Silva et al., 2022). Accordingly, we found severe COVID-19 patients presented high CNS Tau levels, comparable to AD patients, that rose in association with systemic inflammation. COVID-19 patients' CSF Tau levels in our study are in line with previous reports, including the significant variance between individuals (Chaumont et al., 2023; Espíndola et al., 2020b; Paterson et al., 2021; Virhammar et al., 2020). This variability accords with the heterogeneous neurological diseases induced by COVID-19 (Barros-Aragão et al., 2024).

Table 2
COVID-19 patients with neurological symptoms present altered systemic inflammatory biomarkers.

	All patients *n* = *35*	Outside reference range (%)[&]	Severe *n* = *18*	Mild *n* = *17*	p-value
WBC [cells/mm^3], median (n^o > 10,500)	9,700 (**16**)	46 %	11,200 (**10**)	8200 (**6**)	0.311[!]
Lymphocytes [cells/mm^3], mean (n^o <900; >2,900)	1,670 (**5; 4**)	14 %; 11 %	1523 (**4; 2**)	1826 (**1; 2**)	0.420[!]
Monocytes [cells/mm^3], median (n^o >1,000)	582 (**7**)	20 %	694 (**4**)	576 (**3**)	0.811[!]
Neutrophils [cells/mm^3], median (n^o <1,700; >7,000)	7,725 (**1; 21**)	3 %; 60 %	7,966 (**0; 14**)	6117 (**1; 7**)	0.168[!]
Hemoglobin [g/dl], median (n^o <12)	12.8 (**14**)	40 %	11.7 (**9**)	14.1 (**5**)	**0.034**
Platelet [10^3 cells/mm^3], mean (n^o <150; >450)	289 (**2; 4**)	6 %; 11 %	290 (**1; 3**)	288 (**1; 1**)	0.802
D-dimer [ng/ml], median (n^o >500)	1,271.5 (**31**)	89 %	1,986.0 (**18**)	711.6 (**13**)	0.070[!]
C-Reactive Protein [mg/dl], median (n^o >1)	3.7 (**24**)	69 %	5.3 (**18**)	0.75 (**6**)	**0.003**[!]
Neutrophil-Lymphocyte Ratio (NLR), median (IQR)	4.6 (2.2-7.1)	..	5.2 (3.4-11.5)	2.7 (1.7-5.4)	0.157[!]
Monocyte-Lymphocyte Ratio (MLR), median (IQR)	0.4 (0.25-0.5)	..	0.5 (0.3-0.8)	0.3 (0.2-0.5)	0.717[!]

Abbreviations: (WBC) White Blood Cells, (IQR) Interquartile range, (..) reference range not defined. [&]Percentages calculated considering all included patients (n = 35). Multiple linear regression considering age, sex, and comorbidity effects. [!]Data required Log or Box-Cox transformation for statistical analysis, and the results are shown as untransformed mean/median.

We recently established connections between COVID-19 disease severity, more pronounced neuroimaging alterations, and higher neuroinflammatory biomarker levels in this cohort of COVID-19 patients with neurological symptoms (Barros-Aragão et al., 2024). Given that AD patients are at greater risk of developing COVID-19 severe disease (Tahira et al., 2021), we hypothesized that COVID-19 patients with prominent neurological symptoms could already be in the AD pre-clinical spectrum that rendered them more susceptible to COVID-19-induced neurological symptoms associated with disease severity. However, we found no biomarker alterations specific to AD pathology in COVID-19 patients compared to controls, indicating that susceptibility to neurological symptoms after COVID-19 infection in mild or severe patients cannot be explained by an underlying AD pathology. In AD patients, CSF Tau increases early and alongside other biomarkers of Tau pathology (Jack Jr et al., 2024). But CSF Tau is also increased in different conditions, such as traumatic brain injury, stroke, and other neurodegenerative conditions (Jack Jr et al., 2024). Thus, the selective increase of CSF Tau in COVID-19 severe patients may be better interpreted as a possible ongoing neurodegeneration process and not an AD-related tauopathy. It is also important to notice that the COVID-19 group was not homogeneous, and four severe COVID-19 patients presented a higher CSF Tau/Aβ42 ratio at similar levels to AD patients, although without substantial increases in the pTau181/Aβ42 ratio.

