Brain, Behavior, & Immunity - Health 54 (2026) 101268

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Severity of SARS-CoV-2 infection increases the risk of generalized anxiety disorder, major depressive disorder, and post-traumatic stress disorder in COVID-19 survivors: a prospective longitudinal cohort study

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ARTICLE INFO

Keywords:
COVID-19
Mental health outcomes
Generalized anxiety disorder
Major depressive disorder
Post-traumatic stress disorder
SARS-CoV-2
Cohort study
Depression
PTSD

ABSTRACT

Background: The COVID-19 pandemic has significantly impacted global mental health. However, individuals with confirmed SARS-CoV-2 infection, diagnosed either clinically or through serological testing, appear to be at higher risk for developing mental health outcomes (MHOs) such as generalized anxiety disorder (GAD), major depressive disorder (MDD), and post-traumatic stress disorder (PTSD). Despite this, the relationship between the severity of acute SARS-CoV-2 infection and the onset of MHOs remains underexplored.

Methods: This observational, longitudinal cohort study included 1,565 COVID-19 individuals with confirmed COVID-19 who were discharged from emergency departments, inpatient wards, and ICUs in Colombia. Participants were assessed at baseline, 3-, 6-, and 12-months post-infection using validated scales for anxiety, depressive and PTSD symptoms and structured interviews. COVID-19 severity was categorized as mild, moderate, severe, or critical. Propensity-score-based marginal mean weighting through stratification (MMWS) was used to adjust for baseline differences. Multilevel robust Poisson regression weighted by MMWS estimated the risk of MHOs.

Results: High prevalence rates of GAD (23%), MDD (10%), and PTSD (10%) were observed three months post-infection, especially among those with severe or critical COVID-19. The prevalence of anxiety, depressive and PTSD symptoms declined over time across all groups. Multivariate analysis identified COVID-19 severity and early post-discharge onset of disease as significant risk factors for MHOs. Critical cases were associated with an increased risk of GAD (aRR = 1.58; 95% CI [1.07-2.32]) and MDD (aRR = 1.46; 95% CI [1.00-2.16]).

Discussion: The findings highlight the temporal and severity-related dimensions of MHOs post-COVID-19. The observed peak in the onset of GAD, MDD, and PTSD at three months post-infection suggests a critical window for early intervention and targeted mental health support. Declining prevalence trends underscore the potential for recovery, albeit influenced by initial infection severity.

Conclusion: This study underscores the need for targeted mental health interventions during early recovery, particularly for severe and critical COVID-19 cases, to mitigate the long-term psychiatric burden.

This article is part of a special issue entitled: Post-COVID19 condition published in Brain, Behavior, & Immunity - Health.

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https://doi.org/10.1016/j.bbih.2026.101268
Received 20 July 2025; Received in revised form 29 April 2026; Accepted 19 May 2026
Available online 21 May 2026

1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has emerged as a significant global health crisis, not only due to its immediate physical health impacts but also because of its profound psychological repercussions (Xiong et al., 2020). The prevalence of mental health outcomes (MHOs) such as generalized anxiety disorder (GAD), major depressive disorder (MDD), and post-traumatic stress disorder (PTSD) has been widely explored in COVID-19 survivors elsewhere (Xiong et al., 2020; Yuan et al., 2021a; Zeng et al., 2023; Zhang et al., 2022).

Higher rates of MHOs have been reported among COVID-19 survivors compared to the general population. However, most studies have assessed MHOs based on symptoms rather than diagnostic criteria. Consequently, there is limited diagnostic confirmation of the prevalence of disorders such as GAD, MDD, and PTSD. Furthermore, the reported prevalence of new-onset for mental disorders within the first 12 months following acute COVID-19 infection remains unclear.

MDD, GAD, and PTSD are among the most frequently reported psychiatric sequelae of the COVID-19 pandemic, with prevalence estimates varying widely by population and clinical context. In the general population, meta-analyses conducted during the pandemic report pooled prevalences of approximately 28% for depression, 27% for anxiety, and 24% for post-traumatic stress symptoms, exceeding pre-pandemic baselines and showing marked heterogeneity related to sex, age, social restrictions, and socioeconomic vulnerability (Guillen-Burgos et al., 2023; Ceban et al., 2021).

Among individuals infected with SARS-CoV-2, particularly those hospitalized or admitted to intensive care, psychiatric morbidity is substantially higher. Approximately 20% of hospitalized patients develop a new psychiatric diagnosis within six months, and symptom-based studies report even higher rates of depression, anxiety, and PTSD following infection (Saavedra Trujillo, 2020; Osório et al., 2019). ICU survivors and patients with neurological complications represent the highest-risk group (Spitzer et al., 2006). Although prevalence is lower among non-hospitalized survivors, rates remain elevated compared with uninfected controls (Spitzer et al., 2006). Long-term follow-up suggests partial symptom attenuation over time, especially after mild infection, but persistent psychiatric symptoms are more common among individuals with severe disease or pre-existing mental disorders (Uvais et al., 2022; Zhou et al., 2023).

Various risk factors including sociodemographic, clinical, and biological determinants have been identified as contributors to the development of psychiatric symptoms and disorders following acute COVID-19 infection (Martins et al., 2022). Nevertheless, limited clinical research has explored the relationship between the severity of SARS-CoV-2 infection and the onset of mental disorders. Importantly, emerging evidence also suggests a bidirectional association, individuals with pre-existing psychiatric disorders are at increased risk of COVID-19 infection, hospitalization, and mortality (Cassiani-Miranda et al., 2021). A systematic review and meta-analysis demonstrated that mood disorders, in particular, were significantly associated with worse COVID-19 outcomes, underscoring the vulnerability of this population in both directions of the relationship (Cassiani-Miranda et al., 2021).

We hypothesized that severity of acute COVID-19 increases the risk of new-onset GAD, MDD, and PTSD over a 12-month follow-up. Therefore, we decided to carry-out a prospective longitudinal cohort study to assess the prevalence and risk of severe SARS-CoV-2 infection on the development of GAD, MDD and PTSD during the first 12 months of post-acute infection.

2. Methods

2.1. Study design and population

An observational, prospective, longitudinal cohort study was carried-out to identify the prevalence of MHOs over 12-months after SARS-CoV-2 infection and its association between the severity of COVID-19 and the risk to develop major mental disorders such as GAD, MDD, and PTSD. Our study was carried out in a large teaching hospital at Barranquilla, Colombia during the COVID-19 pandemic. Recruitment period extended from April to December 2020. Final assessments were performed August 30, 2022.

We employed a convenience sampling method to select participants from among COVID-19 survivors who had been discharged from the emergency department (ED), inpatient wards, or intensive care units (ICU). The inclusion criteria were as follows: (i) confirmed COVID-19 diagnosis via RT-PCR or antigen testing during hospitalization, (ii) adults aged 18 years or older (both male and female), and (iii) basic literacy skills, including reading and writing. Exclusion criteria included: (i) individuals under 18 years of age, (ii) individuals with previous mental disorders and neurological conditions (stroke, epilepsy, encephalitis, CNS infection, multiple sclerosis, brain tumors), (iii) lack of access to the internet or a smartphone, which would prevent participation in the follow-up surveys at 3-, 6-, 12-months post-discharge.

