International Journal of Mental Health and Addiction (2023) 21:1264–1285
https://doi.org/10.1007/s11469-021-00659-z

ORIGINAL ARTICLE

Mental Health in COVID-2019 Survivors from a General Hospital in Peru: Sociodemographic, Clinical, and Inflammatory Variable Associations

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Accepted: 16 September 2021 / Published online: 28 September 2021

Abstract

The current coronavirus disease-2019 (COVID-19) pandemic constitutes a significant public health problem worldwide, as well as mental health problems. This study aimed to evaluate the mental health of COVID-19 survivors, considering their sociodemographic, clinical, and immune variables. A cross-sectional and correlational study was conducted on 318 COVID-19 survivors from one hospital in Peru. Through telephone interviews, evaluation of the presence of depressive symptoms using the Patient Health Questionnaire-9, anxiety symptoms through the Generalized Anxiety Disorder-7, somatic symptoms through Patient Health Questionnaire-15, and posttraumatic stress disorder (PTSD) symptoms through Impact of Event Scale-Revised was carried out. Poisson regression analyses were performed with their adjusted variances to calculate the prevalence ratio (PR) with their 95% confidence interval. All regression models were adjusted (PRa) for follow-up time. A significant proportion of patients have depressive (30.9%), anxious (31.1%), somatic (35.2%), and PTSD (29.5%) symptoms. The variables associated with a higher frequency of clinically relevant mental symptoms were female sex, self-perception of greater COVID-19 severity, presence of persistent COVID-19 symptoms, loss of a family member due to COVID-19, and prior psychiatric diagnosis or treatment. In addition, the neutrophil-to-lymphocyte ratio was significantly higher in patients with clinically relevant symptoms of depression. COVID-19 survivors showed a high prevalence of negative mental symptoms. Our findings help to identify patients who are vulnerable and require psychiatric care.

Keywords COVID-19 · Depression · Anxiety · Somatic symptoms · Posttraumatic stress disorder · Inflammation · Peru

The current pandemic of the novel coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a significant problem for world mental health (Velavan & Meyer, 2020). Until August 7, 2021,

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200,840,180 confirmed cases and 4,265,903 deaths worldwide were reported (World Health Organization, 2021). During the same period in Peru, one of the countries with the highest mortality per million habitants rate, 2,121,061 confirmed cases and 196,760 deaths were reported with the lethality of 9.28% (Gobierno del Perú, 2021). The COVID-19 pandemic increases the mental health problems of the general population, healthcare workers, patients with COVID-19, and quarantined persons (Wu et al., 2021). In Peru, an increased burden of depressive symptoms and psychosocial reactions has emerged during the COVID-19 pandemic compared to previous years (Antiporta et al., 2021). This mental health burden disproportionately affects women, the younger population, and those with low income and educational levels (Antiporta et al., 20212021).

Previous studies reported that patients with viral respiratory infections, similar to COVID-19, showed varying degrees of mental health problems, such as depression, anxiety, adjustment disorders, acute stress-related disorders, and posttraumatic stress disorder (PTSD), even after disease recovery (Rogers et al., 2020). Hence, research in different countries documented that patients with COVID-19 also experienced the onset or exacerbation of diverse problems in their mental health (Bo et al., 2020; Huarcaya-Victoria et al., 2020; Rogers et al., 2020). Patients with COVID-19 tended to have a high prevalence of adverse psychological events (Wang et al., 2021). This is due to diverse factors from psychosocial problems caused by quarantine, hospitalization, and an invasion of SARS-CoV-2 to the central nervous system or the consequence of the systemic immune response in the form of a "cytokine storm" (Kontoangelos et al., 2020; Raony et al., 2020).

COVID-19 pandemic is a new type of trauma that has never been conceptually or empirically analyzed in mental health and psychiatric research (Kira, et al., 2021a, b). Different factors make COVID-19 a unique trauma type: (a) continuous ongoing traumatic stress, (b) multiple complex trauma, and (c) unnecessarily relationship to the actual infection of COVID-19, but also is more related to the perceived threat of the uncontrolled virus and the direct and indirect social consequences (Kira et al., 2021a, b). This challenged the current paradigms of traumatic stress. Current pathogenic event models focus on past and largely direct trauma exposure to certain kinds of life-threatening events (Bridgland et al., 2021; Kira, 2021). COVID-19 pandemic is understood as a traumatic stressor capable of eliciting PTSD symptoms and exacerbating other mental health problems (Bridgland et al., 2021). COVID-19 continuous PTSD does not fit within the current trauma frameworks; thus, a need arises for a paradigm shift in current stress and trauma frameworks to account for the COVID-19 continuous global stressors and clinical intervention innovations to help its victims (Kira et al., 2021a, b). As evidence of the neurocognitive sequelae of COVID-19 emerges, psychological trauma should not be overlooked as an important contributor to the neuropsychological robustness and quality of life of COVID-19 survivors (Kaseda & Levine, 2020).

When SARS-CoV-2 infects the respiratory tract, an acute respiratory syndrome occurs with the consequent release of proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, producing a "cytokine storm" (Conti et al., 2020). Through their effects on the neurotransmitter systems, cytokines impact neurocircuits in the brain, leading to significant changes in motor activity, motivation, and anxiety (Miller et al., 2013). These neurotransmitter metabolism changes are involved in the pathophysiology of various psychiatric disorders, such as schizophrenia, depression, anxiety, PTSD, and obsessive–compulsive disorder (Bandelow et al., 2017; Grace, 2016; Raony et al., 2020). However, in some circumstances, a study of these cytokines is impossible. Therefore, their increase is indirectly value through elevated various inflammatory parameters with the neutrophil-to-lymphocyte ratio (NLR). This provides a quick and easy way to value the state of systemic

inflammation, which is calculated from a complete blood count. NLR elevations were associated with increased cytokines, such as IL-6 and IL-8 (Karageorgiou et al., 2019). Elevated NLR reflects a transdiagnostic pathological process occurring in a subpopulation of patients with psychiatric problems (Brinn & Stone, 2020). Given the relationship between elevated levels of cytokines in COVID-19 as well as in psychiatric disorders, the immune/inflammatory pathways are considered as one of the mechanisms involved in the mental health problems of this infection (Raony et al., 2020).

