An explanatory model of depressive symptoms from anxiety, post-traumatic stress, somatic symptoms and symptom perception: The role of inflammatory markers in hospitalized COVID-19 patients

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Abstract

Background: The COVID-19 pandemic has caused a bigger problem for mental health in the world. The aim of this study was to propose a model of mental health variables in hospitalized patients of COVID-19 and determine which model explained best the depression symptoms in both groups with and without biological response.

Method: We conducted a cross sectional study, following a simple random sampling. Data from 277 hospitalized patients with COVID-19 in Lima-Peru, were collected to assess mental health variables (i.e., depression, anxiety, post-traumatic stress, somatic symptoms), self-perception of COVID-19 related symptoms, and neutrophil/lymphocyte ratio (NLR) such as inflammatory marker. By performing a structural equation modeling analysis as a technique to evaluate a predictive model of depression.

Results: The results showed a prevalence of depressive symptoms (11.2%), anxious symptoms (7.9%), somatic symptoms (2.2%), and symptoms of post-traumatic stress (6.1%) in the overall sample. No association was found between the prevalence of these mental health problems among people with and without severe inflammatory response. The mental health indicators with the highest prevalence were sleep problems (48%), low energy (47.7%), nervousness (48.77%), worry (47.7%), irritability (43.7%) and back pain (52%) in the overall sample. The model proposed to explain depressive symptoms was able to explain more than 83.7% of the variance and presented good goodness-of-fit indices. Also, a different performance between the proposed model was found between people with and without severe inflammatory response, mainly in the relationship between anxiety and post-traumatic stress, and between the perception of COVID-19 related symptoms and somatic symptoms.

Conclusions: Results demonstrated that our model of mental health variables may explain depression in hospitalized patients of COVID-19 from a third-level hospital in Peru. In the model, perception of symptoms influences somatic symptoms, which influence both anxiety symptoms and post-traumatic stress. Thus, anxious symptoms could directly influence depressive symptoms or through post-traumatic stress. Our findings could be useful to decision-makers for the prevention of depression, using screening tools (i.e. perception of symptoms, somatic symptoms, anxiety) to identify vulnerable patients early.

Background

Several studies have reported that COVID-19 patients had experienced various mental health problems (i.e., depression, anxiety, and post-traumatic symptoms) [1–3]. Systematic reviews with meta-analysis identified a high prevalence of depressive symptoms (52%), anxious symptoms (47%) [4], and post-traumatic stress (26.9%) [5] in COVID-19 cases. The evidence suggests that people who had COVID-19 suffered a negative impact on their mental health, however, this impact was greater in people who were hospitalized for COVID-19 [6]. In this way, hospitalized people had a greater impact on their mental health due to various factors such as demographics (i.e. sex, age, and proceeding outside of the capital); clinical (i.e. self-perception of the severity of COVID-19, the persistence of COVID-19 symptoms, a history of

psychiatric treatment, and history of a family member infected by COVID-19); immune (i.e. neutrophil-lymphocyte index greater of 6.5); and psychosocial characteristics (i.e. isolation or quarantine, fear of COVID-19, being discriminate because of COVID) [7–10].

The mechanisms of action that could explain the presence of mental health problems in hospitalized patients with COVID-19 are two types: biological and psychological response. Although the neuropsychiatric complications of COVID-19 are under study, there is evidence of a possible causality that inflammatory markers may cause mental health problems, such as depression. An invasion of SARS-CoV-2 to the respiratory tract could induce an acute respiratory syndrome with consequent release of proinflammatory cytokines such as IL-1β and IL-6. In consequence, that produces a systemic immune response in the form of a "cytokine storm" [11]. Moreover, studies have reported these cytokines have increased in various psychiatric disorders (i.e. schizophrenia, depression, and post-traumatic stress) [12]. The relationship between elevated cytokine levels in COVID-19 and mental health problems could posit that immune/inflammatory pathways are one of the possible mechanisms involved in mental health problems in this infection [12]. The neutrophil-lymphocyte ratio (NLR) is an inexpensive marker calculated through a complete blood count. Its pathogenic role has been studied in a wide variety of diseases [13–16]. Thus, elevated NLR has been related to an increase of cytokines and C-reactive protein (CRP). Also, it is being used as a variable associated with a state of chronic inflammation. Recent meta-analyses have documented the relevance of NLR in psychiatric diseases such as schizophrenia [14], and mood disorders [17]. In case the performance of a cytokine is not possible, we can indirectly assess an increase in cytokines through an elevation of NLR.

From a psychological point of view, patients hospitalized with COVID-19 experience physical discomfort related to the COVID-19 symptoms themselves and other somatic symptoms, which can lead to stress and subsequently other mental health problems [18, 19]. As a novel and life-threatening disease, COVID-19 can cause fear and stress in patients, even more for those being treated in the isolation ward. Also, the uncertainty regarding the consequences of the infection during the hospitalization may intensify the panic in the patients [20]. Systematic reviews with meta-analysis evidence that the isolation, physical discomfort, and adverse effects of treatment in inpatients may make them oversensitive about symptoms of the infection and could lead to worsening of mental health [18, 21–23]. In addition, the presence of other problems of mental health, such as stress and anxiety, could generate the onset of depressive symptoms [24].

Although there are studies that separately evaluate the relationship between mental health in hospitalized COVID-19 patients with psychological factors and biological markers. Few studies study the role of both factors in explaining mental health problems such as depression in COVID-19 patients. Therefore, we conducted a study proposing a series of a hypothesis to explain the presence of one of the most prevalent mental health problems such as depressive symptoms from subjective psychological factors (i.e. somatic symptoms, anxiety, stress) in people hospitalized for COVID-19 with and without biological markers (i.e. inflammatory markers) (see Fig. 1).

Perception of the severity of COVID-19 symptoms influences somatic symptoms (hypothesis 1) (see Fig. 1**).** Patients' self-perception of the severity of illness (i.e., reducing or increasing symptoms) is related to the severity of mental health problems. A possible explanation could be that concerns about their illness or condition would add to their psychological burden [25]. The perception of COVID-19 related symptoms (i.e., fever, cough, trouble breathing) are moderately related to the presence of somatic symptoms, but their relationship is small directly with other mental health problems such as stress, anxiety, and depression.

Somatic symptoms influence anxiety (hypothesis 2) and post-traumatic stress (hypothesis 3) in people hospitalized for COVID-19 (see Fig. 1**).** It has been evidenced that the prevalence of somatic symptoms is significantly related to psychological outcomes as anxiety and post-traumatic stress. While the evidence reported a high prevalence of moderate or severe anxiety in the COVID-19 pandemic among general people, in many cases, the common comorbidity caused by the anxiety was somatization [26]. Furthermore, longitudinal studies of trauma survivors exposed that while there is a relationship between somatic and PTSD symptoms, results evidenced that somatic symptoms constituted a more consistent relationship with PTSD symptoms at each time point [27, 28].

