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# Association between mental health symptoms and autoimmunity in patients with long COVID

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## Abstract

**Background** Neuropsychiatric symptoms are common features in long COVID. The pathogenesis of neuropsychiatric manifestations in both acute COVID-19 and long COVID remains unclear. This study aimed to examine mental health symptoms—depressive, anxiety, and insomnia symptoms—in COVID-19 survivors with long COVID, and to explore their potential association with autoimmune activity.

**Methods** We conducted an observational, cross-sectional study of 228 adults recruited from a long COVID program in Cartagena, Colombia. Participants underwent clinician-administered interviews and completed validated psychometric scales to assess depressive (PHQ-9), anxiety (GAD-7), and insomnia (ISI) symptoms. Sociodemographic, clinical, and biological data were collected. The autoantibody panel included antinuclear antibodies (ANA), anti-SSA/Ro, anti-SSB/La, anti-RNP, anti-Smith (Sm), rheumatoid factor (RF), anti-thyroglobulin (Tg), and anti-thyroid peroxidase (TPO), measured via ELISA and immunofluorescence. Robust logistic regression models were used to evaluate associations between long COVID, autoantibody positivity, and mental health symptoms, adjusting for age, sex, and relevant covariates.

**Results** 57% of participants with a history of COVID-19 acute infection reported long COVID. In participants with long COVID, we reported high proportions of depressive (21.2%), anxiety (31.2%), and insomnia (28.7%) symptoms. Moreover, an association of all three mental health symptoms with autoantibody positivity (particularly antinuclear antibodies [ANA] isolated or co-occurring with anti-TPO antibodies) was observed in individuals with long COVID. Our findings suggest a potential association between psychopathological symptoms, autoantibody positivity, and distinct clinical profiles of long COVID, warranting further longitudinal investigation.

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**Conclusions** Mental health symptoms (MHS) should be considered one of the main targets involved in translational research in long COVID. There is an urgent need for consultation-liaison physicians to work closely with immunologists, rheumatologists, and pain medicine physicians in clinical settings as well as in research. This will contribute to a better understanding of the impact of MHS during illness in long COVID variants.

**Keywords** Long COVID, Depressive, Anxiety, Insomnia, Autoantibody positivity, Neuroinflammation, Antinuclear - antibodies

## Background

Long COVID is a systemic and multi-complex sequela as a result of SARS-CoV-2 exposure associated with functional impairment and a decline in quality of life [1]. Mental symptoms have been previously described as common features in long COVID patients [1–5]. The physio-pathological mechanisms underlying the association between SARS-CoV-2 acute infection, long COVID, and adverse mental health symptoms (MHS) are still unclear. However, the role of an autoimmune response and thus activation may be a link explaining the aforementioned longitudinal connection between symptomatic expression [6].

MHS have been described in long COVID as common symptoms that persist months and years after suffering from SARS-CoV2 infection [3–5]. Depressive, anxiety, and insomnia symptoms are ranked among the most prevalent MHS related to long COVID [2, 3, 7–10]. While the onset of psychopathological symptoms may be associated with psychosocial (i.e., losses, isolation, or economic deprivation) or clinical factors (e.g., mechanical ventilation or extended hospital stays) [3], plausible causal mechanisms of new-onset and persistent, chronic psychiatric symptoms associated with MHS during long COVID remain to be unraveled.

Different hypotheses have been explored from cellular to clinical approaches in understanding the long COVID [6]. Persistent autoantibody positivity has been proposed as a contributing factor [6].

Evidence from hospitalized COVID-19 patients has demonstrated T-cell dysfunction [11],

and alterations in B-cell function and autoantibody production<sup>12 13</sup> [14]. However, it remains unclear whether immune dysregulation is the primary mechanism driving the development and persistence of MHS associated with long COVID—such as depressive, anxiety, and insomnia symptoms [6]. In addition, it is not yet known whether other biological mechanisms, beyond neurotropism or viral persistence, may contribute to the pathophysiology of MHS in individuals with long COVID [15–17].

Recent studies have suggested that persistent levels of antinuclear antibodies (ANAs) beyond 12 months are associated with lingering somatic symptoms, including fatigue, dyspnea, and cough [18]. While these findings underscore the role of immune dysregulation in the persistence of physical symptoms in post-acute sequelae

of SARS-CoV-2 infection, little is known about whether similar autoimmune mechanisms contribute to neuropsychiatric symptoms such as depressive, anxiety, and insomnia symptoms—core features frequently reported in individuals with long COVID. The role of autoantibody positivity, including ANA and thyroid-specific antibodies (e.g., anti-TPO), in mental health symptoms has not been systematically explored. This study aims to help fill that gap by evaluating the association between autoantibody profiles and MHS in COVID-19 survivors with long COVID, integrating clinical psychopathological screening and biomarker identification as part of a translational research approach.

## Methods

### Study design and setting

An observational, cross-sectional study was conducted on a sample of COVID-19 survivors enrolled at an outpatient clinical site in Cartagena, Colombia from June 14 to July 18, 2023.

This research study was conducted at an outpatient clinical site affiliated with Coosalud EPS, a major health insurance provider in Colombia. The study site is located in Cartagena, Bolívar, a coastal city in northern Colombia that serves as a regional hub for medical and public health services. Coosalud EPS provides healthcare to a large and diverse population, including individuals from urban, peri-urban, and socioeconomically vulnerable communities. The outpatient clinic where this study was conducted specializes in the follow-up care of patients recovering from COVID-19, offering multidisciplinary services for long COVID, including general medicine, mental health, and rehabilitation.