The majority of studies about the impact on mental health in patients with COVID-19 were conducted in hospital settings using convenience samples, and only one study reported depression and anxiety prevalence for outpatients, which was 35% and 33%, respectively (Deng et al., 2020). Moreover, the majority of studies were conducted on the Chinese population since China was the first country affected by the pandemic (Deng et al., 2020). Despite the usefulness of these data, demographic and interindividual characteristics are determining factors in the psychological responses of different populations to a large-scale stressful event such as the current pandemic (Moccia et al., 2020). Hence, to carry out studies that assess the impact of this disease in each of the affected countries, especially in countries like Peru, which was one of the most affected by this pandemic is crucial (Gobierno del Perú, 2021).

Information regarding the impact of this novel pandemic on mental health in patients surviving from COVID-19 is scarce; thus, this study aimed to describe the characteristics of mental health and the main sociodemographic, clinical, and immune factors related to the disease.

Materials and Methods

Study Design

This single-center cross-sectional study evaluated the influence of sociodemographic, clinical, and immune characteristics on the levels of depression, anxiety, somatic, and PTSD symptoms in outpatients who survived COVID-19.

Clinical Context

This study was carried out at Hospital Nacional Guillermo Almenara Irigoyen (HNGAI), which is the second largest hospital of the "Seguridad Social de Salud del Perú" (EsSalud), with a total of 815 hospital beds. Furthermore, it is a tertiary referral hospital with medical specialties. By 2019, the Almenara network met the health needs of 1,634,990 insured (Seguro Social de Salud, 2020). Social security is one of the forms of medical insurance that Peru utilizes; thus, patients treated are those with insurance, whose contribution is paid by the employer. In the case of pensioners, the contribution is charged to the insured. This insurance includes dependent, domestic, civil construction workers, and port, fishermen, and pensioners. EsSalud is financed by the Ministry of Labor (Alcalde-Rabanal et al., 2011).

During the COVID-19 pandemic, HNGAI was a national referral center for the care of patients with COVID-19. Due to the high care demand, hospital beds of different specialties were redistributed to care for patients with COVID-19. Moreover, new hospital

environments were created. COVID-19 diagnoses were made with serological tests, which were later confirmed with molecular tests.

According to EsSalud's records, from the beginning of the pandemic until September 2020, in HNGAI, a total of 3238 patients diagnosed with COVID-19 were discharged. For this study, minors ($n=369$), deceased ($n=843$), referred to another center ($n=88$), and voluntary discharge ($n=14$), as well as those patients with two or more hospitalizations during March to September 2020 ($n=14$), were excluded. Hence, patients who were discharged from the hospital ($n=1910$) were only considered.

Participants

The sample was obtained from a population of 1910 patients with COVID-19 who were discharged from HNGAI services between March and September 2020. The Paz et al. study (Paz et al., 2020) was used to calculate the sample size. In this study, an expected frequency of 55% of mental health problems in patients with COVID-19 was estimated. Considering a margin error of 5% with this data, with a design effect of 1 and a single group, a total of 318 individuals with a 95% confidence interval (CI) were obtained.

The sample was selected through a simple random sampling using the Epidat v4.2 program (Dirección Xeral de Saúde Pública da Consellería de Sanidade, Galicia, España). Each of the 1910 patients had a coding.

Variables were collected in a virtual file through telephone calls to patients between October 22 and November 28, 2020. The cell phone number that was registered in the electronic medical record of each patient was used. Calls were made by the co-investigators, who are psychiatrists with clinical and research experience. Participants who did not answer after two calls were excluded from the study ($n=112$), and a new participant is randomly selected. In addition, a group of selected participants did not wish to continue with the interview ($n=8$). Therefore, they were removed from the database, and new participants were randomly selected (Fig. 1).

Measures

Depression

The Patient Health Questionnaire-9 (PHQ-9) was used to evaluate depressive symptoms. This scale consists of 9 items that evaluated the frequency of depressive symptoms in the previous 2 weeks, which are rated on a Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"). The PHQ-9 scores reflect 5 categories of severity of depressive disorders: None (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). In studies carried out in Latin America, PHQ-9 was proven as a valid and reliable tool to detect depressive symptoms in various types of populations (Cassiani-Miranda et al., 2017; Saldivia et al., 2019). Furthermore, PHQ-9 was validated in Peru. Validity indicators include internal structure, measurement invariance, and acceptable internal consistency values (Villarreal-Zegarra et al., 2019).

Anxiety

Generalized Anxiety Disorder-7 (GAD-7) was used as a valid and efficient scale to assess the severity of anxiety disorders in clinical practice and investigation (Spitzer