Our results contrast with Ziff et al., (2022) who found that COVID-19 patients with neurological symptoms have impaired amyloid processing and lower CSF Aβ42/Aβ40 ratio than controls. These diverging findings could reflect differences in the studies' designs, as we controlled for possible confounders (sex, age, and comorbidities). However, we previously found activation of pathways related to amyloidosis in COVID-19 patients' cohort CSF proteome compared to uninfected controls (Barros-Aragão et al., 2024), possibly reflecting more subtle changes in amyloid processing in the COVID-19 cohort studied here. Frontera et al., (2022) found that COVID-19 patients, particularly severe ones, present neuroinflammatory and neurodegeneration blood biomarkers at higher levels than AD. However, in that study, they could not find clear associations between blood neurodegeneration biomarkers and systemic inflammatory markers at hospital admission. This could reflect differences in the methodology used in the studies. Our study focused on patients presenting neurological symptoms, dosed the neurodegeneration biomarker directly from the CNS, and compared to systemic indicators proximal to the CSF collection date, possibly providing a more accurate assessment of COVID-19-related neurological disturbance.

Extensive follow-up reports suggest that post-COVID global health and cognitive decline are frequent (Fernández-de-Las-Peñas et al., 2022; Huang et al., 2022; Mazza et al., 2021; Seeßle et al., 2021; Sudo et al.,

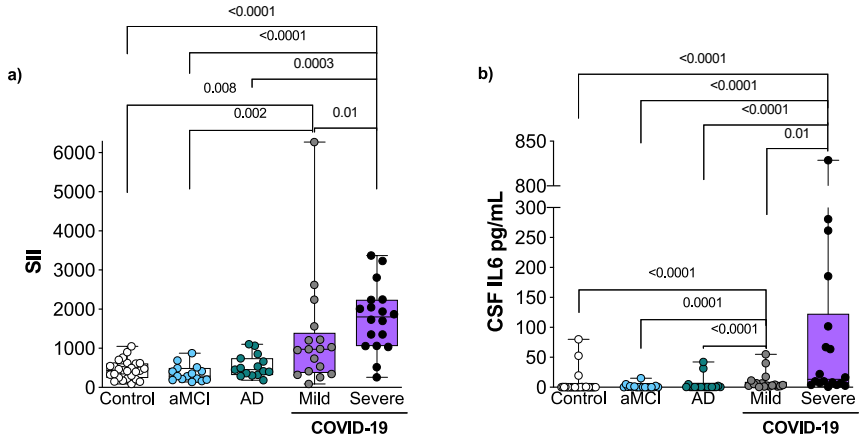

Fig. 2. COVID-19 patients with neurological symptoms present elevated biomarkers of systemic and neuro-inflammation. COVID-19 patients are compared to cognitively healthy controls, amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD) patients. Data are shown as the median, interquartile range (box), and min-max points (whiskers). Symbols indicate individual patients. Numbers over brackets indicate p-values, Multiple linear regression (MLR) of Box-Cox transformed biomarker levels and considering sex, age (months), and comorbidity (CCI) factors.