A total of 1,706 participants were initially enrolled in the study. During the follow-up period, 10 participants died. Additionally, 131 individuals were lost to follow-up for various reasons, including relocation, incomplete questionnaires, non-responsiveness, or voluntary withdrawal. Consequently, the final analysis was conducted on 1,565 participants, representing 91.7% of the initial cohort, all of whom had complete data records available for analysis.

A self-administered questionnaire was developed using REDCap SE v17 (licensed by Vanderbilt University) to collect demographic data, clinical records, and psychometric evaluations. The study implemented four evaluation points during the 12-month follow-up period, specifically at baseline (t1) (determined as the final day of hospital discharge), and at 3- (t2), 6- (t3), and 12-months (t4) post-discharge. The specifications of the clinical assessments were previously published in a recent study in our center (Martins et al., 2022). All personal identifiers, including names and identification numbers, were anonymized and subsequently encrypted to ensure privacy and confidentiality of participants throughout the study.

2.2. Definition of COVID-19 severity

According to the Colombian Association of Infectiology, COVID-19 severity is classified into four distinct levels: mild, moderate, severe, and critical. This classification is based on clinical presentation, respiratory function, and the need for medical intervention. Mild cases involve general symptoms such as fever and cough, without respiratory compromise or imaging evidence of pneumonia. Moderate cases are characterized by clinical or radiological signs of pneumonia without the need for oxygen therapy. Severe cases include patients with acute respiratory distress syndrome (ARDS), oxygen saturation below 90%, and the need for oxygen support. Finally, critical cases require ICU admission due to mechanical ventilation needs or multi-organ failure (Mei et al., 2021).

2.3. Outcomes measures

Two methods were used to evaluate the outcomes of interest. The first approach was to assess the presence or absence of symptoms related to anxiety, depression, and suspected post-traumatic stress disorder using self-administered questionnaires. The second method involved structured interviews using the SCID-5-CV (Structural Clinical Interview for DSM-5-Clinician Version) (Blevins et al., 2015) instrument for GAD, MDD, and PTSD diagnosis. Regarding the self-administered questionnaires used, the following description summarize each scale used. The 7-item Generalized Anxiety Disorder Scale (GAD-7) is a widely valid and reliable, self-administered tool for screening anxiety symptoms, particularly in primary care. A score of 5 or higher is considered the threshold

for identifying anxiety symptoms (Tu et al., 2021). In studies on COVID-19 survivors, this cut-off has been applied to detect mild anxiety symptoms (Martins et al., 2022). Across various assessments, the GAD-7 has demonstrated excellent internal consistency, with a Cronbach's alpha of 0.92, indicating strong reliability (Tarsitani et al., 2021a; Nagarajan et al., 2022; Horn et al., 2022).

The 9-item Patient Health Questionnaire (PHQ-9) is similarly a self-administered scale, commonly used for detecting depressive symptoms in primary care. In this study, a cut-off point of 7 or higher was employed based on prior validation studies in the Colombian population, offering high sensitivity (90.38%) and specificity (81.68%) (Sobczak et al., 2023). The PHQ-9 has been consistently used in COVID-19 survivor studies worldwide, and it showed strong internal consistency with a Cronbach's alpha of 0.92 during assessments (von Elm et al., 2007). Finally, The Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5) is a 20-item self-report measure designed to assess PTSD symptoms according to DSM-5 criteria. It employs a 5-point Likert scale to evaluate symptom severity, with a score of 33 or higher indicating probable PTSD (Tarsitani et al., 2021b). This threshold has been widely applied in research among COVID-19 survivors. The PCL-5 exhibited excellent internal consistency, with a Cronbach's alpha of 0.97, across multiple assessments, ensuring its reliability (Taquet et al., 2021; Groff et al., 2021; Liao et al., 2021; Schopman et al., 2021; Schotanus-Dijkstra et al., 2019).

2.4. Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and adhered to the recommendations of the Equator Network and STROBE guidelines for observational studies (Have et al., 2021). Additionally, the research followed best practices according to the Good Clinical Practices for conducting human research. Ethical approval was obtained from the Universidad Simon Bolivar Ethics Committee (protocol number: CEI-USB-CE-0324-00-00). Informed consent was secured from all participants in written form, ensuring compliance with ethical standards for human research participation.

2.5. Statistical analysis

Statistical analysis was performed using Stata 17 MP software (Texas, United States StataCorp LLC). Relative and absolute frequencies for qualitative variables were calculated as well as a central trend and dispersion measures for quantitative variables. These analyses were performed by COVID-19 severity with the purpose of identifying possible differences among baseline characteristics.

2.5.1. Marginal mean weighting through stratification (MMWS) analysis

A doubly robust analysis based on propensity-score-based marginal mean weighting through stratification (MMWS) and multilevel logistic regression were performed. The MMWS method was employed to reduce the possible selection bias and remove possible imbalances of baseline characteristics in the compared groups. The variables for MMWS constructions were selected based on a literature review, considering clinical and demographic variables with clinical relevance or biological plausibility. An ordinal propensity score model used to generate marginal mean weights included baseline sociodemographic and clinical covariates selected a priori as potential confounders of the association between COVID-19 severity and post-COVID mental health outcomes. These covariates comprised age (years), sex, marital status, health insurance regime, employment status, ethnicity, socioeconomic stratification, body mass index (BMI), diabetes mellitus, and hypertension. All variables were measured at baseline or obtained from electronic health records prior to COVID-19 severity classification. Following the PS estimation, multicollinearity among the covariates included in the ordinal propensity score model was assessed using variance inflation factors (VIF). VIF values $>$ 5 was considered indicative of potentially problematic collinearity. For this analysis, the values were less than 2. A review of common support was made, plotting histograms of ordinal propensity score by COVID-19 severity and describing the distribution of the variables by severity level. Common support and overlap of the ordinal propensity score distributions across COVID-19 severity categories were assessed graphically (Supplementary Fig. S1). Adequate overlap was observed across all severity groups. After checking common support, the propensity score was stratified by quintiles for the construction of the weights. Covariate balance before and after MMWS was assessed using standardized mean differences (SMD), with values less to 0.10 indicating adequate balance.

2.5.2. Multilevel Poisson model to identify risk factors

MMWS weights were used in a multilevel Poisson model for the purpose of estimating the risk of GAD, MDD, and PTSD based on severity of COVID-19 infection estimating a doubly robust model. A multivariate random intercept robust Poisson analysis using an unstructured correlation matrix was carried out to assess de risk (adjusted Risk Ratio [aRR]) between the COVID-19 severity with GAD, MDD, and PTSD. This effect was adjusted considering clinical and demographic variables with clinical relevance or biological plausibility. The model assumptions were validated using a linearity test, Pearson's test, deviation residual analysis, and collinearity analysis through VIF. No covariate exceeded a VIF threshold$<$5.

Two-tailed tests were adopted for analyzing results from this study and a P-value $<$0.05 was inferred as a statistically significant result.

3. Results

The selection of participants is illustrated in Fig. 1. A total of 1565 participants were analyzed, with a median age of 54 years (IQR:34-67), 49.65% (n = 777) were female. Table 1 summarizes the baseline characteristics stratified by COVID – 19 severities after MMWS analysis. There were differences with regards to age, marital status, ethnicity and socioeconomic stratification (Table 1). COVID – 19 severity groups were similar in terms of clinical charts.