Anxious symptoms influence posttraumatic stress (hypothesis 4) in people hospitalized for COVID-19 (see Fig. 1**).** There is much evidence to support the triad of fear, anxiety, and post-traumatic stress, which is a sequence of responses that from a fear trigger (being hospitalized for COVID-19), leads to an anxious response, which in turn leads to post-traumatic stress. Firstly, fear may increase sympathetic nervous system arousal and induce defensive or escape behavior in the face specific and real threatening stimulus. Likewise, anxiety is similar to fear as an emotional reaction, but unlike fear, the source of threat is unclear, thus, it is associated with preventive behaviors such as avoidance [29]. Moreover, fear and anxiety are related to the amygdala, which recruits and expresses the memory of these in both animals and humans [30]. The fear caused by COVID-19 can be implicated in mental health problems (insomnia, increased alcohol and tobacco use, anxiety, among others) because of high infection and death rates, the strict public health measures, among others [7]. In many cases, the excessive exposure to anxiety behaviors triggered post-traumatic stress disorder (PTSD), which is an anxiety disorder. PTSD is a severe psychological consequence when a person experiences a stressful event as highly traumatic [31].

Post-traumatic stress and anxiety symptoms influence the presence of depressive symptoms (hypothesis 5 and 6) in people hospitalized for COVID-19 (see Fig. 1**).** The evidence on the relationship between anxiety, depression, and post-traumatic stress is abundant. Different studies have identified that anxiety and fear of being COVID-19 hospitalized can generate a state of acute stress in individuals [32, 33]. Acute stress and post-traumatic stress in turn often trigger different mental health problems such as depression in hospitalized patients [20, 34]. Therefore, it is hypothesized that PTSD symptoms precede depressive symptoms (**hypothesis 6: post-traumatic stress influences depressive symptoms**). On the other hand, there is ample evidence that both anxiety and depression are closely related [35, 36] even in a COVID-19 pandemic [37]. A previous study also supported this hypothesis, where anxiety, post-traumatic stress, and depression are closely related to each other. The results showed that anxiety had the greatest influence

on the prevalence of depressive symptoms [24, 38] (hypothesis 5: anxious symptoms influence depressive symptoms).

These hypotheses remind us that while studies about mental health in COVID-19 are in ascendant progress, there is a lack of clarity about the functioning of these variables and their subsequent impact on mental health. Therefore, the present study proposes to evaluate these hypotheses to predict the presence of depressive symptoms from subjective psychological factors (i.e., somatic symptoms, anxiety, stress) in persons hospitalized for COVID-19 with and without biological markers (i.e., inflammatory markers).

Methods

Study design

The study design was a cross-sectional investigation.

Participants

The sample was secondary data from another study [39]. Participants were people with COVID-19 who were discharged from the “Hospital Nacional Guillermo Almenara Irigoyen” between March and September 2020 in Lima, Peru. Also, inclusion criteria included: 18 years to more; having been assessed at the beginning and after they were interned to the hospital. Participants were excluded as follows: people who had missing data in the variables of interest (anxious symptoms, depressive symptoms, somatic symptoms, post-traumatic symptoms, and NLR) and demographic variables (age, sex, civil status. degree of education, employment status, partners, relatives with COVID-19).

Using the methodology described in [39], the sample size was calculated. Thus, through the Epidat v44.2 program (Dirección Xeral de Saúde Pública da Consellería de Sanidade, Galicia, España). The sample was selected by a simple random sampling from a total number of 1190 participants and each participant had a coding.

Setting

The data of this second study were collected for the HNGAI from September to November of 2020. “Hospital Nacional Guillermo Almenara Irigoyen” is a hospital classified as a third-level specialized health institute in 2015 which means it has all the medical specialties. It is the second-largest hospital in the “Seguridad Social de Salud del Perú" (ESSALUD) and has a total of 815 hospital beds. During the pandemic COVID-19, the health system was focused on the care of COVID-19 patients. Thus, third-level hospitals were responsible for providing hospital beds from their different specialties to these patients

due to the high demand for care. To diagnose COVID-19, the protocol consisted of taking serological tests to, later on, confirm it with molecular tests.

Variables and measurement instruments

Depressive symptoms

The Patient Health Questionnaire-9 or PHQ-9 is a self-reporting instrument developed to identify possible causes or measure the severity of depressive symptoms within the last two weeks [40]. The PHQ-9 has 9 items based on the 9 criteria diagnostic from the Diagnostic Statistical Manual of Mental Disorders, five editions [DSM-5]. Moreover, it has 4 Likert-type response options from 0 (“not at all”) to 3 (“nearly every day”), the minimum score is 0 and the maximum score is 27. Depending on the total score, the PHQ-9 can indicate the measure of depressive symptoms due to its cut-off points. The levels of severity of depression are: minimal (score 0 to 4), mild (score 5 to 9), moderate (score 10 to 14), moderate-severe (score15 to 19), and severe (score 20 to 27). And a cohort point of 10 or more has been described in systematic reviews and meta-analysis of the PHQ-9 as screening to detect major depression [41, 42].

Anxious symptoms

The General Anxiety Disorder- 7 scale or GAD-7 is a self-report scale that assesses the presence or severity of generalized anxiety disorder (GAD) during the 2 weeks before self-application. The items reflect the most prominent diagnostic features of the DSM-5 symptoms criteria for GAD. Response options were “not at all”, “several days”, “more than half the days” and “nearly every day”, scored as 0, 1, 2, and 3, respectively. The total scores range from 0 to 21 and are categorized as follows: minimal (score 0 to 4), mild (score 5 to 9), moderate (score 10 to 14) and severe levels of anxiety symptoms (score 15 to 21) [43] In addition, the GAD-7 has a cut-off range of 10 points or more to identify the presence of GAD [44–46].

Somatic symptoms

The Patient Health Questionnaire-15 or PHQ-15 is a scale derived from the full PHQ. The PHQ-15 measures 15 somatic symptoms that entail more than 90% of the physical complaints during the past 4 weeks. Also, 15-items are based on the most prevalent DSM-IV somatization disorder somatic symptoms. The total scores range from 0 to 30 and to score, each item has 3-type Likert response options: 0 (“Not bothered at all”), 1 (“Bothered a little”), and 2 (“Bothered a lot”). The total score functions as a measure: minimal (score 1 to 4), low (score 5 to 9), medium (score 10 to 14), and high (score 15 to 30) levels of somatic symptom severity [47, 48]. It presents a cohort point of 15 to consider clinically significant somatization. Due to differences in some samples in terms of the specific factors: one, two, three [49–51] and four factors [48, 52, 53]. The current study conducted a sub-analysis to assess the psychometric

properties of the PHQ-15 through factor analysis and reliability, described in the supplement. As a result, we decided to use a version of 12 items (PHQ-12) due to the instability of the PHQ-15 (see supplement material 1).

Symptoms of post-traumatic stress

The Impact of Events Scale-Revised (IES-R) is a self-report scale that measures the degree of suffering caused by a life event, described as a form of subjective stress during the past 7 days. The IES-R has 22 items, categorized in three dimensions: a) Intrusion dimension (e.g. intrusive distressing thoughts, nightmares, feelings, and images), which items are 1, 2, 3, 6, 9, 14, 16, and 20; b) avoidance dimension (e.g. avoidance of feelings, situations or ideas), which items are 5, 7, 8, 11, 12, 13, 17, and 22; and c) hyperarousal dimension (e.g. anger, hypervigilance, irritability, difficulty concentrating), which items are 4, 10, 15, 18, 19, and 21 [54]. Also, a 5-point Likert scale is used to rate the 22 items ranging from 0 (“not at all”) to 4 (“extremely”). The total score reflects the levels of distress severity as follows: normal (score 0 to 8), mild (score 9- 25), moderate (score 26 to 43), and severe (score 44 to 88) [55]. A sum of these dimensions presents a cohort point of 33 or more that entails post-traumatic stress symptoms [56].