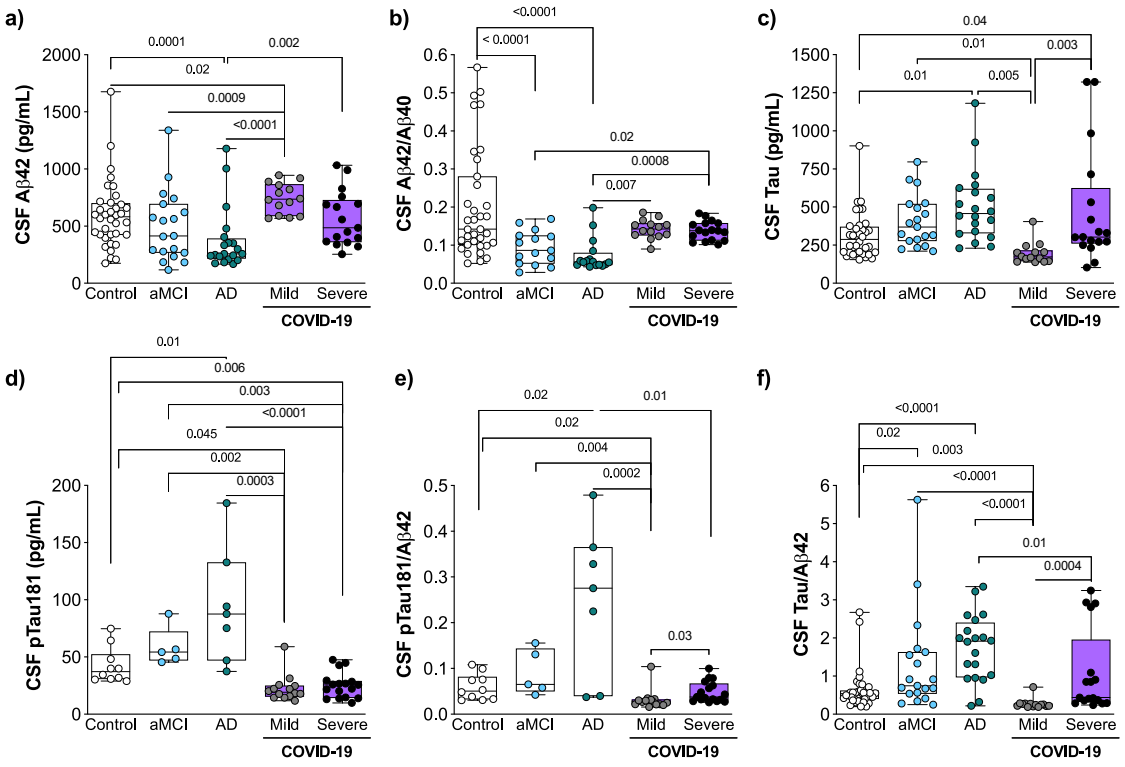

Fig. 3. Comparison of Alzheimer's disease (AD) biomarkers in controls, mild and severe COVID-19 patients, amnestic mild cognitive impairment (aMCI), and AD patients. Data are shown as the median, interquartile range (box), and min-max points (whiskers). Symbols indicate individual patients. Numbers over brackets indicate p-values, Multiple linear regression (MLR) of Box-Cox transformed biomarker levels and considering sex, age (months), and comorbidity (CCI) factors.

2024; Titze-de-Almeida et al., 2022; Wahlgren et al., 2023). Considering the alarming number of COVID-19 survivors, determining specific mechanisms linking disease severity and systemic inflammation at acute disease and neurological biomarkers alterations associated with early AD could contribute to identifying and providing possible therapeutic targets and strategies that attenuate COVID-19-neurological disease or prevent long-term neurological abnormalities associated with infection. Our results align with previous findings that COVID-19 can induce a systemic hyper-inflammatory state (Webb et al., 2020). Systemic cytokine upregulation influences brain function and may cause an acute neurological disturbance (Klein et al., 2017; Lyra e Silva et al. , 2022). SII at hospital admission was positively associated with persistent cognitive impairment and depressive traits in COVID-19 survivors (Mazza et al., 2021). In a previous study using this same cohort of COVID-19 patients, we showed that COVID-19 neurological disease was associated with changes in the CSF proteome related to innate immune system activation and hemostasis (Barros-Aragão et al., 2024). CSF IL6 upregulation was associated with both COVID-19 severity and pronounced neuroimaging alterations (Barros-Aragão et al., 2024). We now show that systemic inflammation (SII) correlated with CNS IL6 cytokine upregulation and several biomarkers associated with early AD pathology. Our group recently found that blood IL6 levels correlate with cognitive decline and neuroimaging traces of neuroinflammation in AD patients (Lyra e Silva et al., 2021). These associations might suggest a common mechanism shared between severe COVID-19 and AD, where inflammation may trigger CNS modifications. In another recent study, we found that COVID-19 survivors with memory impairment present persistent high inflammatory biomarkers (Sudo et al., 2024). Thus, considering AD pathology develops over decades, in future studies, it will be important to evaluate if COVID-19 survivors with persistent systemic inflammation, particularly those with cognitive symptoms, develop further alterations related to AD pathology.