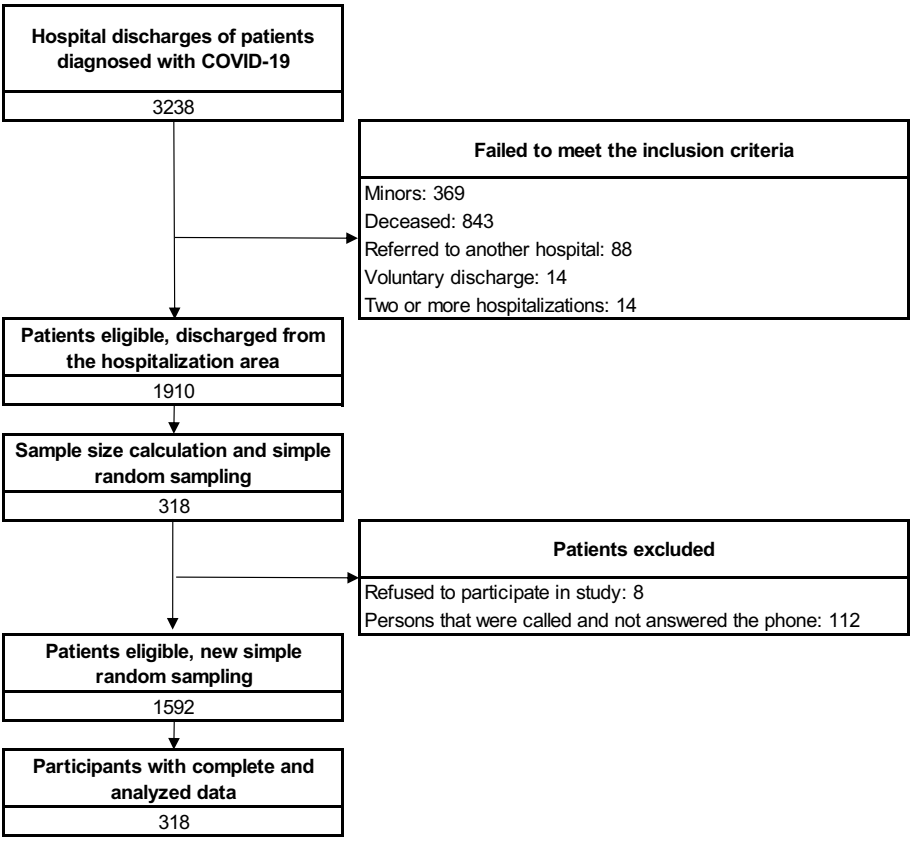

Fig. 1 Selection flowchart

et al., 2006). The scale consists of 7 items that evaluate the anxiety symptomatology during the 2 weeks before the scale application. Each item is rated according to a Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"). GAD-7 reflects 4 categories of severity of the anxiety disorder: none (0–4), mild (5–9), moderate (10–14), and severe anxiety (15–21). This scale was translated into Spanish and was validated (Garcia-Campayo et al., 2010).

Somatic Symptoms

The Patient Health Questionnaire-15 (PHQ-15) was used to evaluate somatic symptoms. It consists of 15 items related to 15 possible somatic symptoms that bothered the patient during the previous 4 weeks (Kroenke et al., 2002). Each item is rated as: "nothing" or absence of the problem (0 points), "a little" or presence of the problem (1 point), or "a lot" or high presence of the problem (2 points). The PHQ-15 scores reflect 4 categories of severity of somatic symptoms: none (0–4), mild (5–9), moderate (10–14), and severe (15–30). This scale was translated into Spanish and was validated (Ros Montalbán et al., 2010).

PTSD Symptoms

The Impact of Event Scale-Revised (IES-R) was used to evaluate PTSD symptoms (Weiss & Marmar, 1997). This scale measures the degree of suffering caused by a life event (for this study, the hospitalization of COVID-19 was considered as a stressful event), which is conceptualized as a form of subjective stress. IES-R consists of 22 items: 7 assessed intrusion symptoms, 8 avoidance, and 7 hyperarousal (Caamaño W et al., 2011). It is rated according to the Likert scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R scores reflect 5 categories of PTSD symptom severity: none (0–8), mild (9–25), moderate (26–43), and severe (44–88). This scale was translated into Spanish and was validated (Caamaño W et al., 2011).

Further Variables

Information regarding the following variables was collected: (a) sociodemographic data, including sex, age, educational degree, job status, place of origin before hospitalization, current place of residence, with whom they live, history of relative infected, and/or deceased due to COVID-19; (b) clinical and hospitalization data, including diagnosis and/or treatment history for psychiatric diagnosis, self-perception of COVID-19 severity, hospitalization area, hospitalization duration, days from discharge to the interview (follow-up time), presence of COVID-19 symptoms during the interview; and (c) immune data, including NLR and monocyte-to-lymphocyte ratio (MLR) at the beginning of hospitalization. Immune variables were obtained by reviewing electronic medical records.

Statistical Analyses

All data analysis followed the random sampling design and used survey data analysis. The general weight of 6.0062893 and the finite population correction of 1910 were considered. In addition, post-stratification weights by the "Hospitalization area" variable were applied for a better sampling adjustment (Kreuter & Valliant, 2007). The relative and absolute frequency of the categorical variables was described. For quantitative variables, the mean and 95% CI are described. Then, the four outcome variables of mental health: depression, anxiety, somatic, and PTSD symptoms were dichotomized as clinically irrelevant (none-mild) and clinically relevant (moderate–severe). Consequently, the hospitalization time was categorized into 1–7 days, 8–14 days, and > 14 days. In the dichotomous analysis, the association between each covariate with each dichotomized mental health outcome variable was evaluated. Chi-2 test was used for categorical covariates and Student's *T* test was used for numerical covariates.

Before the regression analysis, the age variable was categorized into quartiles. Additionally, the NLR was categorized as < 6.5 and ≥ 6.5 (Li et al., 2020), and the MLR was categorized as < 0.364 and ≥ 0.364 (Fois et al., 2020). The cut-off points were chosen considering their ability to predict in-hospital mortality in patients with COVID-19. The COVID-19 symptom variable at admission and during the interview was categorized into asymptomatic (without any symptoms during the follow-up) and symptomatic (at least one symptom during the follow-up).

Poisson regression analyses were performed with their adjusted variances to calculate the prevalence ratio (PR) with their 95% CI. All regression models were adjusted (PRa) for follow-up time. An epidemiologic approach was considered using direct acyclic graphs

for clinical (self-perception of severity and persistent COVID-19 symptoms) and laboratory covariables (NLR and MLR upon admission). The regression model of the covariate "self-perception of COVID-19 severity" was adjusted for COVID-19 symptoms at the moment of admission to hospitalization and during the interview. The regression models for the covariates "NLR at admission" and "MLR at admission" were also adjusted for the self-perception of COVID-19 severity. Finally, the regression model for the covariate of "COVID-19 symptoms during the interview" was adjusted for follow-up time, presence of COVID-19 symptoms at admission, and self-perception of COVID-19 severity. A p value of < 0.05 was considered statistically significant. Stata MP v.16.0 statistical software was used for all analyses.

Ethical Aspects

Verbal informed consent was obtained from each participant. This included an explanation of the objectives of the investigation, as well as the rights of the participants (anonymity and the right to refrain from participating as considered appropriate). Furthermore, psychiatric help was offered when the interviewer considered it necessary at some point, either during or after the phone interview. This investigation was carried out with the authorization of EsSalud's Research Ethics Committee Specific to COVID-19.