3.1. Prevalence of mental disorders

3.1.1. Prevalence of generalized anxiety disorder

The prevalence of GAD was reported across four time points of evaluation (baseline, 3 months, 6 months, and 12 months) in participants categorized into four severity groups: mild, moderate, severe, and critical. At baseline (t1), the prevalence of GAD was relatively low across all groups, with values of 7% for the mild and moderate groups, and 5% for the severe and critical groups. At 3 months (t2), there was a notable increase in the prevalence of GAD in the severe group, where it peaked at 23% and in the critical group were an increase to 10% was also reported. The mild and moderate groups showed smaller non-significant changes (4% and 8%, respectively). At 6 months (t3), the prevalence of GAD decreased across all groups. Severe infection group dropped to 5%, and all other groups followed similar trends. The declining trend continued up to the 12-month evaluation (t4), with the highest peak of prevalence being observed in the severe COVID – 19 infection group at 4%, while other groups showed further reductions. See Fig. 1A.

3.1.2. Prevalence of major depressive disorder

The prevalence of MDD across four time points: baseline, 3 months, 6 months, and 12 months, in participants stratified by severity of COVID-19 infection (mild, moderate, severe, and critical). At baseline (t1), the prevalence of MDD is low across all severity groups, with mild cases showing a prevalence of 4%, moderate 3%, severe 2%, and critical cases 4%. At 3 months (t2), a substantial increase is observed, particularly in the critical group, which reaches a prevalence of 10%, while the severe group rises to 9%, and the mild and moderate groups show more modest increases of 9% and 8%, respectively. By 6 months (t3), the prevalence

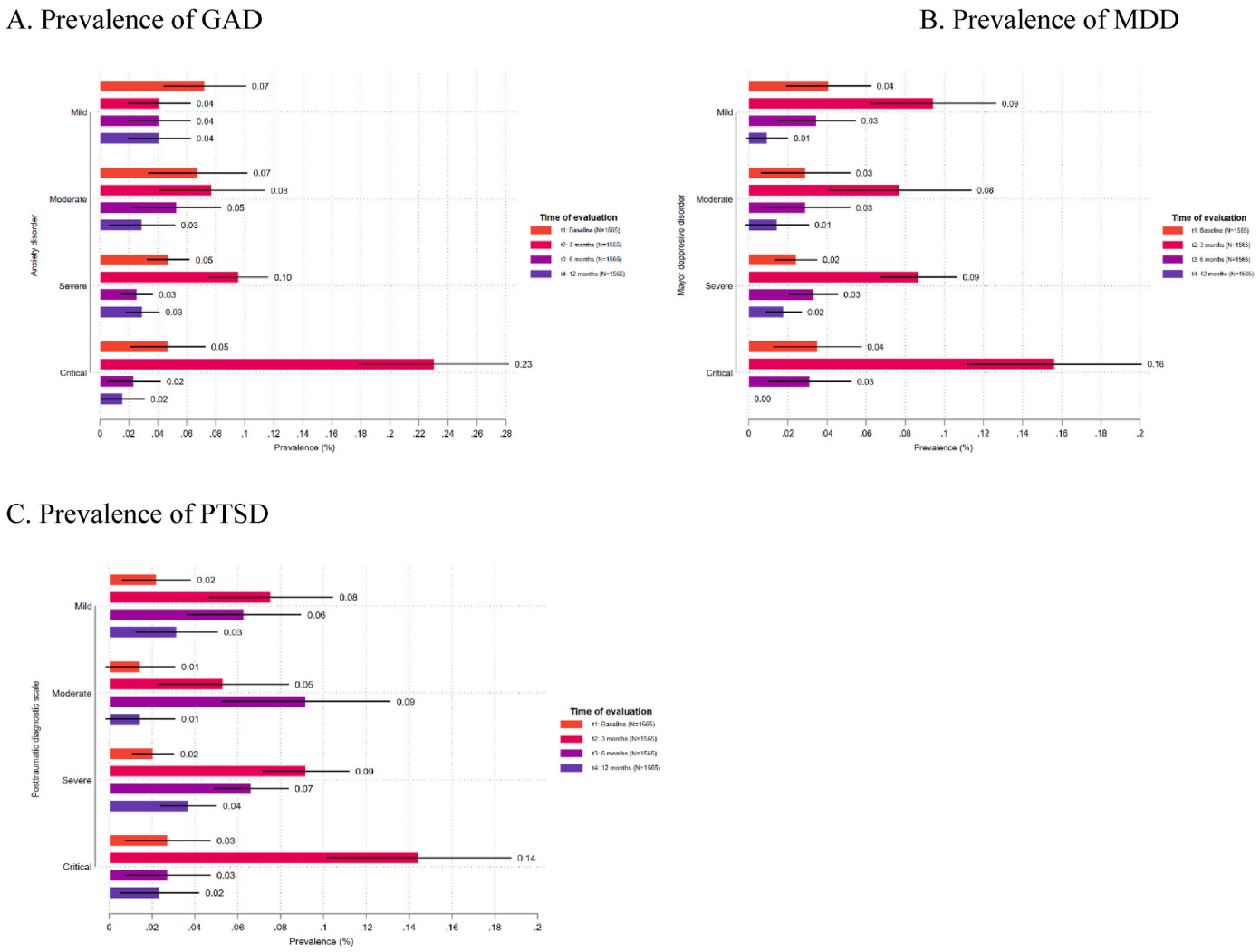

Fig. 1. Prevalence of the mental disorders GAD, MDD, and PTSD over 12-month of follow-up.

of MDD decreases across all groups, with similar values of 3% for each severity level. At 12 months (t4), the prevalence further declines, with the highest value being 2% in the severe group, while the other groups show minimal values (1% or lower). See Fig. 1B.

3.1.3. *Prevalence of post-traumatic stress disorder*

The prevalence of PTSD across four time points: baseline, 3 months, 6 months, and 12 months post-discharge, categorized by COVID-19 severity (mild, moderate, severe, and critical). At baseline (t1), the prevalence of PTSD is relatively low across all groups, with the critical group exhibiting the highest prevalence at 3%. At 3 months (t2), the prevalence increases significantly, with the critical group showing a notable rise to 10%, and the severe group reaching 9%. The mild and moderate groups also experience small increases to 8% and 5%, respectively. At 6 months (t3), the prevalence declined across all groups. Moderate and severe groups remained with a prevalence of 9% and 7%, respectively. At 12 months (t4), the prevalence decreases even further, with the highest value of 4% reported in the severe infection group and critical group declined to 3% respectively. See Fig. 1C.

3.2. *Frequency, severity and evolution of anxiety and depressive symptoms in COVID-19 survivors*

Fig. 2 illustrates the frequency, severity and evolution of anxiety and depressive symptoms in COVID-19 survivors. Overall, the frequency of anxiety symptoms in baseline was higher than the frequency of depressive symptoms for all severity COVID-19 groups. After 12 months of follow up, there is a reduction in the frequency of these mental symptoms among remaining follow-up periods.