### Participants

228 participants were systematically screened for physical and MHS using a semi-structured interview performed by clinicians trained to gather social, clinical, and biological data and collect psychometric measures regarding physical health and MHS as we used in a previous study [1]. The target sample size of participants was determined using the formula  $N = Z_{\alpha}^2 P(1 - P) / d^2$ , in which  $\alpha = 0.05$  and  $Z_{\alpha} = 1.96$ , and the estimated acceptable margin of error for proportion  $d$  was 0.1. In short,  $Z_{\alpha} = 1.96$  for a 95% confidence level.  $P$  was fixed as the proportion of long COVID with mental health symptoms, estimated

at 20%, based on data from a systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 [19]. Finally,  $d=0.10$  was acceptable margin of error. To enhance the analysis and account for potential non-response or incomplete data, we increased the sample size by 100%, targeting at least 122 completed responses. Participants were selected using a convenience sampling strategy from patients attending the long COVID outpatient program at Coosalud EPS in Cartagena, Colombia.

Our sample included participants 18 years and older who attended the service and were recruited in a long COVID clinical program. All participants reported SARS-CoV-2 infection exposure in the last 2 years confirmed by positive RT-PCR or antigen test reported in the Electronic Health Records (EHR).

#### Data collection

This cross-sectional study incorporated both prospective data collection during clinical encounters and retrospective review of EHR to obtain prior SARS-CoV-2 test results and medical history. Participants were enrolled from a long COVID outpatient program, with psychometric, biomarkers and clinical assessments conducted at the time of study inclusion.

A semi-structured survey was administered by a team of trained clinicians, including physicians and psychologists, who received standardized instruction in data collection procedures to ensure consistency across assessments. The survey captured three main types of data: (1) sociodemographic variables (e.g., age, gender, education, ethnicity, and economic status); (2) clinical variables (e.g., comorbidities, vaccination status, physical health, and mental health symptoms); and (3) biological data, specifically a panel of autoantibodies, including antinuclear antibodies (ANA), anti-Smith (Sm), anti-ribonucleoprotein (anti-RNP), anti-Ro (SSA), anti-La (SSB), and rheumatoid factor (RF). The survey was completed electronically using Google Forms, and responses were directly entered into a secure and anonymized electronic database.

Neuropsychiatric data—focused on symptoms of depressive, anxiety, and insomnia—alongside autoantibody results, were the primary variables of interest in assessing associations. Sociodemographic and clinical variables were included primarily as covariates in multivariable models to control for potential confounding factors.

#### Mental health symptoms

Depressive symptoms were recorded through the 9-item Patient Health Questionnaire (PHQ-9) which was auto-filled by participants. The PHQ-9 is widely used in epidemiological studies, with high validity and reliability [20].

The degree of severity was considered according to that proposed by Kroenke and collaborators [21].

Data on the Anxiety variable were recorded using the 7-item Generalized Anxiety Disorder Scale (GAD-7), a self-reported questionnaire widely used in the general population [22] COVID-19 survivors [3] and individuals with physical comorbidities [23]. We used the cutoff point ( $\geq 5$ ) proposed by Spitzer et al. [22] in the validation study to diagnose anxiety.

The insomnia variable was measured using the 7-item Insomnia Severity Index (ISI), a brief screening tool for insomnia symptoms. We used the cutoff point ( $\geq 10$ ) proposed by Morin et al. [24] to diagnose insomnia.

#### Autoantibodies

A panel of serum autoantibodies was evaluated. Detection of IgM rheumatoid factor (RF), IgG anti-thyroglobulin (Tg) antibodies and anti-thyroid peroxidase (TPO) antibodies were all quantified by enzyme-linked-immunosorbent assay (ELISA), as previously reported in detail elsewhere [25]. In addition, antinuclear antibodies (ANA) were evaluated by using an indirect immunofluorescence assay. Positive results were considered from dilution 1/80. In case of ANA positivity, anti-SSA/Ro, anti-SSB/La, anti-ribonucleoprotein (RNP) and anti-smith (Sm) antibodies were further evaluated by a commercial ELISA. All the assay kits were from Inova Diagnostics, Inc (San Diego, CA, USA).

#### Long COVID definition

According to the 2024 National Academies Science, Engineering and Medicine definition, Long COVID is an infection-associated chronic condition that develops after SARS-CoV-2 infection and lasts at least three months. It can affect multiple organ systems, presenting with persistent, relapsing, or progressive symptoms such as fatigue, cognitive impairment, and autonomic dysfunction. Long COVID may follow mild or asymptomatic infection, impacts individuals across all demographics, and is diagnosed clinically in the absence of definitive biomarkers [26].

#### Statistical analysis

Statistical analyses were performed to address three main objectives: (i) to describe the sociodemographic, clinical, and biological characteristics of the total sample and long COVID participants; (ii) to estimate the prevalence of mental health symptoms—depressive, anxiety, and insomnia symptoms—in the full sample and the subgroup of individuals with long COVID; and (iii) to assess the association between long COVID, autoantibody positivity, and MHS.

Descriptive statistics were used to summarize the data: normally distributed continuous variables were expressed

as means and standard deviations (SD); non-normally distributed variables as medians and interquartile ranges (IQR). The Shapiro-Wilk test was applied to assess normality. Categorical variables were reported as absolute and relative frequencies (%). Group comparisons were conducted using Student's *t*-test or Mann–Whitney *U* test for continuous variables, and chi-square or Fisher's exact test for categorical variables, depending on distribution and cell sizes.