Results

In a representative sample of COVID-19 survivors, the majority were men (61.3%), professed religion (92.7%), were from Lima (94.5%), with an average age of 53.1 years, lived with a partner and/or children (79.8%), had at least one family member infected (82.7%), and at least one relative died (30.4%) due to COVID-19. Survey respondents perceived their COVID-19 disease as severe accounting for 31.2%, whereas 32.6% perceived it as moderate. The mean NLR was 8.8 (95% CI, 8.0–9.7), whereas the MLR was 0.4 (95% CI, 0.4–0.4). Regarding the COVID-19 symptoms, 8.3% of the survey respondents were asymptomatic during hospital admission, and 39.4% were asymptomatic during the interview. The mean time of hospitalization was 11.3 days (95% CI, 10.2–12.4). Hospitalization time was correlated with the self-perceived severity of the COVID-19 disease. Those who self-perceived a mild COVID-19 disease had a mean hospitalization time of 6.5 days (95% CI, 5.2 to 7.7). While those who self-perceived a severe and critical-ill COVID-19 disease had 14.8 days (95% CI, 12.4 to 17.1) and 26.3 days (95% CI, 20.7 to 32.0) of mean hospitalization time, respectively. The mean follow-up time was 102.1 days (95% CI, 98.3–106.0).

This study revealed that 30.9% of patients had some type of depressive, 31.1% had anxious, 35.2% had somatic, and 29.5% had PTSD symptoms. Regarding the clinically relevant symptoms (moderate–severe), 10.7% were depressive, 7.6% anxious, 14.5% somatic, and 8.2% PTSD. The rest of the characteristics are described in Table 1.

In the bivariate analysis, women had a higher frequency of clinically relevant symptoms (moderate–severe) of depression ($p = 0.011$), anxiety ($p = 0.007$), somatic ($p = 0.013$), and PTSD ($p = 0.071$). Patients with a history or treatment of psychiatric illness presented a higher frequency of clinically relevant mental symptoms ($p < 0.05$). Those patients who self-reported severe or critical COVID-19 had a higher frequency of clinically relevant depressive ($p = 0.004$) and PTSD symptoms ($p = 0.001$). NLR, in its numerical nature, was

Table 1 Sample characteristics ($n = 318$)

Characteristics	*n* (%)
Male	196 (61.3)
Age (years)*	53.1 (51.8–54.4)
Educational degree	
None or incomplete	42 (13.3)
Secondary school	135 (42.6)
Technical degree	34 (10.3)
University	107 (33.8)
Job status	
Unemployed	95 (30.5)
Informal employment	31 (9.2)
Formal employment	143 (45.5)
Retired	49 (14.8)
Live with	
Alone	17 (5.1)
Couple and/or children	256 (79.8)
Parents and/or other family members	45 (15.1)
Family member infected with COVID-19	264 (82.7)
Loss of *a family member* due to *COVID-19*	97 (30.4)
History of psychiatric diagnosis	32 (10.4)
History of psychiatric treatment	27 (8.7)
Self-perception of COVID-19 severity	
Mild	89 (29.1)
Moderate	107 (32.6)
Severe	99 (31.2)
Critically ill	23 (7.0)
Hospitalization area	
Cardiology	239 (68.9)
Internal medicine	35 (15.9)
High-risk obstetrics	32 (10.8)
Neurology	12 (4.4)
Time of hospitalization	
1–7 days	154 (48.4)
8–14 days	84 (26.4)
> 14 days	80 (25.2)
Depressive symptoms	
None	222 (69.0)
Mild	62 (20.2)
Moderate	18 (5.6)
Moderate–severe	11 (3.7)
Severe	5 (1.4)
Somatic symptoms	
None	210 (64.9)
Mild	65 (20.7)
Moderate	36 (12.1)
Severe	7 (2.4)

Table 1 (continued)

Characteristics	*n* (%)
Anxious symptoms	
None	223 (68.9)
Mild	71 (23.5)
Moderate	17 (5.4)
Severe	7 (2.2)
PTSD symptoms	
None	227 (70.5)
Mild	66 (21.3)
Moderate	18 (5.8)
Severe	7 (2.4)
NLR ≥ 6.5 at income ($n = 277$)	135 (48.1)
MLR ≥ 0.364 upon admission ($n = 277$)	112 (40.4)

*Mean and 95% confidence intervals

NLR neutrophil-to-lymphocyte ratio,

MLR monocyte-to-lymphocyte ratio,

PTSD posttraumatic stress disorder

significantly higher in the clinically relevant symptoms (moderate–severe) of the depressive type compared to that of the clinically irrelevant (11.4, 95% CI, 8.8–14.1 vs. 8.52, 95% CI, 7.62–9.42; $p = 0.041$). Further associations can be found in Table 2.

In the regression analysis, women have a higher frequency of clinically relevant symptoms of depression (PRa = 2.11; 95% CI, 1.16–3.84), anxiety (PRa = 2.70; 95% CI, 1.31–5.57), and somatic (PRa = 1.90; 95% CI, 1.14–3.18). Contrarily, patients with a family member infected or who died due to COVID-19, or those with a history of psychiatric diagnosis, have a higher frequency of developing adverse mental health outcomes. Patients who self-reported having severe or critical COVID-19 are more likely to have clinically relevant depression, anxiety, somatic, and PTSD symptoms, compared to those who self-reported a mild infection. No association was found between the NLR (≥ 6.5) and MLR (≥ 0.364) with adverse mental health outcomes. Lastly, patients with persistent COVID-19 symptoms during the interview were more likely to have a higher frequency of clinically relevant symptoms of depression (PRa = 7.80; 95% CI, 2.16–28.15), somatic (PRa = 6.17; 95% CI, 2.48–15.35), anxiety (PRa = 11.50; 95% CI, 3.07–43.15), and PTSD (PRa = 17.84; 95% CI, 2.07–153.58) (Table 3).