3.3. *Propensity score and MMWS analysis*

Regarding the PS + MMWS analysis, adequate overlap of propensity score distributions was observed across all COVID-19 severity groups, with adequate common support across the range of estimated probabilities, showing overlap in COVID severity probabilities according to the selected covariates (Supplementary Fig. S1).

The marginal mean weighting produced stable weightings across all severity levels, with specific mean weightings for each group close to one and no evidence of extreme values in MMWS weighting preserved majority of the effective sample size (ESS = 1277 of 1565), with no evidence of extreme weights (maximum = 4.54), supporting the stability of the weighted analyses (Supplementary Table S1). Covariates balance improved substantially after weighting, although some residual imbalance persisted in factors such as age, body mass index, hypertension, and diabetes (Supplementary Fig. S2). These variables were further adjusted in the outcome regression as part of a doubly robust estimation strategy.

Table 2 shows MMWS-weighted baseline characteristics across COVID-19 severity categories, illustrating the balanced pseudo-population on which adjusted effect estimates were obtained.

Table 1
Baseline characteristics for the cohort of COVID-19 survivors by severity of COVID-19 exposure.

Variables	Mild	Moderate	Severe	Critical	Total	p-value
	N = 318	N = 207	N = 784	N = 256	N = 1565	
Gender						0.002
Male	136 (42.77%)	105 (50.72%)	429 (54.72%)	118 (46.09%)	788 (50.35%)	
Female	182 (57.23%)	102 (49.28%)	355 (45.28%)	138 (53.91%)	777 (49.65%)	
Age in years at study entry	40.00 (30.00-59.00)	45.00 (31.00-62.00)	56.00 (40.00-70.00)	53.50 (36.00-70.50)	51.00 (34.00-67.00)	<0.001
Marital status at study entry						<0.001
Single	141 (44.34%)	61 (29.47%)	187 (23.85%)	72 (28.13%)	461 (29.46%)	
Married	100 (31.45%)	71 (34.30%)	428 (54.59%)	89 (34.77%)	688 (43.96%)	
Divorced	46 (14.47%)	36 (17.39%)	85 (10.84%)	49 (19.14%)	216 (13.80%)	
Widowed	31 (9.75%)	39 (18.84%)	84 (10.71%)	46 (17.97%)	200 (12.78%)	
Education						<0.001
Primary	78 (24.53%)	52 (25.12%)	206 (26.28%)	60 (23.44%)	396 (25.30%)	
Secondary	102 (32.08%)	64 (30.92%)	332 (42.35%)	75 (29.30%)	573 (36.61%)	
Technician	56 (17.61%)	41 (19.81%)	84 (10.71%)	48 (18.75%)	229 (14.63%)	
Undergraduate	45 (14.15%)	28 (13.53%)	115 (14.67%)	44 (17.19%)	232 (14.82%)	
Postgraduate	37 (11.64%)	22 (10.63%)	47 (5.99%)	29 (11.33%)	135 (8.63%)	
Health insurance						<0.001
Contributory	130 (40.88%)	93 (44.93%)	475 (60.59%)	129 (50.39%)	827 (52.84%)	
Subsidized	188 (59.12%)	114 (55.07%)	309 (39.41%)	127 (49.61%)	738 (47.16%)	
Current employability status						0.065
Unemployment	39 (12.26%)	41 (19.81%)	117 (14.92%)	47 (18.36%)	244 (15.59%)	
Employment	279 (87.74%)	166 (80.19%)	667 (85.08%)	209 (81.64%)	1321 (84.41%)	
Ethnicity						<0.001
White/Hispanic	218 (68.55%)	144 (69.57%)	619 (78.95%)	142 (55.47%)	1123 (71.76%)	
Black/Afro descent	100 (31.45%)	63 (30.43%)	165 (21.05%)	114 (44.53%)	442 (28.24%)	
Socioeconomic status						<0.001
Low	59 (18.55%)	31 (14.98%)	127 (16.20%)	73 (28.52%)	290 (18.53%)	
Low	101 (31.76%)	63 (30.43%)	307 (39.16%)	72 (28.13%)	543 (34.70%)	
Middle low	81 (25.47%)	43 (20.77%)	206 (26.28%)	41 (16.02%)	371 (23.71%)	
Middle	31 (9.75%)	34 (16.43%)	85 (10.84%)	37 (14.45%)	187 (11.95%)	
Middle high	46 (14.47%)	36 (17.39%)	59 (7.53%)	33 (12.89%)	174 (11.12%)	
Length of hospital stays in days	1.00 (0.00-2.00)	2.00 (1.00-3.00)	10.00 (10.00-14.00)	22.00 (17.00-26.00)	10.00 (3.00-14.00)	<0.001
Clinical unit for stay during hospitalization						<0.001
ER	318 (100.00%)	207 (100.00%)	0 (0.00%)	0 (0.00%)	525 (33.55%)	
Inpatient floor	0 (0.00%)	0 (0.00%)	703 (89.67%)	0 (0.00%)	703 (44.92%)	
ICU	0 (0.00%)	0 (0.00%)	81 (10.33%)	256 (100.00%)	337 (21.53%)	
Having an associated physical or mental comorbidity	39 (12.26%)	44 (21.26%)	384 (48.98%)	125 (48.83%)	592 (37.83%)	<0.001
Physical (any) comorbidities confirmed by EHR	32 (10.06%)	42 (20.29%)	369 (47.07%)	119 (46.48%)	562 (35.91%)	<0.001
Mental comorbidities confirmed by EHR	7 (2.20%)	2 (0.97%)	15 (1.91%)	6 (2.34%)	30 (1.92%)	0.71
Stroke confirmed by EHR	0 (0.00%)	0 (0.00%)	11 (1.40%)	2 (0.78%)	13 (0.83%)	0.057
AD confirmed by EHR	0 (0.00%)	0 (0.00%)	8 (1.02%)	0 (0.00%)	8 (0.51%)	0.046
RA confirmed by EHR	0 (0.00%)	0 (0.00%)	3 (0.38%)	2 (0.78%)	5 (0.32%)	0.32
Asthma confirmed by EHR	6 (1.89%)	0 (0.00%)	14 (1.79%)	1 (0.39%)	21 (1.34%)	0.092
BD confirmed by EHR	0 (0.00%)	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.06%)	0.087
Anxiety Disorder confirmed by EHR	5 (1.57%)	0 (0.00%)	9 (1.15%)	2 (0.78%)	16 (1.02%)	0.34
Stress-related confirmed by EHR	0 (0.00%)	0 (0.00%)	1 (0.13%)	2 (0.78%)	3 (0.19%)	0.12
Cancer (any type) confirmed by EHR	0 (0.00%)	0 (0.00%)	11 (1.40%)	24 (9.38%)	35 (2.24%)	<0.001
DM (any type) confirmed by EHR	3 (0.94%)	3 (1.45%)	82 (10.46%)	11 (4.30%)	99 (6.33%)	<0.001
MDD confirmed by EHR	2 (0.63%)	2 (0.97%)	6 (0.77%)	4 (1.56%)	14 (0.89%)	0.64
Malnutrition confirmed by EHR	0 (0.00%)	1 (0.48%)	1 (0.13%)	0 (0.00%)	2 (0.13%)	0.43
SUD confirmed by EHR	0 (0.00%)	0 (0.00%)	3 (0.38%)	0 (0.00%)	3 (0.19%)	0.39
Epilepsy confirmed by EHR	0 (0.00%)	1 (0.48%)	1 (0.13%)	1 (0.39%)	3 (0.19%)	0.53
COPD confirmed by EHR	1 (0.31%)	7 (3.38%)	17 (2.17%)	4 (1.56%)	29 (1.85%)	0.062
MS confirmed by EHR	0 (0.00%)	2 (0.97%)	2 (0.26%)	2 (0.78%)	6 (0.38%)	0.22
Hypothyroidism confirmed by EHR	4 (1.26%)	3 (1.45%)	15 (1.91%)	7 (2.73%)	29 (1.85%)	0.59
Hypertension confirmed by EHR	16 (5.03%)	19 (9.18%)	217 (27.68%)	64 (25.00%)	316 (20.19%)	<0.001
ACS confirmed by EHR	0 (0.00%)	0 (0.00%)	3 (0.38%)	7 (2.73%)	10 (0.64%)	<0.001
AKD confirmed by EHR	0 (0.00%)	0 (0.00%)	1 (0.13%)	0 (0.00%)	1 (0.06%)	0.80
CKD confirmed by EHR	2 (0.63%)	1 (0.48%)	17 (2.17%)	4 (1.56%)	24 (1.53%)	0.15
Obesity confirmed by EHR	2 (0.63%)	4 (1.93%)	10 (1.28%)	13 (5.08%)	29 (1.85%)	<0.001
TB by EHR	0 (0.00%)	1 (0.48%)	11 (1.40%)	1 (0.39%)	13 (0.83%)	0.083
HIV/AIDS confirmed by EHR	0 (0.00%)	0 (0.00%)	12 (1.53%)	7 (2.73%)	19 (1.21%)	0.007
Do you have confirmation of pregnancy?	0 (0.00%)	0 (0.00%)	4 (0.51%)	0 (0.00%)	4 (0.26%)	0.26
BMI						<0.001
Normal	179 (56.29%)	82 (39.61%)	378 (48.21%)	85 (33.20%)	724 (46.26%)	
Overweight	137 (43.08%)	121 (58.45%)	370 (47.19%)	99 (38.67%)	727 (46.45%)	
Obesity	2 (0.63%)	4 (1.93%)	36 (4.59%)	72 (28.13%)	114 (7.28%)	
Did you have to be treated with supplemental oxygen?						<0.001
None	249 (78.30%)	113 (54.59%)	0 (0.00%)	0 (0.00%)	362 (23.13%)	
Nasal canula	69 (21.70%)	94 (45.41%)	531 (67.73%)	26 (10.16%)	720 (46.01%)	