Perception of symptoms

Self-perception of COVID-19 related symptoms was assessed through two questions. The first question asked about how many symptoms the person self-reported at the time of admission to hospitalization and the second question asked about the number of symptoms the person reported at the time of assessment with the psychological instruments. To determine the self-perception of symptoms, the difference between these two questions was assessed. It was expected that if the number of symptoms increased the person self-perceived that his or her illness worsened (positive values) and if the number of symptoms decreased the person perceived that his or her health status improved (negative values). The symptoms were fever, fatigue, myalgia, cough, dyspnea, odynophagia, rhinorrhea, diarrhea, nausea or vomiting, anosmia, ageusia, headache, dizziness, ataxia, and convulsions.

Neutrophil-lymphocyte ratio (NLR)

The neutrophil-lymphocyte ratio (NLR) was obtained from the patients' complete blood counts on admission. It consists of the ratio between the neutrophil count and the lymphocyte count. The NLR was categorized into < 6.5 and ≥ 6.5. This cutoff point was chosen considering its ability to predict mortality in patients with COVID-19 [57].

Sociodemographic variables

Information was provided on Age, Sex, Civil status, Employment status, do you have a religion? Have you had a family member with COVID-19? Has any member of your family died by COVID-19? if you have a previous psychiatric diagnosis, and if have previous psychological treatment.

Data Analysis

Descriptive and prevalence

A descriptive analysis of participants was conducted. The prevalence of depressive symptoms (PHQ-9 > 10 or more) [41, 42], anxious symptoms (GAD-7 > 10 or more) [44, 45], post-traumatic stress symptoms (IES-R > 33 or more) [56]). We performed a differentiated analysis of the symptoms and indicators of the PHQ-9, GAD-7, IES-R and PHQ-12. The results were stratified based on those with high neutrophil counts (NLR≥ 6.5), indicating risk of mortality in patients with COVID-19 [57].

Relation between variables

To measure the degree of association between variables Spearman was used, categorized the size of the correlation coefficient as follows: a large (r > 0.70), moderate (r > 0.50), or small (r > 0.30) ratio [58].

Structural regression model

A structural regression model was used using the weighted least squares means and variance adjusted (WLSMV) estimator due to non-normal data (i.e. categorical indicators) [59]. Also, a polychoric correlation matrix for the nature of the items was used. Four goodness-of-fit indices were used to evaluate the proposed model for hospitalized persons with high and low NLR: Comparative Fit Index (CFI), Tucker-Lewis index (TLI), standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA). Also, its points cohort is as follows: a) CFI and TLI > 0.95 or more; b) SRMR and RMSEA < 0.08 or flew [59, 60]. In addition, we evaluate the R2 of the outcome variable (depressive symptoms) to determine how much variance explains the proposed model [61].

Statistical software

All analyses were done in R studio, with the packages “lavaan”, “semTools” and “semPlot”.

Results

General characteristics and prevalence

From 319 patients with a diagnosis of COVID-19, we excluded 42 of them because they did not have NLR measurements. Thus, we analyzed data from 277 participants (86.8% of the total number of patients). The average age was 54.2 (± 14.9) years and most patients were men (61.4%). Also, 225 (81.2%) had at least one family member with COVID-19, and 85 (30.7%) had at least one relative die by COVID-19. The majority of participants did not have a psychiatric diagnosis (93.1%) and did not receive psychological treatment (91%) prior to infection by COVID-19. Regarding the prevalence of mental health problems, 11.2% was the overall prevalence of depression, 7.9% for anxiety, 2.2% for somatic symptoms, and 6.1 % for post-traumatic stress.

The 48.7% of the participants had a severe inflammatory response, the analysis differentiated by those with and without severe response can be seen in Table 1. In addition, an association was found between age and sex with severe inflammatory response ($p < 0.05$).

Table 1

Socio-demographic characteristics (n= 277)

		Overall		With severe inflammatory response (n=135)		Without severe inflammatory response (n=142)		*p*
		n	%	n	%	n	%	
Age	20 a 39	53	19.1%	15	11.1%	38	26.8%	0.004
	40 a 59	119	43.0%	65	48.1%	54	38%	
	60 a 94	105	37.9%	55	40.7%	50	35.2%	
Sex	Men	170	61.4%	99	73.3%	71	50%	<0.001
	Women	107	38.6%	36	26.7%	71	50%	
Civil status	Single	34	12.3%	15	11.1%	19	13.4%	0.505
	Married	195	70.4%	99	73.3%	96	67.6%	
	Divorced	18	6.5%	6	4.4%	12	8.5%	
	Widowed	30	10.8%	15	11.1%	15	10.6%	
Employment status	Unemployed	120	43.3%	55	40.7%	65	45.8%	0.469
	Employed	157	56.7%	80	59.3%	77	54.3%	
Do you have a religion?	No	21	7.6%	11	8.1%	10	7%	0.904
	Yes	256	92.4%	124	91.9%	132	93%	
Have you had a family member with COVID-19?	No	52	18.8%	27	20%	25	17.6%	0.722
	Yes	225	81.2%	108	80%	117	82.4%	
Has any member of your family died by COVID-19?	No	192	69.3%	91	67.4%	101	71.1%	0.589
	Yes	85	30.7%	44	32.6%	41	28.9%	
Previous psychiatric diagnosis	No	258	93.1%	128	94.8%	130	91.5%	0.403
	Yes	19	6.9%	7	5.2%	12	8.5%	
Previous psychological treatment	No	252	91.0%	124	91.9%	128	90.1%	0.774
	Yes	25	9.0%	11	8.1%	14	9.9%	
Depressive symptoms	No	246	88.8%	116	85.9%	130	91.5%	0.196
	Yes	31	11.2%	19	14.1%	2	8.5%	
Anxious symptoms	No	255	92.1%	121	89.6%	134	94.4%	0.217
	Yes	22	7.9%	14	10.4%	8	5.6%	

Somatic symptoms	No	271	97.8%	132	97.8%	139	97.9%	0.919
	Yes	6	2.2%	3	2.2%	3	2.1%	
Symptoms of post-traumatic stress	No	260	93.9%	126	93.3%	134	94.4%	0.914
	Yes	17	6.1%	9	6.7%	8	5.6%	

Note. The p-value is obtained from the chi-square analysis.