Discussion

Main Findings and Meaning of the Results

This study sought to describe the characteristics of mental health in Peruvian patients surviving from COVID-19, as well as the main related sociodemographic, clinical, and immune factors. In our study, the number of female patients is less than that of males. Similar trends were reported in other studies (Mertz Schou et al., 2021). These results probably relate to gender differences in the infection and admission rates (Gomez et al., 2021). Mental symptoms were present after an average of 100 days after patient discharge. A previous

Table 2 Bivariate association between variables and depressive, somatic, anxious, and PTSD symptoms ($n=318$)

Characteristics	Depression, *n* (%) Moderate–severe	*p*	Somatic symptoms, *n* (%) Moderate–severe	*p*	Anxiety, *n* (%) Moderate–severe	*p*	PTSD, *n* (%) Moderate–severe	*p*
Gender†		0.011		0.013		0.007		0.071
Male ($n=196$)	14 (7.5)		19 (10.7)		9 (4.6)		11 (6.1)	
Female ($n=122$)	20 (16.0)		24 (20.3)		15 (12.3)		14 (11.5)	
Age (years)*	56.4 (51.8–61.0)	0.140	55.8 (51.6–59.9)	0.174	51.5 (46.7–56.3)	0.504	52.8 (47.6–58.0)	0.899
Marital status†		0.666		0.731		0.822		0.699
Single ($n=49$)	4 (9.5)		5 (12.0)		3 (7.5)		3 (7.5)	
Married ($n=225$)	23 (10.3)		32 (15.4)		18 (8.1)		19 (8.9)	
Divorced or widower ($n=49$)	7 (14.2)		6 (12.3)		3 (5.6)		3 (5.6)	
Educational degree†		0.532		0.380		0.245		0.157
None or incomplete ($n=42$)	7 (15.2)		9 (22.0)		4 (9.9)		7 (16.4)	
Secondary school ($n=135$)	11 (8.4)		17 (12.5)		7 (4.9)		8 (6.3)	
Technical degree ($n=34$)	4 (12.8)		3 (10.5)		2 (5.6)		1 (4.4)	
University ($n=107$)	12 (11.6)		14 (15.0)		11 (10.7)		9 (8.5)	
Job status†		0.223		0.125		0.186		0.668
Unemployment ($n=95$)	14 (14.5)		18 (20.5)		10 (10.7)		8 (9.4)	
Informal employment ($n=31$)	1 (4.9)		1 (4.9)		0 (0.0)		1 (3.1)	
Formal employment ($n=143$)	12 (8.3)		17 (12.2)		11 (7.6)		13 (8.9)	
Retired ($n=49$)	7 (14.8)		7 (14.8)		3 (5.9)		3 (7.0)	
Profess a religion†		0.371		0.139		0.369		0.460
No ($n=23$)	4 (15.7)		6 (23.6)		3 (11.8)		3 (11.8)	
Yes ($n=295$)	30 (10.4)		37 (13.7)		21 (7.3)		22 (7.9)	
Place of origin before hospitalization†		0.426		0.348		0.580		0.672
Lima ($n=300$)	31 (10.5)		39 (14.0)		22 (7.4)		23 (8.1)	
Other provinces ($n=18$)	3 (15.9)		4 (21.2)		2 (10.6)		2 (10.6)	
Current home†		0.830		0.727		0.157		0.518
Lima ($n=299$)	32 (10.7)		40 (14.2)		24 (8.1)		24 (8.4)	

Table 2 (continued)

Characteristics	Depression, *n* (%) Moderate–severe	*p*	Somatic symptoms, *n* (%) Moderate–severe	*p*	Anxiety, *n* (%) Moderate–severe	*p*	PTSD, *n* (%) Moderate–severe	*p*
Other provinces (*n* = 19)	2 (12.3)		3 (17.0)		0 (0.0)		1 (4.8)	
Live with†		0.030		0.163		0.061		0.288
Alone (*n* = 17)	1 (5.7)		0 (0.0)		0 (0.0)		0 (0.0)	
Couple and/or children (*n* = 256)	32 (12.8)		37 (15.6)		23 (9.2)		22 (9.1)	
Fathers and/or other family members (*n* = 45)	1 (1.9)		6 (13.1)		1 (1.9)		3 (6.1)	
History of family member infected by COVID-19†		0.085		0.101		0.039		0.101
No (*n* = 54)	3 (5.0)		4 (7.6)		1 (1.7)		2 (3.3)	
Yes (*n* = 264)	31 (12.0)		39 (15.8)		23 (8.8)		23 (9.2)	
Loss of a family member due to the COVID-19†		0.019		0.045		0.739		0.973
No (*n* = 221)	19 (8.3)		25 (11.9)		16 (7.3)		17 (8.2)	
Yes (*n* = 97)	15 (16.6)		18 (20.1)		8 (8.3)		8 (8.3)	
History of psychiatric diagnosis†		0.022		0.002		0.015		0.005
No (*n* = 286)	27 (9.5)		33 (12.4)		19 (6.4)		19 (6.8)	
Yes (*n* = 32)	7 (21.8)		10 (31.8)		5 (17.9)		6 (20.7)	
History of psychiatric treatment†		0.027		0.001		0.004		0.001
No (*n* = 291)	28 (9.7)		34 (12.5)		19 (6.3)		19 (6.7)	
Yes (*n* = 27)	6 (22.5)		9 (34.3)		5 (21.2)		6 (24.4)	
Self-perception of the COVID-19 severity†		0.002		0.273		0.296		0.001
Mild (*n* = 89)	3 (3.3)		8 (9.0)		4 (4.3)		2 (2.2)	
Moderate (*n* = 107)	9 (8.7)		15 (15.4)		9 (8.7)		7 (6.6)	
Severe (*n* = 99)	19 (19.2)		17 (18.4)		8 (7.9)		11 (12.3)	
Critically ill (*n* = 23)	3 (14.7)		3 (14.7)		3 (14.7)		5 (22.9)	
Time hospitalized†		0.076		0.873		0.534		0.448

Table 2 (continued)