To examine associations between MHS and exposure variables (long COVID status and autoantibody positivity), we performed robust logistic regression models, clustering by COVID-19 exposure. Dependent variables included positive scores for depressive (PHQ-9 $\geq$ 7), anxiety (GAD-7 $\geq$ 5), and insomnia (ISI $\geq$ 10) symptoms. Primary independent variables were long COVID status and specific autoantibodies (e.g., ANA, anti-TPO). Models were adjusted for covariates selected based on prior evidence and biological plausibility: age, gender, and autoantibody status (ANA and anti-TPO). Potential confounding and interaction effects were evaluated.

Interaction terms (e.g., long COVID  $\times$  ANA positivity) were explicitly introduced into the logistic regression models to assess effect modification on the multiplicative scale. To evaluate interaction on the additive scale, we calculated the Relative Excess Risk due to Interaction (RERI) and corresponding 95% confidence intervals using the delta method [27]. We also presented stratified odds ratios to facilitate interpretation of interaction effects across exposure levels.

Model fit was assessed using both the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). Lower values of AIC and BIC were interpreted as indicative of better model performance [28]. We compared nested models with and without interaction terms and evaluated improvements in fit based on changes in AIC/BIC. Model diagnostics included assessment of multicollinearity, linearity of the logit, Hosmer–Lemeshow goodness-of-fit test, comparison of crude vs. adjusted models, and examination of deviance residuals and Cook's distance.

Analyses were performed using STATA v18/SE, and visualizations were generated with the ggplot2 package in R.

### Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and national ethical guidelines for human subjects' research in Colombia. Ethical approval was obtained from the Research Ethics Committee of Universidad Simón Bolívar in Barranquilla, Colombia. Additionally, the study protocol was reviewed and approved by the Institutional Review Board (IRB) of Coosalud EPS. All participants provided

informed consent prior to enrollment. Data were anonymized and stored in a secure electronic database to ensure confidentiality and data protection throughout the study.

## Results

### Participants

A total of 140 with a history of COVID-19 exposure, with a mean age of 38.9 years (SD=11.5), and 75% were women. About three-fifths (57.1%) of participants reported long COVID, with a mean age of 40.4 years (SD=11.4). A large percentage (81.2%) were women.

Statistical differences were reported in all three psychometric scales performed for MHS in the post-COVID – 19 groups ( $n=80$ ). The PHQ-9 scale had a mean of 4.4 (SD=4.4) compared to 1.6 (SD=2.1) in the non-post-COVID group ( $p<0.001$ ). For the GAD-7 scale, the post-COVID group had a higher mean of 3.3 (SD=3.2) compared to the non-post COVID – 19 group mean of 1.5 (SD=2.2) ( $p<0.0019$ ). The ISI scale also reported a higher mean of 6.7 (SD=5.4) than the non-post-COVID group mean of 3.8 (SD=3.6) ( $p<0.001$ ). (Table 1)

According to the cutoff points, the proportion of depressive symptoms in long COVID participants was 21.2% compared to 5.0% in non-long COVID. Anxiety and insomnia symptoms were reported in 31.2% and 28.7% of long COVID participants, respectively. In non-long COVID participants, these proportions were reported to be 11.7% and 11.7%, respectively (Fig. 1).

The main long COVID physical symptoms were headache (10.3%), myalgia (9.9%), fatigue (7.8%), dyspnea with physical activity (7.1%), and nasal congestion (5.7%). There was a reduction in the frequency of some acute symptoms reported by patients (Fig. 2).

### Association between mental health symptoms and autoantibodies

#### *Mental health symptoms in participants with a history of COVID – 19 exposure with or without long COVID.*

In post-COVID participants, the median of PHQ-9 total score was 3.0 (6–2) compared to 1.0 (2.5–0) in participants without long COVID ( $z=-5.0$ ,  $p<0.001$ ). (Fig. 3). For GAD-7 total score in comparison groups between long COVID or without long COVID symptoms, the median was 3 (5–0.5) against 0 (3–0) ( $z=-3.8$ ,  $p<0.001$ ). (Fig. 3) The comparison medians for ISI total score were 6 (10–2.5) versus 3 (5.5–1) with statistical differences between comparison groups ( $z=-3.4$ ,  $p<0.001$ ). (Fig. 3)

#### *Autoantibody profiles in participants with a history of COVID-19 exposure*

More than half (54.3%) of covid survivors reported positive ANAs. There are no positive results for anti-SM, anti-RNP, anti-SSB, and anti-SSA in COVID-19 survivors.