Regarding the prevalence of the overall sample, it observed a prevalence in sleep problems (48%) and low energy (47.7%) as depression indicators. Nervousness (48.77%), worry (47.7%) and irritability (43.7%) were the highest prevalence of anxiety. Back pain (52%) and trouble sleeping (46.6%) were the more common somatic symptoms. In terms of prevalence by inflammatory responses, similarities were observed. Sleeping problems (over 45.9%), low energy (over 46.5%) were the most common depressive indicators in both groups with and without an inflammatory response. Likewise, while worry (over 46.7%) and nervousness (over 48.6%) were prevalent in both groups, irritability (47.4%) was observed higher in patients with severe inflammatory responses than those without inflammatory responses. About somatic symptoms indicators, differences between groups were also observed, back pain (over 50%) and trouble sleeping (over 46.5%) were the most prevalent indicators in both samples, however, pain in arms, legs (48.1%), feeling tired (43.7%), and shortness of breath indicators (34.8%) were higher in the group with inflammatory responses in comparison with the other group. The clinical indicators for each of the mental health problems by the group are summarized in Figure 2 and detailed in Supplementary material 1.

Relationship between variables

The findings in Table 2 indicate that correlations between scores for depression, anxiety, and somatization were high for overall participants ($r > .70$, $p < 0.05$). Also, a moderate relationship was also observed between post-traumatic stress with depressión, anxiety as well as somatic symptoms ($r > 0.50$, $p < 0.05$). On the other hand, a small relationship was found between the perception of COVID-19 symptoms with the other variables, in the group of all participants.

When the strength of the correlation between the group of people with and without severe inflammatory response was analyzed differentially, it was found that in the case of people without inflammatory response the relationship between posttraumatic stress and symptom perception was small and significant ($r > 0.20$, $p < 0.05$). However, in the group of inflammatory responders, this same correlation was not significant. The strength of the relationship between the other variables was not found to have changed.

Table 2

Correlations between depressive symptoms, anxious symptoms, somatic symptoms, post-traumatic stress, and perception of physical symptom (n=277)

Group	Variable	1	2	3	4	4.1	4.2	4.3	5
Overall	1. Depressive symptoms	1							
(n=277)	2. Anxious symptoms	0.77*	1						
	3. Somatic symptoms	0.73*	0.71*	1					
	4. Symptoms of post-traumatic stress disorder	0.64*	0.65*	0.67*	1				
	4.1 Intrusion	0.63*	0.63*	0.65*	0.93*	1			
	4.2 Avoidance	0.52*	0.57*	0.59*	0.92*	0.82*	1		
	4.3 Hiperarousal	0.68*	0.65*	0.69*	0.90*	0.81*	0.74*	1	
	5. Perception of physical symptoms	0.17*	0.17*	0.22*	0.11	0.13*	0.10	0.13*	1
With severe inflammatory response (NLR≥ 6.5) (n=135)	1. Depressive symptoms	1							
	2. Anxious symptoms	0.79*	1						
	3. Somatic symptoms	0.72*	0.70*	1					
	4. Symptoms of post-traumatic stress disorder	0.62*	0.64*	0.65*	1				
	4.1 Intrusion	0.62*	0.67*	0.64*	0.92*	1			
	4.2 Avoidance	0.45*	0.54*	0.56*	0.91*	0.81*	1		
	4.3 Hiperarousal	0.68*	0.63*	0.69*	0.91*	0.83*	0.73*	1	
	5. Perception of physical symptoms	0.18*	0.08*	0.15*	0.02*	0.03	-0.01	0.05	1
Without severe inflammatory response (NLR< 6.5) (n=142)	1. Depressive symptoms	1							
	2. Anxious symptoms	0.76*	1						
	3. Somatic symptoms	0.73*	0.72*	1					

4. Symptoms of post-traumatic stress disorder	0.66*	0.65*	0.69*	1				
4.1 Intrusion	0.64*	0.60*	0.66*	0.93*	1			
4.2 Avoidance	0.59*	0.60*	0.61*	0.92*	0.82*	1		
4.3 Hiperarousal	0.67*	0.66*	0.68*	0.88*	0.79*	0.75*	1	
5. Perception of physical symptoms	0.17*	0.27*	0.29*	0.21*	0.23*	0.23*	0.22*	1

Note. The relationship was assessed using Spearman's coefficient. *$p < 0.05$: significant correlation between variables.

Structural regression model

The general model that includes people with and without severe inflammatory response identified an optimal overall fit, reaching adequate goodness-of-fit indices in all the indexes evaluated (see Table 3). In addition, it is possible to identify that the proposed model explains 85% of the variance of depressive symptoms.

It was identified that in the model with all participants (see Figure 3A), the perception of symptom influences somatic symptoms (β = 0.223, p < 0.05). In addition, somatic symptoms influence anxious symptoms (β = 0.922, p < 0.05) and posttraumatic stress (β = 0.623, p < 0.05). However, a non-significant relationship was found between anxious symptoms and posttraumatic stress (β = 0.205, p = 0.262), and stress-posttraumatic stress with depression (β = 0.026, p = 0.727). Finally, the relationship between anxious and depressive symptoms was high and significant (β = 0.902, p < 0.05).

When analyzing separately the overall performance of the models for persons with and without inflammatory response, it is found that both models present adequate goodness-of-fit indices, and both models manage to explain more than 83% of the variance of depressive symptoms. However, the SRMR values are high, possibly due to the small sample size (n<200) (see Table 3).

The specific assessment between the relationships of the proposed models identified different performances for persons with a severe inflammatory response (see Figure 3B) and for persons without severe inflammatory response (see Figure 3C). The relationship between perception of COVID-19 symptoms and somatic symptoms was found to be significant for the group of persons without severe inflammatory response (β = 0.289, p < 0.05), but the relationship was not significant in the group of persons with a severe inflammatory response (β = 0.289, p = 0.117). Also, the relationship found between post-traumatic stress and anxiety symptoms in the group without severe inflammatory response was direct, significant, and high (β = 0.684, p < 0.05). However, the relationship was inverted and not

significant in the group with a severe inflammatory response (β = -0.277, p = 0.531). On the other hand, a non-significant relationship was found between post-traumatic stress and depressive symptoms in both groups with and without a severe inflammatory response.

Table 3

Goodness-of-fit indices of the structural regression model.

Model	n	X^2	X^2 /df	CFI	TLI	RMSEA [90% CI]	SRMR	R^2
Overall	277	1963.3	1.61	0.984	0.984	0.047 [0.043 - 0.051]	0.085	0.850
With severe inflammatory response	135	1667.8	1.37	0.971	0.971	0.053 [0.046 - 0.059]	0.109	0.837
Without severe inflammatory response	142	1552.1	1.28	0.960	0.959	0.044 [0.037 - 0.051]	0.128	0.898

Note: X^2 = chi-square; CFI = comparative fit index; TLI = Tucker-Lewis index; RMSEA = root mean square error of approximation; CI = confidence intervals; SRMR = standardized root mean square. R^2 = coefficient of determination; Degrees of freedom =1,216.

Discussion

Main findings and significance of the results

There is extensive discussion on the role of biological and psychological variables in the occurrence of depressive symptoms in patients with COVID-19. Previous studies found higher values in inflammatory markers (i.e., NLR) in patients with depression, compared with the non-depression groups [25, 57]. Our research presents evidence that a model about subjective perception of symptoms (psychosomatic and COVID-19 symptoms), as well as anxiety and post-traumatic stress explains the presence of depressive symptoms in hospitalized COVID-19 with and without severe inflammatory response in NLR.