Characteristics	Depression, *n* (%) Moderate–severe	*p*	Somatic symptoms, *n* (%) Moderate–severe	*p*	Anxiety, *n* (%) Moderate–severe	*p*	PTSD, *n* (%) Moderate–severe	*p*
1–7 days (*n* = 154)	12 (7.9)		20 (13.4)		14 (9.0)		10 (6.3)	
8–14 days (*n* = 84)	9 (10.5)		12 (15.5)		6 (7.2)		8 (10.0)	
More than 14 days (n = 80)	13 (16.9)		11 (15.2)		4 (5.2)		7 (10.0)	
NLR upon admission* (*n* = 277)	11.4 (8.8–14.1)	0.041	9.3 (7.3–11.2)	0.636	11.2 (8.1–14.4)	0.122	11.0 (7.9–14.0)	0.151
MLR upon admission* (*n* = 277)	0.4 (0.3–0.5)	0.787	0.3 (0.3–0.4)	0.096	0.4 (0.3–0.5)	0.800	0.4 (0.3–0.5)	0.733
Follow-up time (days)*	98.6 (87.9–109.3)	0.500	102.9 (93.6–112.2)	0.859	107.5 (92.4–122.6)	0.465	115.4 (102.3–128.6)	0.041
Persistent COVID-19 symptoms		< 0.001		< 0.001		0.000		< 0.001
No (*n* = 124)	3 (2.3)		5 (3.8)		2 (1.6)		1 (0.9)	
At least 1 symptom (*n* = 194)	31 (16.3)		38 (21.3)		22 (11.5)		24 (13.0)	

*Mean and 95% confidence intervals with Student's *t* test

†Chi-2 test corrected for the survey design

NLR neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PTSD* posttraumatic stress disorder

Table 3 Association between variables and depression, somatic symptoms, anxiety, and PTSD symptoms ($n = 318$)

Characteristics	Depression moderate–severe		Somatic symptoms moderate–severe		Anxiety moderate–severe		PTSD moderate–severe	
	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*
Gender								
Male	Ref		Ref		Ref		Ref	
Female	2.11 (1.16–3.84)	0.014	1.90 (1.14–3.18)	0.014	2.70 (1.31–5.57)	0.007	1.97 (0.99–3.92)	0.054
Age (years)								
20–41 years	Ref		Ref		Ref		Ref	
42–53 years	0.94 (0.38–2.33)	0.893	1.04 (0.48–2.24)	0.925	0.55 (0.19–1.62)	0.277	1.38 (0.55–3.49)	0.489
54–65 years	1.41 (0.64–3.07)	0.392	1.36 (0.68–2.71)	0.387	1.22 (0.54–2.74)	0.631	1.30 (0.50–3.37)	0.585
66–94 years	1.17 (0.50–2.73)	0.712	1.37 (0.67–2.80)	0.382	0.41 (0.13–1.29)	0.127	0.84 (0.27–2.58)	0.760
Marital status								
Single	Ref		Ref		Ref		Ref	
Married	1.07 (0.41–2.77)	0.890	1.30 (0.57–2.96)	0.538	1.12 (0.36–3.49)	0.840	1.33 (0.42–4.18)	0.622
Divorced or widower	1.44 (0.48–4.32)	0.512	1.05 (0.37–2.97)	0.933	0.81 (0.19–3.44)	0.776	0.91 (0.21–3.95)	0.900
Educational degree								
None or incomplete	Ref		Ref		Ref		Ref	
Secondary school	0.56 (0.25–1.27)	0.165	0.57 (0.29–1.12)	0.102	0.47 (0.16–1.43)	0.185	**0.36 (0.15–0.86)**	**0.021**
Technical degree	0.85 (0.30–2.43)	0.764	0.47 (0.15–1.46)	0.192	0.56 (0.12–2.49)	0.441	0.26 (0.04–1.62)	0.149
University	0.77 (0.35–1.71)	0.520	0.68 (0.34–1.36)	0.272	1.07 (0.39–2.93)	0.898	0.51 (0.22–1.18)	0.115
Job status								
Unemployment	Ref		Ref		Ref		Ref	
Informal employment	0.34 (0.06–2.00)	0.233	0.24 (0.04–1.41)	0.114			0.34 (0.05–2.21)	0.256
Formal employment	0.58 (0.29–1.13)	0.107	0.59 (0.34–1.03)	0.065	0.70 (0.33–1.46)	0.338	0.90 (0.42–1.94)	0.792
Retired	1.00 (0.46–2.20)	0.991	0.73 (0.35–1.55)	0.412	0.57 (0.18–1.81)	0.338	0.83 (0.25–2.72)	0.751
Profess a religion								
No	Ref		Ref		Ref		Ref	
Yes	0.67 (0.28–1.62)	0.375	0.58 (0.29–1.16)	0.120	0.60 (0.21–1.70)	0.333	0.62 (0.22–1.78)	0.373

Table 3 (continued)

Characteristics	Depression moderate–severe		Somatic symptoms moderate–severe		Anxiety moderate–severe		PTSD moderate–severe	
	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*
Place of origin before hospitalization								
Lima	Ref		Ref		Ref		Ref	
Other provinces	1.51 (0.55–4.10)	0.419	1.52 (0.65–3.53)	0.333	1.44 (0.40–5.13)	0.575	1.32 (0.37–4.74)	0.666
Current home								
Lima	Ref		Ref				Ref	
Other provinces	1.15 (0.34–3.93)	0.824	1.20 (0.44–3.25)	0.725			0.56 (0.09–3.34)	0.524
Live with								
Alone	Ref							
Couple and/or children	2.24 (0.38–13.19)	0.372	Ref		Ref		Ref	
Fathers and/or other family members	0.34 (0.03–4.08)	0.393	1.61 (0.76–3.41)	0.217	6.64 (1.06–41.52)	0.043	2.17 (0.75–6.29)	0.152
History of family member infected with COVID-19								
No	Ref		Ref		Ref		Ref	
Yes	2.40 (0.83–6.89)	0.105	2.07 (0.82–5.20)	0.121	5.32 (0.85–33.14)	0.073	2.83 (0.76–10.64)	0.122
Loss of a family member due to COVID-19								
No	Ref		Ref		Ref		Ref	
Yes	2.00 (1.12–3.58)	0.019	1.69 (1.01–2.82)	0.046	1.13 (0.53–2.42)	0.750	1.00 (0.47–2.11)	0.995
History of psychiatric diagnosis								
No	Ref		Ref		Ref		Ref	
Yes	2.27 (1.13–4.54)	0.021	2.57 (1.47–4.50)	0.001	2.84 (1.25–6.46)	0.013	3.19 (1.49–6.80)	0.003
History of psychiatric treatment								
No	Ref		Ref		Ref		Ref	
Yes	2.29 (1.10–4.77)	0.027	2.78 (1.57–4.92)	0.001	3.50 (1.56–7.87)	0.002	4.02 (1.93–8.39)	<0.001