(*continued on next page*)

Table 1 (*continued*)

Variables	Mild	Moderate	Severe	Critical	Total	p-value
	N = 318	N = 207	N = 784	N = 256	N = 1565	
High flow	0 (0.00%)	0 (0.00%)	253 (32.27%)	69 (26.95%)	322 (20.58%)	
Mechanical ventilation	0 (0.00%)	0 (0.00%)	0 (0.00%)	161 (62.89%)	161 (10.29%)	
Did you have to be treated in ICU?	0 (0.00%)	0 (0.00%)	81 (10.33%)	256 (100.00%)	337 (21.53%)	<0.001
Had mechanical ventilation during hospitalization?	0 (0.00%)	0 (0.00%)	0 (0.00%)	161 (62.89%)	161 (10.29%)	<0.001
Length of hospital stays in days	1.18 (1.09)	2.39 (2.99)	12.23 (5.03)	21.43 (5.95)	10.19 (8.20)	<0.001

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. MDD: Major Depressive Disorder; BD: Bipolar Disorder; AD: Alzheimer Disease; RA: Rheumatoid Arthritis; DM: Diabetes Mellitus; SUD: Substance Use Disorder; COPD: Chronic-Obstructive Pulmonary Disease; MS: Multiple Sclerosis, ACS: Acute Coronary Syndrome, AKD: Acute Kidney Disease; CKD: Chronic Kidney Disease, TB: Tuberculosis, HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; BMI: Body Mass Index; ICU: Intensive Care Unit; ER: Emergency Room; EHR: Electronic Health Record.

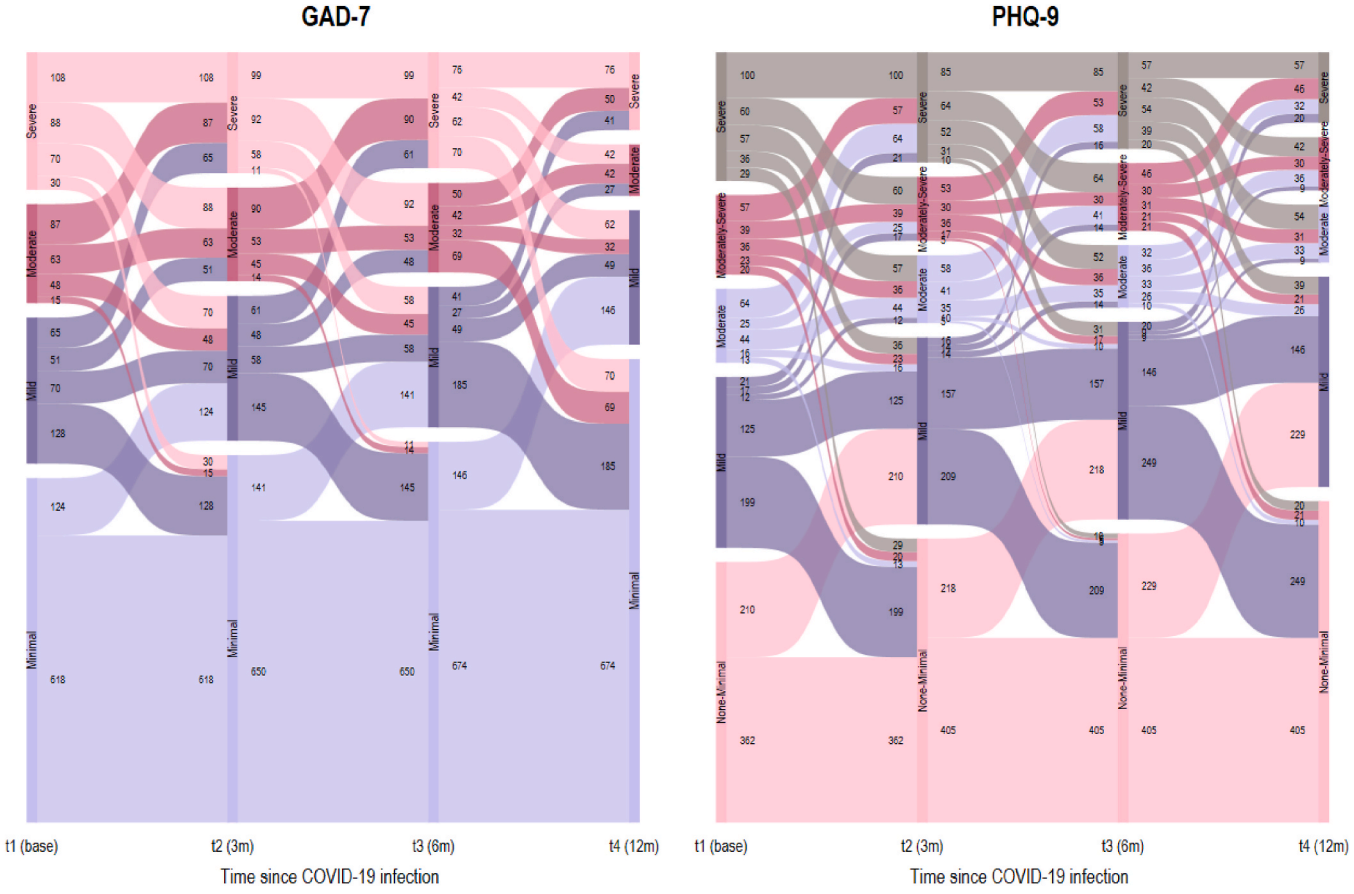

Fig. 2. Evolution of severity transitions in mental health symptom severity categories (GAD-7 and PHQ-9) over follow-up
Color indicates mental health symptom severity category (GAD-7/PHQ-9).