**Table 1** Demographic characteristics in COVID-19 survivors ( $n = 140$ )

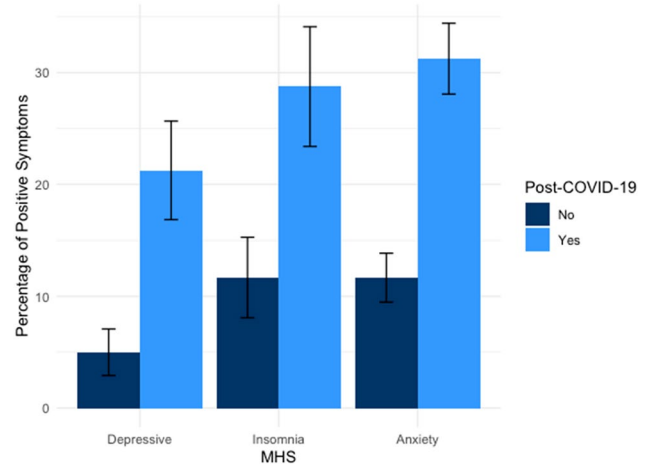
| Sociodemographic Characteristics |                  |                        |                  |         |
|----------------------------------|------------------|------------------------|------------------|---------|
| Characteristic                   | Total            | Post-COVID-19 Syndrome |                  | P value |
|                                  |                  | No                     | Yes              |         |
| Age (mean, SD)                   | 140              | 60                     | 80               | 0.079   |
|                                  | 38.96<br>(11.52) | 36.98<br>(11.48)       | 40.44<br>(11.40) |         |
| Gender                           |                  |                        |                  |         |
| Female                           | 105 (100)        | 40 (38.10)             | 65 (61.90)       | 0.049   |
| Male                             | 35 (100)         | 20 (57.14)             | 15 (42.86)       |         |
| Education                        |                  |                        |                  |         |
| Elementary                       | 5 (100)          | 1 (20.00)              | 4 (80.00)        | 0.289   |
| High School                      | 11 (100)         | 2 (18.18)              | 9 (81.82)        |         |
| Technician                       | 24 (100)         | 13 (54.17)             | 11 (45.83)       |         |
| Undergraduate                    | 47 (100)         | 20 (42.55)             | 27 (57.45)       |         |
| Graduate                         | 53 (100)         | 24 (45.28)             | 29 (54.72)       |         |
| ANA                              |                  |                        |                  |         |
| Negative                         | 64 (100)         | 33 (51.56)             | 31 (48.44)       | 0.056   |
| Positive                         | 76 (100)         | 27 (35.53)             | 49 (64.47)       |         |
| Anti-TPO                         |                  |                        |                  |         |
| Negative                         | 95 (100)         | 42 (42.21)             | 53 (55.79)       | 0.638   |
| Positive                         | 45 (100)         | 18 (40.00)             | 27 (60.00)       |         |
| ISI, (mean, SD)                  | 5.5 (4.89)       | 3.85 (3.59)            | 6.73 (5.36)      | <0.001  |
| PHQ-9 (mean, SD)                 | 3.2 (3.85)       | 1.61 (2.08)            | 4.38 (4.41)      | <0.001  |
| GAD-7 (mean, SD)                 | 2.57 (2.93)      | 1.55 (2.19)            | 3.33 (3.17)      | <0.001  |
| Insomnia Symptoms                |                  |                        |                  |         |
| No                               | 110 (100)        | 53 (48.18)             | 57 (51.82)       | 0.015   |
| Yes                              | 30 (100)         | 7 (23.33)              | 23 (76.67)       |         |
| Depressive Symptoms              |                  |                        |                  |         |
| No                               | 120 (100)        | 57 (47.50)             | 64 (52.50)       | 0.007   |
| Yes                              | 20 (100)         | 3 (15.00)              | 17 (85.00)       |         |
| Anxiety Symptoms                 |                  |                        |                  |         |
| No                               | 108 (100)        | 53 (49.07)             | 55 (50.93)       | 0.006   |
| Yes                              | 32 (100)         | 7 (21.88)              | 25 (78.12)       |         |

\* Euthyroidism was confirmed in all the participants (based on TSH and FT4)

35.5% ( $n = 27$ ) of COVID-19 survivors with positive ANA reported positive anti-TPO.

#### Mental health symptoms in participants with a history of COVID-19 exposure with positive anti-nuclear antibodies

From a subgroup of 76 COVID-19 survivors reported to have positive ANAs, about two-thirds (64.5%) had reported long COVID, and a third (35.5%) did not report long COVID. The median total score of PHQ-9 in participants with long COVID was 3.0 (7–2) compared to 1.0 (3–0) in participants without long COVID ( $z = -3.2$ ,  $p = 0.001$ ). For participants with long COVID, the median total score of GAD-7 and ISI were 3 (6–0) and 6 (10–2) compared to 1 (3–0) and 3 (6–1) in participants without long COVID, respectively ( $z = -1.9$ ,  $p = 0.053$ ,  $z = -1.9$ ,  $p = 0.060$ , respectively).



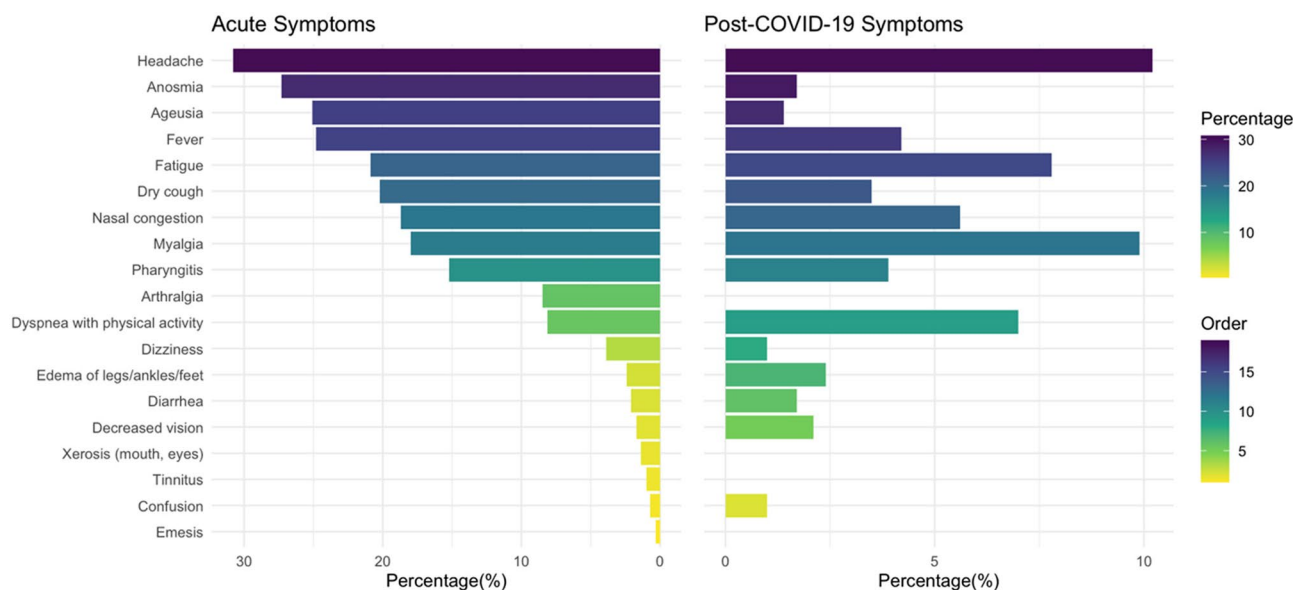
**Fig. 1** Proportion of Mental Health Symptoms in Post-COVID-19 Syndrome