Table 3 (continued)

Characteristics	Depression moderate–severe		Somatic symptoms moderate–severe		Anxiety moderate–severe		PTSD moderate–severe	
	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*	PRa* (95% CI)	*p*
Self-perception of COVID-19 severity**								
Mild	Ref		Ref		Ref		Ref	
Moderate	3.24 (0.96–10.95)	0.059	1.15 (0.53–2.49)	0.722	1.93 (0.56–6.70)	0.298	2.87 (0.46–18.05)	0.261
Severe	6.90 (2.09–22.78)	0.002	1.27 (0.59–2.74)	0.535	1.60 (0.44–5.75)	0.471	4.69 (0.80–27.43)	0.086
Critically ill	5.05 (1.10–23.26)	0.038	1.07 (0.33–3.44)	0.913	3.53 (0.80–15.57)	0.096	12.94 (1.86–90.07)	0.010
NLR upon admission ($n=277$)***								
< 6.5	Ref		Ref		Ref		Ref	
≥ 6.5	1.39 (0.73–2.64)	0.316	0.89 (0.53–1.50)	0.663	1.75 (0.79–3.91)	0.169	1.13 (0.58–2.18)	0.723
MLR upon admission ($n=277$)***								
< 0.364	Ref		Ref		Ref		Ref	
≥ 0.364	1.18 (0.66–2.11)	0.582	0.85 (0.51–1.44)	0.553	0.84 (0.40–1.78)	0.647	0.99 (0.51–1.93)	0.975
Persistent COVID-19 symptoms****								
No								
At least 1 symptom	7.80 (2.16–28.15)	0.002	6.17 (2.48–15.35)	< 0.001	11.50 (3.07–43.15)	< 0.001	17.84 (2.07–153.58)	0.009

*Poisson regression model adjusted for follow-up time; ** Regression models adjusted for the presence of COVID-19 symptoms at admission and during the interview; ***Regression models, adjusted for COVID-19 severity; ****Regression models adjusted for follow-up time, presence of COVID-19 symptoms at admission, and COVID-19 severity; *95% CI*, 95% confidence interval; *NLR*, neutrophil-to-lymphocyte ratio; *MLR*, monocyte-to-lymphocyte ratio; *PRa*, adjusted prevalence ratio; *PTSD*, posttraumatic stress disorder

respiratory infection epidemic in South Korea reported that mental symptoms are present for up to a year after the epidemic outbreak (Park et al., 2020). In addition, a cohort study revealed a prevalence of any psychiatric disorder at 30 months post-SARS outbreak of 33.3% (Mak et al., 2009).

The reported prevalence of depressive (30.9%) and anxious (31.1%) symptoms in COVID-19 survivors is similar to the reports in other studies that included patients with mild COVID-19 (Ma et al., 2020; Zhang et al., 2020). Notwithstanding, a recent meta-analysis documented a prevalence of depression of 52% and anxiety of 47% (Deng et al., 2020), which is higher than that in our study since most of the included studies were conducted in a hospital setting. An alternative explanation is that the meta-analysis included patients from the early stages of the pandemic (January–March 2020), during which the fear regarding the disease was likely more heightened compared to the current study. The mentioned meta-analysis also reported that depression and anxiety prevalence was lower in outpatients (35% and 33%, respectively) compared to hospitalized patients (48% and 42%, respectively) (Deng et al., 2020). However, only one study was included in the outpatient subgroup; thus, the outpatient population was not truly represented.

The prevalence of clinically relevant depressive symptoms (moderate–severe) (10.7%) reported in this study is higher than that of the Peruvian population before the pandemic, in which a prevalence of 6.4% was reported using the PHQ-9 (Hernández-Vásquez et al., 2020). Therefore, COVID-19 infection impacts the mental health of the Peruvian population by increasing the prevalence of clinically relevant depressive symptoms.

A high prevalence of PTSD symptoms (29.5%) was found. Data presented by Dawra et al. showed different patterns in 101 patients who are newly diagnosed with COVID-19; using the IES-R, respondents suffered severe (30.7%), moderate (18.8%), mild (19.8%), and minimal (30.7%) PTSD symptoms (Dawra et al., 2021). In a systematic review for psychiatric sequelae in patients with COVID-19, PTSD results ranged from 6.5% to 42.8%. Of potential risk factors, PTSD was most pronounced after intensive care unit admission, previous psychiatric history or past traumatic events increased the risk of PTSD, and depressive and anxiety symptoms during acute COVID-19 was a predictor of PTSD (Mertz Schou et al., 2021).

Regarding the somatic symptoms (35.3%), collected data are consistent with Lee et al., who found that somatic symptoms were more frequent in patients with COVID-19. In another study carried out in the general population in China during the peak of the pandemic, researchers found a prevalence of 45.9% of somatic symptoms (Ran et al., 2020), higher than that of our study. These symptoms are directly related to COVID-19 infection or occur because of psychological distress (Lee et al., 2021). Physical symptoms, such as fatigue and shortness of breath, occur even after very mild COVID-19 infection in the outpatient setting, making it harder for COVID-19 survivors to return to their work and normal life, and posing major medical, social, and economic challenges (Augustin et al., 2021; Lee et al., 2021).

Variables Associated with Mental Symptoms

Some sociodemographic variables had a relation to a higher prevalence of clinically relevant mental symptoms. Gender (female) is one of the main variables, which is similar to what was reported in other studies (Guo et al., 2020; Hu et al., 2020; Ma et al., 2020; Mazza et al., 2020; Paz et al., 2020) since women tend to have greater symptoms

of hyperactivity, recurrent distressing memories, and negative cognitive and mood disturbances (Liu et al., 2020).