Finally, our results must be interpreted in light of the study's limitations, namely, limited sample size, lack of cognitive and psychiatric evaluation of included COVID-19 patients, and cross-sectional assessment of AD biomarkers. Additionally, the included patients were probably infected with the same SARS-CoV-2 variant predominant in Brazil at the time of the study (Barros-Aragão et al., 2024). More extensive longitudinal cohort studies are necessary to understand the mechanisms behind COVID-19 outcomes' heterogeneity and determine possible risks for late-onset AD with the advent of other variants and vaccines.

To conclude, our study shows that COVID-19 mild and severe patients with neurological symptoms present elevated CSF Tau, indicating an ongoing neurodegeneration process. Although we could not detect molecular changes suggestive of AD, COVID-19-induced systemic inflammation and disease severity correlated with CNS AD biomarkers. Future studies are imperative to evaluate if long-COVID-associated persistent inflammation will drive further ADNPC and increased risk of AD.

CRediT authorship contribution statement

Fernanda G.Q. Barros-Aragão: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Thaís L. Pinheiro:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Talita P. Pinto:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Bart Vanderborgh:** Project administration, Methodology, Investigation, Formal analysis, Data curation. **Nathane B.S. Rezende:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Guilherme B. de Freitas:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Gabriel R. de Freitas:** Supervision, Project administration, Investigation, Formal analysis,