#### Mental health symptoms in participants with positive ANA and positive anti-TPO

From the subgroup of 76 COVID-19 survivors with positive ANA, 35.5% also had positive anti-TPO association. The comparison of MHS between participants with long COVID and those without long COVID reported significant differences in PHQ-9 scale ( $z = -2.8$ ,  $p = 0.005$ ) with a median score of 3 (7–2) compared to 0 (2–0). For GAD-7, there are no differences reported [ $M = 3.5$  (6–1) against  $M = 2$  (3–0),  $z = -0.9$ ,  $p = 0.389$ , respectively]. The ISI scale reported differences between participants with long COVID compared to non-long COVID participants [ $M = 8$  (12–4) versus  $M = 2$  (6–1),  $z = -2.2$ ,  $p = 0.027$ ].

#### Multivariate associations of mental health symptoms with long COVID and autoantibodies

Three robust logistic regression models were performed for MHS included in the study (depressive, anxiety, and insomnia symptoms). There is an increased indirect risk of 84.4% to suffer from depressive symptoms if long COVID was present (OR=1.84, 95% CI=1.02–3.31,  $p = 0.041$ ). If ANAs was positive, a stronger association for depressive symptoms was reported (OR=2.25, 95% CI=1.90–2.67,  $p < 0.001$ ). For anxiety symptoms, there were not statistical associations with long COVID and positive ANA. However, there was a significant association with an indirect risk of 95% of significant anxiety symptoms if anti-TPO was positive (OR=1.95, 95% CI=1.25–3.05,  $p = 0.003$ ). Insomnia symptoms were strongly associated (OR=2.04, 95% CI=1.26–3.30,  $p = 0.003$ ) with long COVID. However, there were not significant associations between insomnia symptoms and positive antibodies (ANA and anti-TPO). (Table 2)



**Fig. 2** Comparison between acute COVID-19 and post-COVID-19 symptoms

## Discussion

Our findings suggest that participants with long COVID exhibit a higher prevalence of depressive, anxiety, and insomnia symptoms. We also observed that mental health symptoms were more frequent among individuals with long COVID who demonstrated immunological activity, particularly those with positive ANA and anti-TPO antibodies. Importantly, we identified statistically significant associations between mental health symptoms, long COVID status, and autoantibody positivity. While these results support the hypothesis that immune dysregulation may contribute to the neuropsychiatric manifestations of long COVID, causality cannot be inferred due to the cross-sectional nature of the study. Further longitudinal and mechanistic research is needed to clarify the role of autoantibodies in the pathogenesis of mental health symptoms following COVID-19.