3.4. Risk factors for GAD, MDD, and PTSD

Fig. 3 shows the results of the doubly robust Poisson multilevel model using MMWS weights, expressing risk factors for GAD, MDD and PTSD. The model shows an increase in the incidence of anxiety for the second assessment compared to baseline assessment (aRR = 2.08; 95% CI: [1.56-2.79]) and a reduction in the incidence of GAD for third assessment (aRR = 0.57; 95%CI: [0.39-0.83]) and fourth assessment (aRR = 0.54; 95%CI: [0.36-0.79]) compared to baseline. Critical COVID-19 survivors reported a higher risk of GAD (aRR = 1.58; 95%CI: [1.07-2.32]). Employed population had a lower risk of GAD (aRR = 0.61; 95% CI: [0.45-0.83)].

The risk of MDD increased for the second assessment (aRR = 3.34; 95%CI: [2.3-4.85]) and decreased for the last assessment (aRR = 0.43; 95%CI: [0.25-0.75]). Critical COVID-19 participants presented a higher risk of MDD (aRR = 1.46; 95%CI: [1.00-2.16]). Participants with a partner showed a higher risk of MDD (aRR = 1.43; 95%CI: [1.12-1.82]).

Regarding PTSD, there was a higher risk in the first (aRR = 4.32; 95% CI: [2.76-6.74]) and second follow-up (aRR = 2.64; 95%CI: [1.67-4.18]) compared to the initial assessment.

4. Discussion

This study underscores the risk for GAD, MDD and PTSD in COVID-

Table 2
Baseline characteristics after MMWS weighting, by COVID-19 severity.

Variable	Mild Covid	Moderate Covid	Severe Covid	Critical Covid
Female sex (%)	57.23	49.28	45.28	53.91
Age, years (mean)	44.63	47.01	55.20	52.20
Married (%)	31.45	34.30	54.59	34.77
Divorced (%)	14.47	17.39	10.84	19.14
Widowed (%)	9.75	18.84	10.71	17.97
Subsidized health insurance (%)	59.12	55.07	39.41	49.61
Currently employed (%)	87.74	80.19	85.08	81.64
Black/Afro-descendant ethnicity (%)	31.45	30.43	21.05	44.53
Medium-income levels (%)	35.22	37.20	37.12	30.47
High-income levels (%)	14.47	17.39	7.53	12.89
Body mass index, kg/m^2 (mean)	24.19	25.17	24.92	27.03
Diabetes mellitus (%)	0.94	1.45	10.46	4.30
Hypertension (%)	5.03	9.18	27.68	25.00

Values express weighted means (continuous) or weighted percentages (categorical) after MMWS.
Categories not shown are reference categories and are included in the weighting model.

19 survivors during the first 12-months after SARS-CoV-2 infection. We observed a higher prevalence of GAD, MDD and PTSD at 3 months after acute COVID-19 infection. Participants with severe or critical illness were among the groups with highest prevalence that gradually decrease over time. Additionally, two key risk factors for mental health outcomes were identified in our cohort. The first one is the early post-acute phase vulnerability. At the three-month period, post-infection survivors exhibited a significantly increased risk to develop mental health outcomes, with the highest risk observed for PTSD, followed by MDD, and GAD. The second risk factor is the severity of the acute COVID-19. A significant risk for GAD was observed for participants with critical COVID-19. We also reported a marginal risk associated with critical COVID-19 and MDD. Surprisingly, no statistically significant association was reported between critical COVID-19 and PTSD onset. Our findings postulate the importance of early monitoring and prompt intervention, especially in persons with severe COVID infection and this effort may mitigate long-term mental health outcomes.

Previous reported consistent elevated risk of anxiety disorders (AD), MDD, and PTSD among survivors of COVID-19 (Jaquet et al., 2022; Kim, 2024). A meta-analysis by Groff et al. reported a pooled prevalence of 29.6% (95% CI: 14.0%-44.0%) for AD during the post-acute COVID-19 infection, along with the significant psychological impact of the pandemic in itself (Walker et al., 2024). At 3 months post-infection, we reported a similar prevalence (23.0%) of COVID-19 survivors diagnosed with GAD. Consequently, AD emerge as the most prevalent psychiatric diagnosis during the COVID- 19 post-infection period (Wang et al., 2024). Previous studies focused on survivors of latter infectious outbreaks reported that about less than a third suffered from AD (29%). However, heterogeneity with regards to measuring anxiety symptoms vs. psychometric evaluation of probable diagnosis followed by confirmation through a structured diagnostic interview are important factor with a substantial impact. In other words, this should be considered when interpreting our results, given that most previous trials measured anxiety symptoms without any psychometric or structured diagnostic tool follow up for specific anxiety disorders such as GAD.

Regarding the early post-acute phase as risk factor, Taquet et al. (Kim, 2024) observed an elevated hazard ratio for mental health outcomes after 3 months of post-COVID-19 infection, followed by a decrease at the 6-month follow up. In the same line, we reported a significantly higher adjusted risk ratio at 3 months post-infection, which declined at both the 6-month and 12-month follow-up periods. Thus, declining prevalence of AD over time suggests that the risk of new-onset AD is highest during the recovery phase and progressively decrease thereafter. AD prevalence reduction among COVID-19 survivors after six months can be attributed to several interrelated factors, including but