Using the anxiety-PTSD-depression triad as a base model, we added the variables related to the subjective perception of symptoms, and finally our model explained 85% of depressive symptoms in the overall sample. This demonstrates that several mood disorders occur at the same time prior to the development of depression [62].

The model also showed that psychosomatic symptoms and anxiety are the variables with the highest influence. These both variables can be explained from biological perspectives due to an increase of anxiety has been found to be associated with presence of somatic symptoms such as headaches and

shoulder and limb pain [63]. Besides, the relationship between psychosomatic symptoms and post-traumatic stress represents a relevant effect, which can be explained due to somatic symptoms being more prevalent during periods of stress [64].

Contrasting findings with existing literature

Prevalence and indicators

In our study, the most prevalent mental health problems were anxiety (11.2%), depression (7.1%) and PTSD (6.1%). These results are below those reported in previous studies. A systematic review indicated a prevalence of depression at 45% (95% CI: 37–54%) and 47% for anxiety (95% CI: 37–57%) in COVID-19 patients [4]. In the case of PTSD, a systematic review, which evaluated 13 studies in 1093 participants with severe cases of COVID-19, reported a prevalence of PTSD at 16% (95%CI: 9% to 23%) [65]. Similarly, another study conducted with 190 patients indicated that the prevalence of PTSD was 22.6% [66]. These differences among researchers could be explained due to the different socio-demographic compositions, different study designs, and measurement instruments used, which may influence the degree of prevalence. Even so, results evidenced that the patients with COVID-19 present several mental health problems at the same time. This could mean that, during the treatment, patients may develop multiple related psychiatric diseases which form a mutually influential symptom network; in turn, influences their recovery [67].

Sleep problems were one of the most frequent indicators of mental health problems. Although a systematic review reported that sleep problems are common during the COVID-19 pandemic, being associated with higher levels of mental health problems [68]. Another study showed that this indicator had been prevalent in healthcare workers even before COVID-19 [69]. The prevalence of sleep problems could be explained by fear of COVID-19. Due to worries about the disease, patients cannot take rest and consequently develop insomnia [70]. Moreover, if the individual cannot manage the fear for a specific time, it leads to mental health problems (e.g. depression, anxiety) [71]. We also found that low energy was the second indicator with the highest prevalence, which is a comorbid symptom of many psychiatric problems in patients with COVID-19 [72]. In addition, low energy could be caused by lack of sleep or one of the other mental health problems such as depression.

The main indicators related to anxiety were nervousness, irritability and worry. This finding was also reported in other studies in people with COVID-19, being the most common symptoms of anxiety, insomnia, irritability, restlessness, and excessive worrying [73]. As previously mentioned, being hospitalized, patients may experience fear of COVID-19 and worries related to their health, family, financial issues, and environmental conditions (e.g., isolation, uncertainty about the evolution of the disease). On the other hand, for somatic complaints, backache, arms and legs pain, and feeling exhausted were the most prevalent in our sample. Reasons might be related to similarities with the physiological symptoms of COVID-19.

Structural equation model and relationship between variables

Previous studies that identified pose predictive models between mental health problems in COVID-19 (i.e., depression, anxiety, stress, fear of COVID-19, among others) indicated that concern of COVID-19 has a negative impact on some mental health. Two studies proposed models in which fear of COVID is significantly and positively related to depression, anxiety and insomnia [74, 75]. Moreover, studies that reported the influence of biological responses (i.e., C-reactive protein, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, among others) during COVID-19 on mental health problems reported COVID-19 virus could lead to system immune changes, which in turn could reflect in mental health problems. These psychiatric outcomes can be influenced by other factors as well (i.e., biological, factor social isolation, adverse effects of treatments, among others) [12, 76]. However, a small number of studies has proposed predictive models about the relationship of biological responses with these mental clinical problems. For example, a study, using SEM, proposed a model that evening salivary cortisol (as an indicator of Hypothalamic pituitary adrenal) predicts depression, which predicts circulating pro-inflammatory cytokines (IL-2, IL-6, TNF-α) in patients diagnosed with Chronic Fatigue Syndrome (CFS) [77]. Another study explored the relationship between biological factors (i.e., sex, disease duration, self-perceived illness severity, and inflammatory markers) and mental health status in inpatients with COVID-19. In the SEM, inflammatory markers (i.e., NLR, IL-1β as observed variables) and mental health (i.e., insomnia, depression and anxiety as observed variables) were set as latent variables. Results indicated the inflammatory markers had a significant and direct effect on mental health. Moreover, the disease duration and inflammatory markers indirectly influenced mental health, through self-perceived illness severity as a mediator [25]. Although these models are not the same as ours, these findings suggest that inflammatory responses could be related to psychological disorders.

Following this hypothesis, studies have found a heterogeneous influence of NLR in psychological mental problems. First, one study, using regression analysis, demonstrated the influence of NLR markers in both the prevalence of depression and anxiety in Chinese patients with gastric cancer [78]. In contradiction to this finding, a multi-linear regression study showed a weak association between inflammatory biomarkers and depression in a three-month cohort of stroke patients [79]. Reasons could be related to there are immune responses in both COVID-19 infection and mood disorders, suggesting a similar biological response between them. Both states induce the production of abnormal levels of cytokines, chemokines, and other inflammatory mediators [80], showing a hyperinflammatory state [81]. While patients with mental health problems show high levels of biomarkers [17], a meta-analysis, with 16 studies, evidenced higher counts of biomarkers (i.e. IL-6, CRP, PCT, among others) in severe cases of COVID-19 [82].

Another interesting result was the high influence of anxiety on depression in all three models. This finding is in accordance with other studies which evidenced that anxious symptoms had a direct and significant relationship with depression. One study that proposed a model of the triad fear-anxiety-stress in the development of depression symptoms in pandemic disease symptoms in health-workers, indicated that the fear to COVID-19, anxiety and posttraumatic symptoms explains depression symptoms. The SEM demonstrated that anxiety was the most influential variable in the depression symptoms in comparison

with post-traumatic stress [24]. Even before COVID-19 exploded, researchers have shown that anxiety may contribute directly or as mediating variables in depression. These results show how the different variables (i.e. stress, self-esteem, stressful negative events) influences depression, where increases in anxiety may lead to increases in depression [83, 84]. To sum up, these findings suggest that the role of anxiety in the occurrence of depressive symptoms is significant and is even maintained in the COVID-19 pandemic. Anxiety is a common adaptive response against threatening situations, which could be increased due to factors such as stress or fear, and could trigger prolonged anxiety. Thus, pathological anxiety can affect functioning in the daily routine of patients, which in turn may cause or be comorbid with other mental disorders such as depression [85].

Besides, another result was the influence of the PTSD variable on depression. Our results demonstrated that PTSD does not present a significant influence on depression in hospitalized patients both with and without severe inflammatory markers. This finding might be related to the PTSD symptoms changes over time. Other studies have found the different prevalences of PTSD symptoms in each stage of COVID-19 disease (i.e. recovering from COVID-19 infection, being quarantined) [86, 87]. Likewise, another reason could be the similarity between our variables. There are studies that report a high association between PTSD and somatic symptoms, whose findings support that somatic symptom may be related to the patient's psychophysiological dysregulation and lead to psychological symptoms (e.g. PTSD) [88, 89].