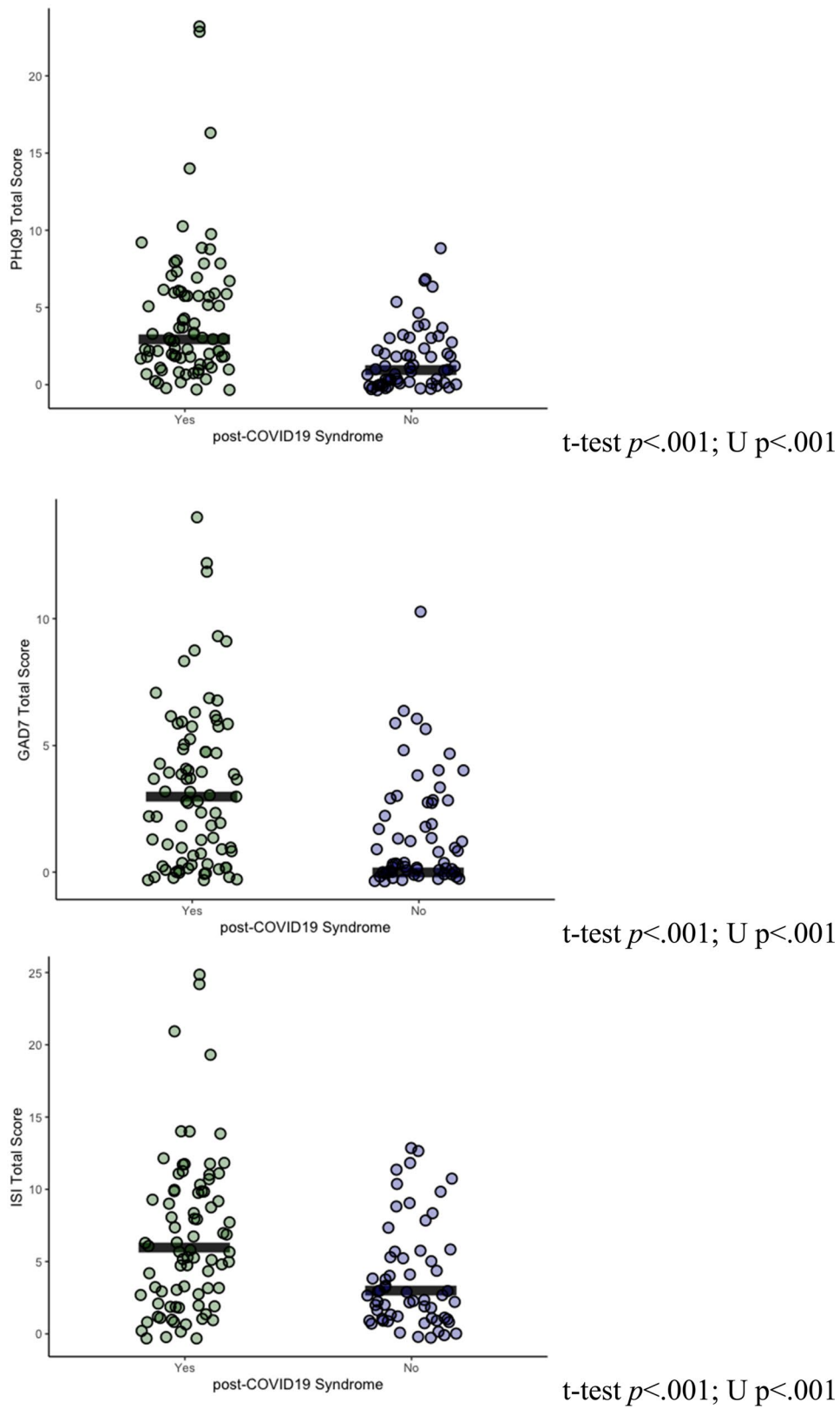
Neuropsychiatric symptoms have been described as a common sequela of SARS-CoV-2 infection. Up to 20% of COVID-19 survivors reported significant psychiatric symptoms. Cognitive impairment was the most prevalent (19.7%, 95% CI 8.8–33.4) followed by depressive (18.3%, 95% CI 13.3–23.8), PTSD (17.9%, 95% CI 11.6–25.3), anxiety (16.2%, 95% CI 12.0–20.8), and insomnia (13.5%, 95% CI 8.7–19.2) symptoms [19].

Authors have previously published a long-term follow-up in 1565 Latin American COVID-19 survivors [3]. After 24 months, the prevalence of anxiety (16.55%), depressive (21.79%), PTSD (35.27%), and insomnia symptoms (23.86%) remained higher than expected. Social factors, location of hospital stays, physical comorbidities, and the severity of COVID-19 symptoms were also associated with anxiety, depressive, PTSD, and insomnia

symptoms. Hence, there seems to be a continuous and deleterious impact on MHS in long COVID patients. In the same line, we have also reported a higher-than-expected prevalence of anxiety, insomnia, and depressive (31.2%, 28.7%, and 21.2% respectively) symptoms in COVID-19 survivors with positive ANA. This seems to be associated with significant autoantibody positivity and thus post-COVID-19 symptoms (11.7%, 11.7%, and 5% respectively) compared to participants without autoantibody positivity.

Although subgroup analysis from a recent meta-analysis reported a higher proportion of psychiatric symptoms associated with long COVID in high-income countries (HIC) [19], our study—conducted in a low- and middle-income country (LMIC)—showed an even higher prevalence of depressive, anxiety, and insomnia symptoms. These findings highlight the potentially underestimated mental health burden of long COVID in LMICs and underscore the need for context-specific research and public health strategies in resource-limited settings.

We consider that this clinical phenomenon may be influenced by a higher burden of adverse social determinants of health, as well as environmental factors specific to certain geographic regions. Factors such as economic deprivation, limited access to education, malnutrition, income inequality, housing instability, reduced productivity, and unemployment have been previously identified as relevant social determinants associated with mental health symptoms. In this context, a greater overall psychosocial burden in low- and middle-income countries may contribute to the higher prevalence of depressive, anxiety, and insomnia symptoms observed in our sample. However, given the observational nature of this study,



**Fig. 3** Distribution of PHQ-9, GAD-7, and ISI total scores in COVID-19 survivors;  $t\text{-test } p < 0.001; U p < 0.001$

**Table 2** Multivariate robust logistic regression models to predict mental symptoms

| Variables              | Depressive Symptoms |               | 95% CI |      | p value | R2 |
|------------------------|---------------------|---------------|--------|------|---------|----|
|                        | B                   | OR            | Min    | Max  |         |    |
|                        | ANA                 |               |        |      |         |    |
| No                     |                     | 1 [Reference] | NA     | NA   | NA      |    |
| Yes                    | 0.81                | 2.25          | 1.90   | 2.67 | < 0.001 |    |
| Post-COVID-19 Syndrome |                     |               |        |      |         |    |
| No                     |                     | 1 [Reference] | NA     | NA   | NA      |    |
| Yes                    | 0.61                | 1.84          | 1.02   | 3.31 | 0.041   |    |
| anti-TPO               |                     |               |        |      |         |    |
| No                     |                     | 1 [Reference] | NA     | NA   | NA      |    |
| Yes                    | 0.51                | 1.66          | 1.11   | 2.50 | 0.013   |    |

these interpretations should be considered exploratory and warrant further investigation in larger, multisite cohorts.<sup>[30]</sup>