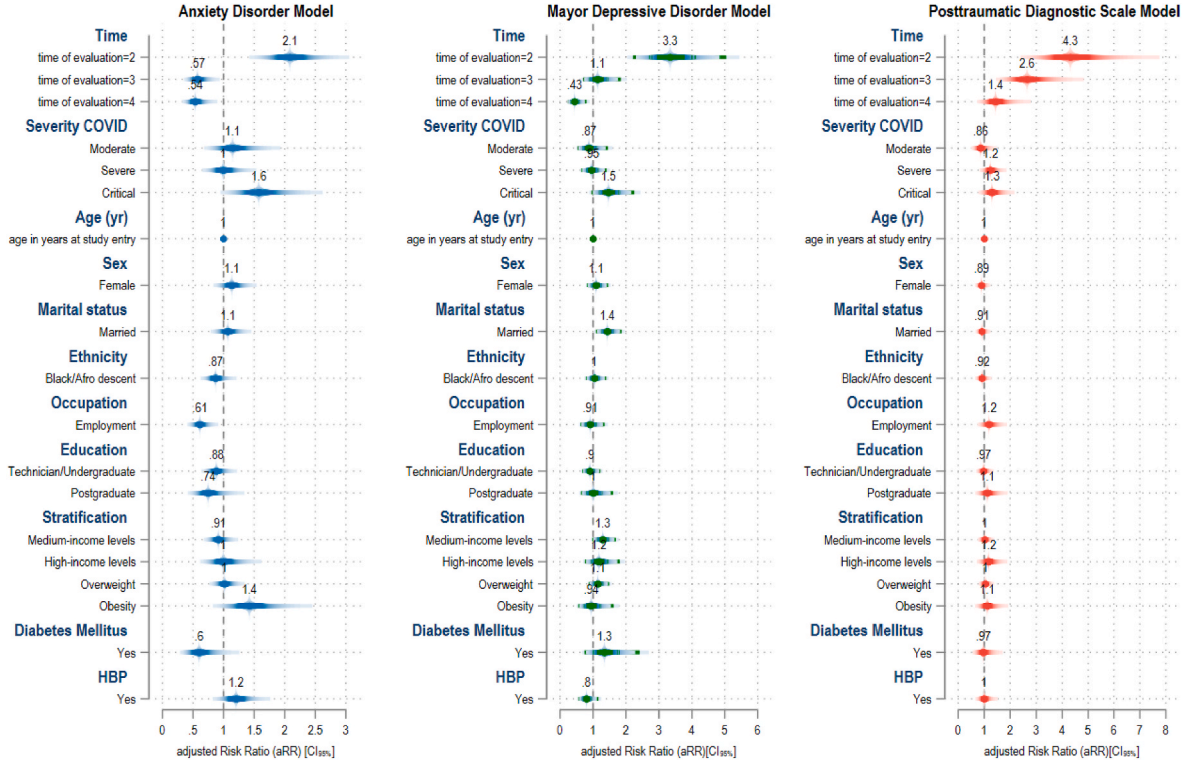

Fig. 3. Factors associated with GAD, MDD, and PTSD diagnosis based on multilevel Poisson weighted MMWS model. Multivariate models can be found in Supplementary Table 1.

not limiting to the natural course of recovery, psychological adaptation, vaccination, resilience, and the impact of ongoing healthcare support (Gómez-Restrepo et al., 2016; World Health Organization, 2017; Anaya et al., 2021; Guillen-Burgos et al., 2025; Dantzer et al., 2008; Brunoni et al., 2020).

In the largest-population study thus far published, authors reported that in the first three months of acute COVID–19 infection, survivors have an increased risk of MDD diagnosis (Miller and Raison, 2016). In the same line, we reported increased risk for MDD diagnosis 3 months after acute SARS-CoV-2 infection. Furthermore, our study reported a 3-month prevalence of MDD of 10%, notably higher than the general population prevalence in both Colombia and worldwide. According to the 2015 National Mental Health Survey, the lifetime prevalence of MDD in the general Colombian population was 4.3% (Alpert et al., 2020). Similarly, this figure exceeds the global lifetime prevalence of 4.4% (Yuan et al., 2021b). Hence, other risk factors associated with acute COVID–19 infection might be involved (Koenen et al., 2017). Recently, our group reported that a higher cytokines profile within pro-inflammatory markers panel during acute SARS-CoV-2 infection, usually associated with severe and critical cases, was associated with new-onset of MDD during post-acute COVID-19 period (Bovin and Marx, 2023). This is consistent with previous reported associations between immune response activation and MDD (Guillén-Burgos and Gutiérrez--Ruiz, 2018; McIntyre and Lee, 2020; Moreno et al., 2020; Bonde et al., 2022).

PTSD is another common mental health outcome in pandemic survivors (Yong, 2021). A previous study demonstrated that in post-acute COVID-19, the proportion of suspected PTSD during 3, 12 and 24 months were 49.9%, 47.3%, and 35.3% respectively (Martins et al., 2022). In fact, PTSD symptoms are considered the most prevalent mental health outcome in COVID-19 survivors (Martins et al., 2022). In the same line, we reported a higher prevalence (10%) compared with the cross-national lifetime prevalence (3.9%) (Ely et al., 2024). Quantitative discrepancies may be due to our methodological design. Perhaps, our initial screening with psychometric instruments PCL-5, along with structured interview brought to some extend double-check for PTSD diagnosis. Therefore, lower prevalence was reported after using structured interviews (Zakia et al., 2023).

Outbreaks and pandemics are considered as a subtype of trauma exposure. In fact, previous studies have reported pandemics and outbreaks as risk factor for PTSD (Yuan et al., 2021a; Davis et al., 2023; Tremblay et al., 2020). Even though PTSD is reported to be lower during the first 6 months post-infection and increase 6 months later (Yuan et al., 2021a), our findings did not show this trend. This may be due to several factors, including trauma-focused interventions due to the experience of previous outbreaks, vaccination, and presence of subsyndromal symptoms during the first 12 months but without developing a diagnosis of PTSD (Brunoni et al., 2020; Lee et al., 2022). Diagnostic waves or delayed onset is also possible (Wilkialis et al., 2021), however, in this study we did not measure that specific outcome with regards to PTSD delayed onset.

Risk factors contributing to the onset of mental health outcomes following acute SARS-CoV-2 infection include previous lockdowns, disease severity, and cumulative social and clinical stressors, which may vary over time in response to broader pandemic dynamics. Fluctuations in symptom burden at specific follow-up points may reflect the influence of external COVID-19–related factors, such as the reimplementation of public health restrictions, employment instability, or periods of heightened community transmission, underscoring the potential role of time-varying contextual stressors in shaping mental health trajectories (Park et al., 2020; Guillen-Burgos et al., 2025). We should further highlight the multifaceted challenges faced by participants recovering from COVID-19. In our model, early diagnosis following discharge and critical severity during acute infection emerged as primary risk factors. While no additional risk factors reached statistical significance, female gender demonstrated a higher risk for both GAD and MDD, which holds social and clinical. Nevertheless, the relationship between gender and the prevalence of depression or anxiety remains subject to discrepancies that might be related to differences in approaches to diagnostic tools (McIntyre et al., 2024).