Patients with family members who were diagnosed and died of COVID-19 had a higher prevalence of somatic and anxious symptoms. This finding was reported in other studies in China (Nie et al., 2020; Zhang et al., 2020). Specifically, in a study carried out in Wuhan in patients with COVID-19, family members diagnosed and/or deceased with the same disease were independent predictors of the depression severity index, as well as presenting higher anxiety scores (Nie et al., 2020). Likewise, a history of psychiatric diagnosis and treatment was associated with a higher frequency of clinically relevant mental symptoms in COVID-19 survivors since the current pandemic causes reactive symptoms such as stress, depression, and anxiety, which in combination with hospitalization, can aggravate the mental health of people with a previous psychiatric diagnosis (Yao et al., 2020).

Self-perception regarding a greater COVID-19 severity was a variable associated with a higher prevalence of mental symptoms in survivors. A study carried out in patients admitted due to COVID-19 in Wuhan reported a similar result since the patients' concerns about their disease are added to their psychological burden, which is associated with anguish and a poor result in their mental health (Hu et al., 2020). Similarly, another study from Turkey reported that perception of COVID-19 severity was associated with the risk of having PTSD symptoms; however, this association became nonsignificant after controlling the effects of other variables (Poyraz et al., 2020).

A high frequency of persistent COVID-19 symptoms (61%) was found. This is a similar finding to a study conducted in Chinese patients who survived COVID-19, where it was found that up to 76% of patients reported at least one COVID-19 symptom after 6 months of follow-up (Huang et al.). The persistence of these symptoms was associated with a higher prevalence of mental symptoms.

Role of the Immune System in Mental Symptoms

The NLR was significantly higher in patients with clinically relevant symptoms of depression. In a study conducted in patients who survived from COVID-19, researchers found that those who reported depressive symptoms showed a greater immune response evidenced by a higher mean of NLR in their convalescent phase (2.4 vs. 1.8; $p < 0.001$) (Yuan et al., 2020). Another study from China conducted on admitted patients with COVID-19 revealed that those with mental symptoms have higher levels of IL 1β and NLR and lower levels of IL-10 and lymphocyte count (Hu et al., 2020). Thus, COVID-19 infection resulted in prolonged systemic inflammation that predisposes patients to persistent depression (Gennaro et al., 2021).

Considering the impact of COVID-19 infection on mental health and the involvement of the immune system, evaluating the psychopathology of COVID-19 survivors is necessary. Consequently, the investigation of inflammatory biomarkers should be deepened to adequately diagnose, treat, and monitor emerging psychiatric conditions (Mazza et al., 2020). Nonetheless, related biological factors (such as advanced age, female sex, and excess fat), along with other factors inherent to COVID-19 (such as social isolation, financial stress, and adverse effects of treatment) can influence psychiatric outcomes should be considered. As a consequence, the psychiatric symptoms in patients with COVID-19 are due to a combination of the processes involved in the virus-host relationship and the psychosocial and therapeutic problems associated with the pandemic and the disease (Raony et al., 2020).

Implications for Public Health and Decision-making

This study evidences a high impact on the mental health of COVID-19 survivors. Hence, Peruvian Public Health must focus on the early diagnosis and treatment of the mental health problems of these patients. All factors that influence these problems, including sociodemographic, proper clinical, and immune factors, should be evaluated. This allows healthcare professionals to establish individual management to improve the psychological well-being of the survivors.

Moreover, implementing health policies that aim to implement diverse mental health services is suggested. These policies include screenings with standardized online evaluations, educational interventions in mental health, provision of psychological support after vulnerable patient detection, systemic inflammation assessment using a complete blood count, and adequate psychiatric care for mental health management. All of these measures will empower Peru in the containment and future eradication of the COVID-19 pandemic (Huarcaya-Victoria, 2020).

Strengths and Limitations of the Study

Strengths of this study include the sample size and the fact that a random sample was made. Furthermore, to our knowledge, the study provides first-time exploratory data on different factors associated with mental health problems in patients that survived COVID-19 in Peru during a follow-up.

Notwithstanding, this study must be understood in the context of its methodological limitations; since the study is cross-sectional, causal relationship evaluation and evolution of different mental health outcomes from hospital discharge to the moment of evaluation were not achieved. Future studies should evaluate the modification of anxiety, depression, and PTSD levels as the pandemic evolve in Peru. Since we only evaluate patients from one single hospital, results are not generalized to all patients from other hospitals. Further, our results were not compared to control groups, making it difficult to differentiate between direct and indirect effects of the COVID-19 pandemic. Regarding the measurement instruments, the IES-R for DSM-IV, which is a measure for PTSD based on the old version of DSM was used in this study. An additional bias must be considered relating to an erroneous classification of participants, as the validated self-administered tests do not substitute an individualized evaluation performed by a mental health specialist. Finally, because a self-administered scale was used, the risk of different types of biases, such as social desirability is present. Nonetheless, our findings are in line with the reports from other countries.

Conclusions

Study results indicated a high prevalence of mental symptoms in COVID-19 survivors from a third-level hospital in Peru. Female sex, self-perception of greater COVID-19 severity, presence of persistent COVID-19 symptoms, loss of a family member due to COVID-19, and prior psychiatric diagnosis or treatment were associated with a higher prevalence of clinically relevant mental symptoms. In addition, the NLR was significantly higher in patients with clinically relevant symptoms of depression. All these variables were useful in identifying vulnerable patients who require timely psychiatric care.

Author Contributions Jeff Huarcaya-Victoria: Conceptualization, investigation, project administration, supervision, and manuscript drafting, review, and editing.

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Funding Self-financing.

Declarations

Ethics Approval and Consent to Participate This study was approved by the Research Ethics Committee Specific for COVID-19 of the "Seguro Social del Perú" (EsSalud). Informed consent was obtained from each participant for study participation.

Conflict of Interest The authors declare no competing interests.

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