Since the first clinical description by Maes et al. [29] and Levine et al. [30] in the past century, several biological correlates associated with neuroinflammation, autoantibody positivity, and resulting positive peripheral inflammatory biomarkers have been reported for unipolar depression in several systematic reviews and meta-analyses [31–33]. A previous meta-analysis reported higher amounts of granulocytes, monocytes, and natural killers, and lower only CD16+ natural killers in unipolar depression. It is important to mention that these findings are not limited to one specific immune cell subset [34]. Moreover, cytokines such as IL-1 $\beta$ , IL-6, TNE, and IFNs have been also reported in several studies in participants with unipolar depression [35]. Another recently published meta-analysis reported C-reactive protein (CRP) and IL-6 to be associated with depressive symptoms such as anhedonia and psychomotor retardation [36].

Previously, other theories that contributed to the understanding of the role of ANA and neuroinflammation in the pathogenesis of depression have been amongst others: (i) immune related factors associated with microglial activation; (ii) neurotoxic factor expression and leakage from a resulting damaged brain blood barrier (BBB); (iii) depressive - like behaviors in animal models and human trials associated with positive ANAs; (iv) positive thyroid antibodies as predictors of postpartum depression; and (v) associations between neuroinflammation, severity, chronicity, and resulting brain atrophy in translational models of depression [37]. However, precise interactions between neuroinflammation, ANA expression, neurobiology of depressive disorder, and therapeutics are yet to be unraveled.

Although long COVID has been described as a systemic illness [38] it is difficult at this point to argue that MHS are associated with persistent systemic inflammation and subsequent neuroinflammation in COVID-19

survivors. Furthermore, there is no clear association thus far between persisting MHS with underlying psychiatric or psychological illness. To date, only the female gender has been associated as a significant socio-demographic risk factor for depression in COVID-19 survivors after six months of follow-up [4]. Previously, we did not report any significant differences associated with gender in four different MHS (depressive, anxiety, PTSD, and insomnia symptoms) in a 24-month follow-up of COVID-19 survivors, some of them with persistent COVID-19 symptoms or syndrome subtypes [3].

With regards to depressive disorders, we reported a four times higher prevalence in participants with long COVID compared to participants without long COVID. A similar trend was reported for anxiety and insomnia symptoms with a three times higher prevalence in participants with long COVID. We also were able to report positive ANA in more than half (54,3%) of the sample. About two-thirds of participants (64,5%) with positive ANA also reported long COVID. While participants with long COVID had global non-specific autoantibody positivity associated with all MHS, one-third of participants with long COVID also reported positive anti-TPO antibodies. Surprisingly, autoantibody positivity with positive anti-TPO antibodies could be associated with both depressive and insomnia symptoms. Our findings are supported by statistically significant psychometric change registered in PHQ-9 and ISI respectively. Hence, we can hypothesize that MHS are more prevalent in participants with long COVID and positive ANA. Moreover, we can argue that subgroups of participants with long COVID and additional positive anti-TPO antibodies may be not associated with positive anxiety symptoms due to the absence of psychometric change in GAD-7. Conversely, depressive and insomnia symptoms might be accentuated by positive anti-TPO antibodies.

However, we acknowledge that the PHQ-9, GAD-7, and ISI are validated screening tools, not diagnostic instruments. While they are widely used in epidemiological

studies, they do not replace clinical evaluation or longitudinal psychiatric diagnosis. Therefore, our findings should be interpreted as indicative of symptom burden, rather than definitive diagnostic prevalence. Interestingly, participants with long COVID and positive anti-TPO antibodies did not exhibit significantly elevated GAD-7 scores, suggesting a selective association with depressive and insomnia symptoms, but not anxiety. This may reflect a distinct autoimmune-psychiatric phenotype, which warrants further investigation using longitudinal and clinical diagnostic approaches.

After logistic regression analysis, participants with long COVID had significantly higher odds of experiencing at least one mental health outcome. For depressive symptoms, the odds were 1.84 times higher (OR = 1.84) in individuals with long COVID compared to those without. This association was even stronger in the subgroup of participants with long COVID and positive ANA, where the odds of depressive symptoms increased to 2.25 (OR = 2.25). Regarding anxiety, the odds were also elevated—up to 1.95 (OR = 1.95)—in participants with long COVID and positive ANA but without anti-TPO antibodies. Similarly, for insomnia, we observed increased odds (OR = 2.04) among participants with long COVID and ANA positivity, regardless of anti-TPO antibody status. Interestingly, the subgroup of participants with long COVID, positive ANA, and anti-TPO antibodies did not exhibit a statistically significant association with anxiety symptoms.

Our findings highlight a meaningful association between mental health symptoms and ANA seropositivity in individuals with long COVID, which may reflect the complex interplay between psychosocial stress, immune dysregulation, and neuropsychiatric vulnerability. Psychosocial stress has been recognized as a key contributor not only to mental health disturbances but also to the development and persistence of long COVID and autoimmune conditions. This framework may help explain the higher burden of long COVID and autoimmunity among women, particularly during their reproductive years, when exposure to psychosocial stress is often greater and shaped by sex-specific societal and biological factors [39, 40]. These dynamics could account, at least in part, for the increased likelihood of depression observed in ANA-seropositive individuals. Recognizing the role of psychosocial stress in shaping both immune function and psychiatric outcomes may be essential for developing integrative approaches to care in long COVID populations [39].