From a biological perspective, the mechanisms underlying these neuropsychiatric conditions during post-acute COVID-19 infection are still being elucidated. One proposed mechanism involves disruption of the blood-brain barrier, potentially exacerbated by inflammatory responses triggered by SARS-CoV-2, leading to leukocyte infiltration, hemorrhage, cerebral infarct and finally a loss of physiological functions.[58,59] Furthermore, the neuroinflammatory response to SARS-CoV-2 may lead to activation of complement cascade, endothelial cell damage, platelet aggregation, and microglia activation, which is implicated in neurodegenerative processes and cognitive decline in mayor mental disorders such as bipolar disorder, schizophrenia and MDD.[60] Hence, a combination of biological factors, psychological stressors, illness severity and hospitalization, may produce a multifaceted risk profile for the onset of neuropsychiatric disorders in COVID-19 survivors. In addition to the direct effects of infection, factors such as stigma, loneliness, social isolation, and health care insecurities further compound the risk of developing mental illness during and after the pandemic.[61,62]

In the present cohort, sex distribution differed significantly across COVID-19 severity groups ($p = 0.002$), with women overrepresented among mild cases (57.23%) and critical cases (53.91%), while comprising a minority of the severe group (45.28%) — a distribution consistent with the well-characterized paradox in COVID-19 literature whereby men experience worse acute disease severity, yet women bear a disproportionate post-acute psychiatric burden.[63] In the doubly robust MMWS-weighted multilevel Poisson model, female gender demonstrated a directionally elevated adjusted risk ratio for both GAD and MDD that did not reach statistical significance, a finding that must be interpreted in light of the study being powered primarily for the COVID-19 severity exposure rather than sex-stratified comparisons. Nevertheless, this directional pattern aligns with a meta-analysis of longitudinal cohort data demonstrating that women experienced greater worsening in anxiety (SMD = 0.20, 95% CI 0.12–0.29) and depressive symptoms (SMD = 0.22, 95% CI 0.05–0.40) compared to men during the pandemic,[64] and with the finding of Mazza et al. that female COVID-19 survivors suffered more anxiety and depression despite lower baseline systemic inflammatory markers — implicating neuroendocrine and psychosocial rather than purely inflammatory mechanisms.[65]

Within the Latin American context, a cross-sectional study encompassing over 1.3 million adults confirmed that female sex was independently associated with higher prevalence of both anxiety and depressive symptoms across the region,[66] a pattern further corroborated specifically in Colombia, where female sex predicted high depressive symptom burden during the pandemic lockdown (Martins et al., 2022). Regarding PTSD, Janiri et al. identified female sex as an independent predictor of PTSD among severe COVID-19 survivors,[67] and a prospective Chinese cohort reported an adjusted OR of 7.82 (95% CI 3.18–18.21) for PTSD in women relative to men.[68] Biologically, this vulnerability is plausibly mediated by sex-specific HPA axis hyperreactivity, estrogen-dependent neuroinflammatory dysregulation, and the sexually dimorphic inflammatory cytokine profiles documented in COVID-19 survivors.[69,70] Taken together, these findings indicate that female sex constitutes a clinically relevant, if statistically non-confirmed in this cohort, vulnerability factor for post-COVID-19 psychiatric morbidity, warranting sex-stratified analyses in adequately powered future studies.

Additionally, the information provided by this study is relevant to the treatment that could be provided to subjects with mental disorders such as MDD and post-COVID syndrome. Recently, our team identified, in both a RCT and Real-World Evidence study, the efficacy and effectiveness of vortioxetine in managing mood and cognitive symptoms in subjects with MDD during the post-COVID period.[71,72] Further studies of this type should be implemented to identify the best

psychopharmacological and psychotherapeutic strategies for this population subgroup.

This study has several methodological strengths. A longitudinal cohort design to investigate the prevalence and progression of mental health outcomes as well as new onset diagnosis such as GAD, MDD, and PTSD among COVID-19 survivors over a 12 month follow up. Moreover, utilizing validated diagnostic instruments, such as SCID-5-CV, and standardized screening scales such as GAD-7, PHQ-9, and PCL-5, ensured reliability and accuracy of psychiatric diagnoses and symptomatology, therefore more hierarchy and credibility to our findings. Furthermore, study stratification of COVID-19 severity into mild, moderate, severe, and critical categories provided insight into how acute COVID-19 infection severity may impact mental health outcomes. It may be that application of propensity-score-based marginal mean weighting minimizes confounding bias and thus enhances internal validity. We should also highlight a high follow-up retention rate of 91.7% which demonstrates exceptional participant engagement, reducing the risk of attrition bias in this study.

Additionally, this study addresses key gaps in the current literature regarding the timing and longitudinal trajectory of mental health outcomes following COVID-19. Prior studies have largely relied on cross-sectional designs or short-term follow-up, limiting the ability to characterize the persistence, resolution, or delayed onset of psychiatric disorders after acute infection. By employing a 12-month longitudinal follow-up with repeated assessments, the present study captures both early and sustained mental health outcomes, allowing for a more precise evaluation of temporal patterns and symptom trajectories.

Despite its strengths, the study has several limitations. The use of convenience sampling and the restriction to a single institution/site in Barranquilla, Colombia. Both issues limited the generalizability of our findings to broader populations and geographical contexts. Self-administered questionnaires, although standardized, may introduce reporting biases due to subjective participant interpretations. Furthermore, the absence of biological markers, such as neuroinflammatory markers also limited the model to the mechanisms underlying mental health outcomes and confirmed psychiatric diagnoses. The follow-up period, though robust, is limited to 12 months. Finally, although the psychiatric symptoms and diagnoses examined in this study can be conceptually situated within the broader long COVID syndrome, the study did not include a systematic assessment of persistent physical symptoms such as fatigue, dyspnea, pain, or cognitive complaints. These symptoms are common in both long COVID and mental disorders and may influence psychiatric outcomes. The absence of longitudinal data on physical long COVID sequelae limits the ability to disentangle the contribution of somatic symptoms to the observed mental health outcomes and should be considered when interpreting the findings.

Therefore, long-term MHOs of acute COVID-19 infection in survivors further down the line remains unexplored. Perhaps, above highlight the need for more comprehensive, multi-site studies to validate and expand upon these findings after being acutely infected during and outbreak or pandemic.

5. Conclusion

This study highlights a significant relationship between the severity of acute SARS-CoV-2 infection and the development of mental disorders, including GAD, MDD, and PTSD, within the first 12 months post-infection. The observed decline in prevalence over time suggests a critical need for targeted mental health interventions in the early recovery phase rather than afterwards in the course of illness. Our findings provide valuable evidence to understand the impact COVID-19 infection produces over mental health. It also emphasizes over the importance of integrating mental health care into the broader management of post-COVID-19 recovery. By identifying key periods of vulnerability for the onset of mayor mental disorders, this effort contributes to tailor pragmatic and effective strategies to mitigate psychiatric burden of COVID-19.

Funding

This work was supported by the Universidad Simón Bolívar in Barranquilla, Colombia [grant number: 0324-00-00].

CRediT authorship contribution statement

Hernan F. Guillen-Burgos: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Sergio Moreno-López:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Juan F. Gálvez-Flórez:** Conceptualization, Supervision, Writing – review & editing. **Roger S. McIntyre:** Supervision, Writing – review & editing. **Juan-Manuel Anaya:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

Dr. Hernan F. Guillen-Burgos has received research grant support from the Ministry of Science, Technology, and Innovation (Minciencias) in Colombia, UKRI in the United Kingdom; and speaker fees from Abbott, GSK, Roche, Pfizer, Synergy R&D.

Dr. Roger S. McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Bristol Myers Squibb (BMS) and Atai Life Sciences.

Dr. Sergio Moreno-Lopez, Dr Juan F. Galvez and Dr. Juan-Manuel Anaya declare no competing interests.

Acknowledgment

The authors extend their gratitude to the clinicians at Clínica La Misericordia in Barranquilla, Colombia, for their dedicated patient care, and to the research assistants at the Center for Clinical and Translational Research for their invaluable contributions to data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101268.

Data availability

Data will be made available on request.

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