Implications in public health and making decisions

These findings provide a theoretical model, which permits establishing policies to prevent depression in inpatients. Specifically, the model revealed that somatic and anxious symptoms are the most relevant predictors to develop depression. Health workers could employ screening measures for anxiety and somatic symptoms in order to prioritize the care of patients with high levels in these conditions, and thus avoid possible cases of depressive symptoms. It is a necessity because Peru is one of the countries that reported worse mental health levels than overall average during the pandemic [90] and the prevalence of depression in 2020 was five times higher than previous years [91].

Interventions to reduce symptoms of anxiety, fear and worry in hospitalized patients could be an effective strategy to prevent subsequent cases of mental illness [92]. Telephone-based intervention also has been useful to reduce symptoms of anxiety and depression, which provides psychological support, information about the process of the disease and promotes a sense of emotional stability [93, 94]. Thus, the implementation of telephones during hospitalizations could be a strategy to prevent psychological problems in hospital isolated patients. This also could be used as a facility for patients to have access to make calls or send messages to their relatives.

Strengths and limitations

This study has limitations that should be mentioned. First, some patients did not have inflammatory markers recorded, so they were eliminated. This elimination could lead to an information bias. Second, NLR was evaluated as the only inflammatory measure, however this is not a gold standard so it could cause errors in grouping people with and without severe inflammatory response. Third, this study has a cross-sectional design and we cannot infer causality in the interpretation of the findings. Fourth, we employed self-reported measures, which could be influenced by social desirability or memory bias. Fifth, the data includes a single hospital in a Peruvian city, so the results should not be extrapolated to other cities or contexts. Sixth, we used a validated scale such as the IES-R to measure PTSD, however the IES-R apparently does not include the entire concept of PTSD, since the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) considers four dimensions and the IES-R only assesses three of these dimensions. This could imply a partial evaluation of the symptoms of PTSD. Finally, other confounding variables were not considered, such as fear of COVID-19 ([24] and coping [95], so it is possible that the model is partial or influenced by other variables.

On the other hand, our study has three main strengths. This investigation presents a larger sample compared to previous studies evaluating hospitalized patients [25, 96]. Besides, we employed structural equation modeling, as a solid technique that allows us to assess several variables at the same time. Moreover, to our knowledge, this is the first study that provides a framework of biological and psychological variables that explain depressive symptoms as an outcome in the context of the COVID-19.

Conclusions And Recommendations

Results demonstrated that our model of mental health variables may explain depression in hospitalized patients of COVID-19 from a third-level hospital in Peru. In the model, perception of symptoms influences somatic symptoms, which influence both anxiety symptoms and post-traumatic stress. Thus, anxious symptoms could directly influence depressive symptoms or through post-traumatic stress. In addition, our model was found to have a good overall fit and explains more than 83% of the depressive symptoms.

Regarding clinical indicators, patients presented a high prevalence of depression, anxiety and psychosomatic indicators. Our findings could be useful to decision-makers for the prevention of depression, using screening tools (i.e. perception of symptoms, somatic symptoms, anxiety) to identify vulnerable patients early.

Declarations

Ethics of approval and consent to participate

This study has been approved by the Institutional Review Board (IRB) for COVID-19 of the “Seguro Social del Perú” (EsSalud). All methods were carried out in accordance with relevant guidelines and regulations. The guidelines of the Helsinki Declaration were followed. Each participant provided signed virtual

informed consent. The data collected were codified and duly protected to guarantee the confidentiality of the information and the results of the patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Competing interests

The authors report no conflict of interest when conducting the study, analyzing the data, or writing the manuscript.

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Authors' contributions

David Villarreal-Zegarra: Formal Analysis, Methodology, Supervision, Validation, Writing – Original version, Approval of the final version.

Rubí Paredes: Conceptualization, Formal Analysis, Methodology, Validation, Writing – Original version, Approval of the final version.

Nikol Mayo: Conceptualization, Methodology, Validation, Writing – Original version, Approval of the final version.

Anthony Copez-Lonzoy: Methodology, Validation, Writing – Original version, Approval of the final version.

Ana L. Vilela-Estrada: Methodology, Validation, Writing – Original version, Approval of the final version.

Jeff Huarcaya-Victoria: Conceptualization, Methodology, Validation, Writing – Review & Editing, Approval of the final version.

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References

1. Alamri HS, Mousa WF, Algarni A, Megahid SF, Al Bshabshe A, Alshehri NN, et al. Mental Health of COVID-19 Patients-A Cross-Sectional Survey in Saudi Arabia. Int J Environ Res Public Health. 2021;18.
2. Ismael F, Bizario JCS, Battagin T, Zaramella B, Leal FE, Torales J, et al. Post-infection depressive, anxiety and post-traumatic stress symptoms: A prospective cohort study in patients with mild COVID-19. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111:110341.
3. Li T, Sun S, Liu B, Wang J, Zhang Y, Gong C, et al. Prevalence and Risk Factors for Anxiety and Depression in Patients With COVID-19 in Wuhan, China. Psychosom Med. 2021;83:368–72.
4. Deng J, Zhou F, Hou W, Silver Z, Wong CY, Chang O, et al. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci. 2021;1486:90–111.
5. Yuan K, Gong Y-M, Liu L, Sun Y-K, Tian S-S, Wang Y-J, et al. Prevalence of posttraumatic stress disorder after infectious disease pandemics in the twenty-first century, including COVID-19: a meta-analysis and systematic review. Mol Psychiatry. 2021. https://doi.org/10.1038/s41380-021-01036-x.
6. Mohammadian Khonsari N, Shafiee G, Zandifar A, Mohammad Poornami S, Ejtahed H-S, Asayesh H, et al. Comparison of psychological symptoms between infected and non-infected COVID-19 health care workers. BMC Psychiatry. 2021;21:170.
7. Huarcaya-Victoria J, Villarreal-Zegarra D, Podestà A, Luna-Cuadros MA. Psychometric Properties of a Spanish Version of the Fear of COVID-19 Scale in General Population of Lima, Peru. Int J Ment Health Addict. 2020. https://doi.org/10.1007/s11469-020-00354-5.
8. Huarcaya-Victoria J, Barreto J, Aire L, Podestá A, Caqui M, Guija-Igreda R, et al. Mental health in COVID-19 survivors from a general hospital: association with sociodemographic, clinical, and inflammatory variables. preprint. In Review; 2021.
9. Kontoangelos K, Economou M, Papageorgiou C. Mental Health Effects of COVID-19 Pandemia: A Review of Clinical and Psychological Traits. Psychiatry Investig. 2020;17:491–505.
10. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis. J Affect Disord. 2021;281:91–8.
11. Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-

inflammatory strategies. J Biol Regul Homeost Agents. 2020;34:327–31.