#### Strengths and limitations

To the best of our knowledge, this is the first study to report a potential subtype of long COVID characterized by autoantibody positivity and adverse mental

health symptoms in a Colombian population. Our findings suggest that this subgroup may represent a biologically distinct clinical profile, particularly among female participants—who comprised nearly 80% of those with long COVID. This sex-based overrepresentation may reflect a heightened vulnerability to sustained systemic inflammation and immune dysregulation, processes that could contribute to long-term neuroinflammation and increased psychopathological burden. Although these observations are preliminary, they support the hypothesis that biological factors such as autoantibody activity may serve as important “pieces of the puzzle” in understanding the nature, course, and prognosis of specific long COVID subtypes.

Notably, most participants in our study reported mild to moderate symptoms during the acute phase of COVID-19. This suggests that the observed associations between autoantibody positivity and mental health symptoms are unlikely to be explained solely by the severity of the initial infection. These findings are consistent with prior studies indicating that even mild infections may trigger persistent neuropsychiatric symptoms and immune dysregulation, supporting the role of alternative mechanisms such as autoimmunity, systemic inflammation, and psychosocial stress [3, 41–43].

However, this study has several important limitations. First, we were unable to control for the time elapsed since acute SARS-CoV-2 infection, a variable that could influence both mental health symptom severity and immune system markers, including autoantibody positivity. Future studies should incorporate standardized measures of time from infection to better address this potential confounder. Second, we could not determine whether autoantibody positivity was pre-existing or induced by COVID-19, as baseline serological data prior to infection were not available. Longitudinal studies with pre- and post-infection immune profiling are essential to clarify causal relationships between SARS-CoV-2 infection, autoimmunity, and mental health symptoms.

#### Conclusions

In line with our study's aim, we explored the association between autoantibody positivity and mental health symptoms in participants with long COVID. Our findings suggest that certain subgroups of individuals with long COVID—particularly those with positive ANA and/or anti-TPO antibodies—may present distinct clinical profiles characterized by higher prevalence of depressive and insomnia symptoms. While our results are not sufficient to define new clinical subtypes, they do highlight the potential role of autoantibody positivity and MHS as important variables that may modify the clinical expression of long COVID. These preliminary findings support the need for future translational research aimed

## at elucidating underlying mechanisms and validating immunopsychiatric subtypes of long COVID.

### Abbreviations

|             |  |
|-------------|--|
| AIC         | Akaike Information Criterion                             |
| ANA         | Antinuclear antibodies                                   |
| anti-SSA/Ro | anti-Sjögren's syndrome-related antigen A autoantibodies |
| anti-SSB/La | Sjögren syndrome type B antigen                          |
| anti-RNO    | Anti-ribonucleoprotein antibodies                        |
| anti-Smith  | anti-smith antibodies                                    |
| BBB         | Brain blood barrier                                      |
| BIC         | Bayesian Information Criterion                           |
| COVID-19    | Coronavirus disease                                      |
| CRP         | C-reactive protein                                       |
| EHR         | Electronic Health Records                                |
| ELISA       | Enzyme-Linked Immunosorbent Assay                        |
| PHQ-9       | The 9-items Patient Health Questionnaire                 |
| GAD-7       | 7-items Generalized Anxiety Disorder Scale               |
| IL          | Interleukin  |
| IQR         | Interquartile ranges                                     |
| IRB         | Institutional Review Board                               |
| ISI         | Insomnia Severity Index Scale                            |
| MHS         | Mental Health Symptoms                                   |
| LMCI        | Low-and-middle income country                            |
| OR          | Odds Ratio   |
| PTSD        | Post-traumatic Stress Disorder                           |
| RF          | rheumatoid factor  |
| RERI        | Relative Excess Risk                                     |
| SARS-CoV-2  | Severe Acute Respiratory Syndrome Coronavirus 2          |
| SD          | Standard Deviations                                      |
| Tg          | anti-thyroglobulin                                       |
| TPO         | anti-thyroid peroxidase                                  |

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### Authors' contributions

JMA, HFGB and MS conceived the study. HFGB, MS, JFGF, CR, YBL, ILM, MCD, GIBACUS, MR, JCSU, JMA contributed to the development and conduct of the study. HFGB, JMA, MR, and JCSU acquired, managed, and analyzed the data. HFGB, JFGF and JMA drafted the first version of the manuscript. All coauthors provided critical comments and approved the final version of the manuscript.

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### Data availability

Data are available upon request from the corresponding authors.

### Declarations

#### Ethics approval and consent to participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and national ethical guidelines for human subjects research in Colombia. Ethical approval was obtained from the Research Ethics Committee of Universidad Simón Bolívar in Barranquilla, Colombia. Additionally, the study protocol was reviewed and approved by the Institutional Review Board (IRB) of Coosalud EPS. All participants provided informed consent prior to enrollment. Data were anonymized and stored in a secure electronic database to ensure confidentiality and data protection throughout the study.

### Consent for publication

Not applicable.

### Competing interests

HFGB: He has received research grant support from Ministry of Science, Technology, and Innovation (MinCiencias) in Colombia, United Kingdom Research & Innovation Unit (UK); and speaker/consultation fees from Abbott, GSK, Roche Pharmaceuticals, Pfizer, Synergy R&D. JFGF: works for Zerenia Clinic a clinical unit by Khiron Pharmaceuticals Life Corporation. He is also a General Manager for Latin American Society of Consultation - Liaison Psychiatry (SOLAPSIQUE). Bogotá, Colombia. The other authors have no conflict of interest to report.

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