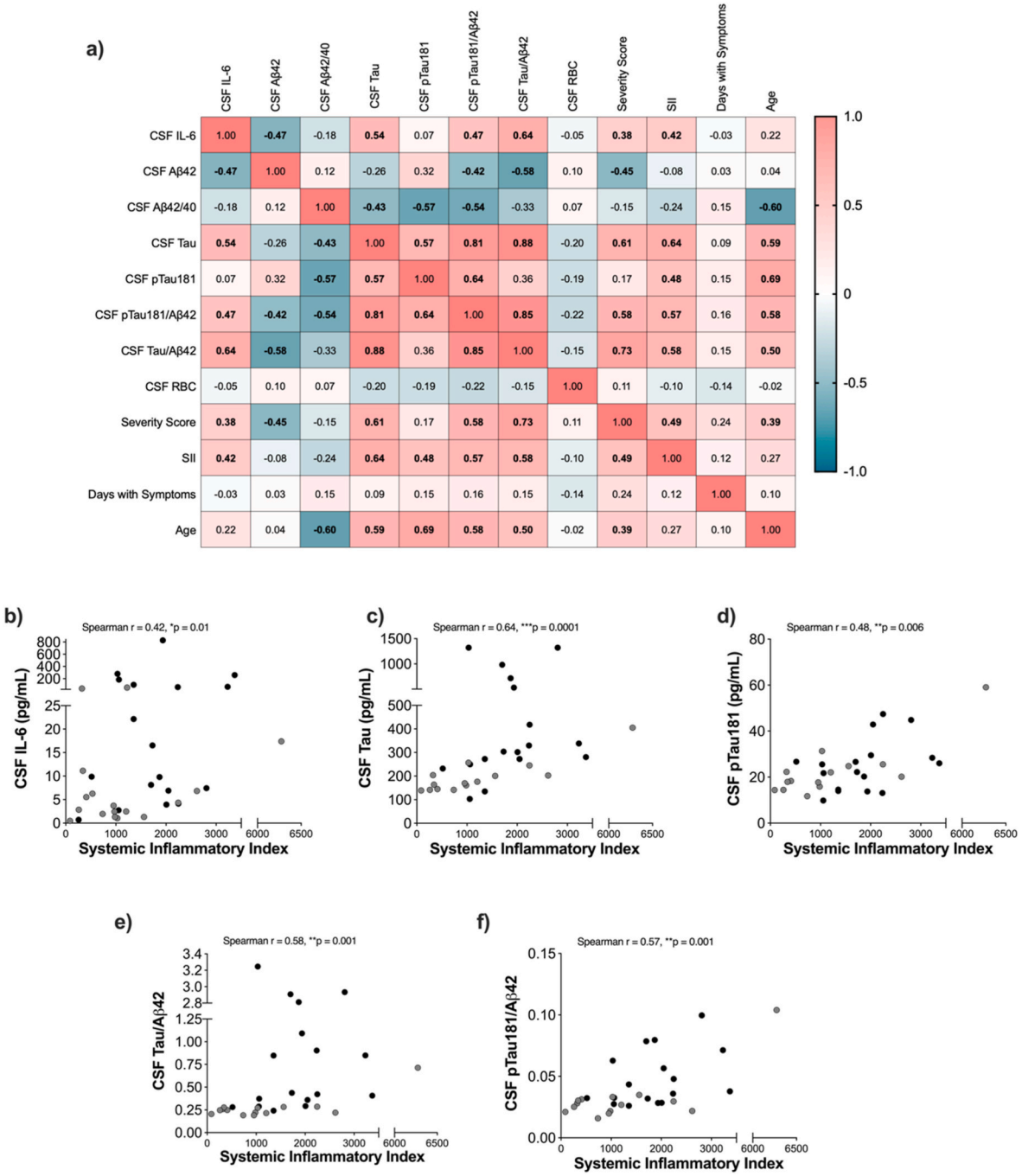

Fig. 4. Systemic inflammation correlates with neuroinflammation and changes in AD biomarkers in COVID-19 patients with neurological symptoms. (a) Spearman correlation matrix (n = 31-35 patients). Spearman r's are shown inside boxes, colors indicate direction, bold values indicate significant correlations. Multiple comparisons are corrected by the false-discovery rate (FDR) method. (b–f) Grey symbols indicate mild disease cases; black symbols represent severe cases or death, (n = 31 or 35). Spearman correlation. Abbreviations: (CSF) cerebrospinal fluid; (IL-6) interleukin-6; (Aβ) amyloid-beta; (pTau 181) tau phosphorylated at threonine 181; (RBC) red blood cells count; (SII) systemic inflammatory index; Days with symptoms are calculated considering the CSF sampling and symptoms' start dates. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Data curation, Conceptualization. **Fernando A. Bozza:** Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Andrea S. Souza:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Erika C. Rodrigues:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carlos O. Brandão:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Paulo Mattos:** Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Felipe K. Sudo:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fernanda F. Tovar-Moll:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fernanda G. De Felice:** Writing – review

& editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

The study protocol and all amendments were approved by the National Commission for Research Ethics (CONEP) from the Brazilian Ministry of Health and the Committee for Research Ethics of D'Or Institute of Research and Education (IDOR), CAAE #29496920.8.0000.5262; CAAE #41576620.7.0000.5249 and CAAE #47163715.0.0000.5249.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files. Additional data may be available upon request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly to polish the English, correct grammar, and improve clarity and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the publication's content.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101007.

List of abbreviations

AD: Alzheimer's disease; ATN: Amyloid pathology, pathologic Tau, and Neurodegeneration; aMCI: amnestic mild cognitive impairment; Aβ: amyloid-beta; CCP: clinic characterization protocol; CNS: central nervous system; CONEP: Brazilian National Commission for Research Ethics; IDOR: D'Or Institute of Research and Education; CRF: clinical research form; CSF: cerebrospinal fluid; DIA: data-independent acquisition; ICU: intensive care unit; IL6: interleukin-6; IQR: interquartile range; ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium; RBC: red blood cell; RT-qPCR: reverse transcriptase-quantitative polymerase chain reaction; SD: standard deviation; SEM: standard error of the mean; SII: Systemic Inflammatory Index; WBC: white blood cells; WHO: World Health Organization.

Data availability

Data will be made available on request.

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