12. Raony Í, de Figueiredo CS, Pandolfo P, Giestal-de-Araujo E, Oliveira-Silva Bomfim P, Savino W. Psycho-Neuroendocrine-Immune Interactions in COVID-19: Potential Impacts on Mental Health. Front Immunol. 2020;11.
13. Beltrán BE, Paredes S, Cotrina E, Sotomayor EM, Castillo JJ. The impact of the neutrophil:lymphocyte ratio in response and survival of patients with de novo diffuse large B-cell lymphoma. Leuk Res. 2018;67:82–5.
14. Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2019;206:4–12.
15. Seropian IM, Romeo FJ, Pizarro R, Vulcano NO, Posatini RA, Marenchino RG, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictors of survival after heart transplantation. ESC Heart Fail. 2018;5:149–56.
16. Yoshitomi R, Nakayama M, Sakoh T, Fukui A, Katafuchi E, Seki M, et al. High neutrophil/lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. Ren Fail. 2019;41:238–43.
17. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84 Pt A:229–36.
18. Wang M, Hu C, Zhao Q, Feng R, Wang Q, Cai H, et al. Acute psychological impact on COVID-19 patients in Hubei: a multicenter observational study. Transl Psychiatry. 2021;11:1–9.
19. Willis C, Chalder T. Concern for Covid-19 cough, fever and impact on mental health. What about risk of Somatic Symptom Disorder? J Ment Health. 2021;0:1–5.
20. Xiang Y-T, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry. 2020;7:228–9.
21. Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. J Hosp Infect. 2010;76:97–102.
22. Kang E, Lee SY, Kim MS, Jung H, Kim KH, Kim K-N, et al. The Psychological Burden of COVID-19 Stigma: Evaluation of the Mental Health of Isolated Mild Condition COVID-19 Patients. J Korean Med Sci. 2021;36.
23. Purssell E, Gould D, Chudleigh J. Impact of isolation on hospitalised patients who are infectious: systematic review with meta-analysis. BMJ Open. 2020;10:e030371.
24. Villarreal-Zegarra D, Copez-Lonzoy A, Vilela-Estrada A, Huarcaya-Victoria J. Depression, Post-traumatic Stress, Anxiety, and Fear of COVID-19 in the General Population and Health-Care Workers: Prevalence, Relationship, and Explicative Model in Peru. 2021.
25. Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, et al. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. Brain Behav Immun. 2020;89:587–93.

26. Shangguan F, Quan X, Qian W, Zhou C, Zhang C, Zhang XY, et al. Prevalence and correlates of somatization in anxious individuals in a Chinese online crisis intervention during COVID-19 epidemic. J Affect Disord. 2020;277:436–42.
27. McAndrew LM, Lu S-E, Phillips LA, Maestro K, Quigley KS. Mutual maintenance of PTSD and physical symptoms for Veterans returning from deployment. Eur J Psychotraumatology. 2019;10:1608717.
28. Stensland SØ, Thoresen S, Jensen T, Wentzel-Larsen T, Dyb G. Early Pain and Other Somatic Symptoms Predict Posttraumatic Stress Reactions in Survivors of Terrorist Attacks: The Longitudinal Utøya Cohort Study. J Trauma Stress. 2020;33:1060–70.
29. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The Fear-Avoidance Model of Musculoskeletal Pain: Current State of Scientific Evidence. J Behav Med. 2007;30:77–94.
30. Gonzalez P, Martinez KG. The role of stress and fear on the development of psychopathology. Psychiatr Clin North Am. 2014;37:535–46.
31. Longo MS de C, Vilete LMP, Figueira I, Quintana MI, Mello MF, Bressan RA, et al. Comorbidity in post-traumatic stress disorder: A population-based study from the two largest cities in Brazil. J Affect Disord. 2020;263:715–21.
32. Beck K, Vincent A, Becker C, Keller A, Cam H, Schaefert R, et al. Prevalence and factors associated with psychological burden in COVID-19 patients and their relatives: A prospective observational cohort study. PloS One. 2021;16:e0250590.
33. Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: A mixed-method study. Brain Behav Immun. 2020;88:17–27.
34. Bo H-X, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, et al. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol Med. 2021;51:1052–3.
35. Jacobson NC, Newman MG. Anxiety and depression as bidirectional risk factors for one another: A meta-analysis of longitudinal studies. Psychol Bull. 2017;143:1155–200.
36. Silk JS, Price RB, Rosen D, Ryan ND, Forbes EE, Siegle GJ, et al. A Longitudinal Follow-up Study Examining Adolescent Depressive Symptoms as a Function of Prior Anxiety Treatment. J Am Acad Child Adolesc Psychiatry. 2019;58:359–67.
37. Choi EPH, Hui BPH, Wan EYF. Depression and Anxiety in Hong Kong during COVID-19. Int J Environ Res Public Health. 2020;17.
38. Ni MY, Jiang C, Cheng KK, Zhang W, Gilman SE, Lam TH, et al. Stress across the life course and depression in a rapidly developing population: the Guangzhou Biobank Cohort Study. Int J Geriatr Psychiatry. 2016;31:629–37.
39. Huarcaya-Victoria J, Barreto J, Aire L, Podestá A, Caqui M, Guija-Igreda R, et al. Mental Health in COVID-2019 Survivors from a General Hospital in Peru: Sociodemographic, Clinical, and Inflammatory Variable Associations. Int J Ment Health Addict. 2021;:1–22.

40. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.
41. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. The BMJ. 2019;365.
42. Manea L, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. Gen Hosp Psychiatry. 2015;37:67–75.
43. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092–7.
44. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. Gen Hosp Psychiatry. 2016;39:24–31.
45. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care. 2008;46:266–74.
46. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Löwe B. Anxiety Disorders in Primary Care: Prevalence, Impairment, Comorbidity, and Detection. Ann Intern Med. 2007;146:317–25.
47. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a New Measure for Evaluating the Severity of Somatic Symptoms. Psychosom Med. 2002;64:258–66.
48. Witthöft M, Hiller W, Loch N, Jasper F. The Latent Structure of Medically Unexplained Symptoms and Its Relation to Functional Somatic Syndromes. Int J Behav Med. 2013;20:172–83.
49. Liao S-C, Huang W-L, Ma H-M, Lee M-T, Chen T-T, Chen I-M, et al. The relation between the patient health questionnaire-15 and DSM somatic diagnoses. BMC Psychiatry. 2016;16.
50. Zhang L, Fritzsche K, Liu Y, Wang J, Huang M, Wang Y, et al. Validation of the Chinese version of the PHQ-15 in a tertiary hospital. BMC Psychiatry. 2016;16:89.
51. Grover S, Sahoo S, Chakrabarti S, Avasthi A. Anxiety and somatic symptoms among elderly patients with depression. Asian J Psychiatry. 2019;41:66–72.
52. Zhou Y, Xu J, Rief W. Are comparisons of mental disorders between Chinese and German students possible? An examination of measurement invariance for the PHQ-15, PHQ-9 and GAD-7. BMC Psychiatry. 2020;20:480.
53. Walentynowicz M, Witthöft M, Raes F, Van Diest I, Van den Bergh O. Sensory and affective components of symptom perception: A psychometric approach. J Exp Psychopathol. 2018;9:jep.059716.
54. Weiss DS. The Impact of Event Scale: Revised. In: Wilson JP, Tang CS, editors. Cross-Cultural Assessment of Psychological Trauma and PTSD. Boston, MA: Springer US; 2007. p. 219–38.
55. Guest R, Tran Y, Gopinath B, Cameron ID, Craig A. Prevalence and psychometric screening for the detection of major depressive disorder and post-traumatic stress disorder in adults injured in a motor vehicle crash who are engaged in compensation. BMC Psychol. 2018;6:4.

56. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. Behav Res Ther. 2003;41:1489–96.
57. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care Lond Engl. 2020;24:647.
58. Akoglu H. User's guide to correlation coefficients. Turk J Emerg Med. 2018;18:91–3.
59. Brown TA. Confirmatory factor analysis for applied research. New York, NY, US: The Guilford Press; 2006.
60. Iacobucci D. Structural equations modeling: Fit Indices, sample size, and advanced topics. J Consum Psychol. 2010;20:90–8.
61. Hair JF, Anderson RE, Tatham RL, Black WC. Análisis multivariante. 2004.
62. Shah SMA, Mohammad D, Qureshi MFH, Abbas MZ, Aleem S. Prevalence, Psychological Responses and Associated Correlates of Depression, Anxiety and Stress in a Global Population, During the Coronavirus Disease (COVID-19) Pandemic. Community Ment Health J. 2021;57:101–10.
63. Wong JY-H, Fong DY-T, Chan KK-W. Anxiety and insomnia as modifiable risk factors for somatic symptoms in Chinese: a general population-based study. Qual Life Res. 2015;24:2493–8.
64. Basant MM. Revision Notes in Psychiatry. 2014;:204.
65. Nagarajan R, Krishnamoorthy Y, Basavarachar V, Dakshinamoorthy R. Prevalence of post-traumatic stress disorder among survivors of severe COVID-19 infections: A systematic review and meta-analysis. J Affect Disord. 2022;299:52–9.
66. Sun L, Yi B, Pan X, Wu L, Shang Z, Jia Y, et al. PTSD Symptoms and Sleep Quality of COVID-19 Patients During Hospitalization: An Observational Study from Two Centers. Nat Sci Sleep. 2021;13:1519–31.
67. Chen Y, Huang X, Zhang C, An Y, Liang Y, Yang Y, et al. Prevalence and predictors of posttraumatic stress disorder, depression and anxiety among hospitalized patients with coronavirus disease 2019 in China. Bmc Psychiatry. 2021;21:80.
68. Alimoradi Z, Broström A, Tsang HWH, Griffiths MD, Haghayegh S, Ohayon MM, et al. Sleep problems during COVID-19 pandemic and its' association to psychological distress: A systematic review and meta-analysis. EClinicalMedicine. 2021;36.
69. Villarreal-Zegarra D, Torres-Puente R, Alfaro SO, Al-kassab-Córdova A, de Castro JR, Mezones-Holguín E. Spanish version of Jenkins Sleep Scale in physicians and nurses: psychometric properties from a Peruvian nationally representative sample. J Psychosom Res. 2022;:110759.
70. Lin C-Y, Broström A, Griffiths MD, Pakpour AH. Investigating mediated effects of fear of COVID-19 and COVID-19 misunderstanding in the association between problematic social media use, psychological distress, and insomnia. Internet Interv. 2020;21:100345.
71. Kuriyama K, Soshi T, Kim Y. Sleep deprivation facilitates extinction of implicit fear generalization and physiological response to fear. Biol Psychiatry. 2010;68:991–8.

72. Zou S, Liu Z-H, Yan X, Wang H, Li Y, Xu X, et al. Prevalence and correlates of fatigue and its association with quality of life among clinically stable older psychiatric patients during the COVID-19 outbreak: a cross-sectional study. Glob Health. 2020;16:119.
73. Medeiros G, Beach S. Exacerbation of anxiety symptoms in the setting of COVID-19 pandemic: An overview and clinically-useful recommendations. 2021;48:69–70.
74. Caycho-Rodríguez T, Tomás JM, Vilca LW, Carbajal-León C, Cervigni M, Gallegos M, et al. Socio-Demographic Variables, Fear of COVID-19, Anxiety, and Depression: Prevalence, Relationships and Explanatory Model in the General Population of Seven Latin American Countries. Front Psychol. 2021;12.
75. Vilca LW, Chávez BV, Fernández YS, Caycho-Rodríguez T, White M. Impact of the fear of catching COVID-19 on mental health in undergraduate students: A Predictive Model for anxiety, depression, and insomnia. Curr Psychol N B NJ. 2022;:1–8.
76. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020;89:594–600.
77. Milrad SF, Hall DL, Jutagir DR, Lattie EG, Czaja SJ, Perdomo DM, et al. Depression, evening salivary cortisol and inflammation in chronic fatigue syndrome: A psychoneuroendocrinological structural regression model. Int J Psychophysiol. 2018;131:124–30.
78. Xu L, Pan Q, Lin R. Prevalence rate and influencing factors of preoperative anxiety and depression in gastric cancer patients in China: Preliminary study. J Int Med Res. 2016;44:377–88.
79. Liegey JS, Sagnier S, Debruxelles S, Poli M, Olindo S, Renou P, et al. Influence of inflammatory status in the acute phase of stroke on post-stroke depression. Rev Neurol (Paris). 2021;177:941–6.
80. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. J Neuroinflammation. 2013;10:43.
81. Chakrabarti S. Mental Health in Hospitalised COVID 19 Patients in Quarantine During Second Wave in a South Indian Private Teaching Hospital. J Multidiscip Healthc. 2021;14:2777–89.
82. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis. 2020;96:467–74.
83. Anyan F, Worsley L, Hjemdal O. Anxiety symptoms mediate the relationship between exposure to stressful negative life events and depressive symptoms: A conditional process modelling of the protective effects of resilience. Asian J Psychiatry. 2017;29:41–8.
84. Nima AA, Rosenberg P, Archer T, Garcia D. Anxiety, affect, self-esteem, and stress: mediation and moderation effects on depression. PloS One. 2013;8:e73265.
85. Kessler RC, Wang PS. The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu Rev Public Health. 2008;29:115–29.
86. Janiri D, Carfì A, Kotzalidis GD, Bernabei R, Landi F, Sani G, et al. Posttraumatic Stress Disorder in Patients After Severe COVID-19 Infection. JAMA Psychiatry. 2021;78:567–9.

87. Ripon RK, Mim SS, Puente AE, Hossain S, Babor MdMH, Sohan SA, et al. COVID-19: psychological effects on a COVID-19 quarantined population in Bangladesh. Heliyon. 2020;6:e05481.
88. KetchesonFelicia, St C, KingLisa, Don R. Influence of PTSD and MDD on somatic symptoms in treatment-seeking military members and Veterans. J Mil Veteran Fam Health. 2018. https://doi.org/10.3138/jmvfh.2017-0029.
89. McFarlane ACAO, Graham K. The ambivalence about accepting the prevalence somatic symptoms in PTSD: Is PTSD a somatic disorder? J Psychiatr Res. 2021;143:388–94.
90. Ipsos. One year of COVID-19. 2021. https://www.ipsos.com/sites/default/files/ct/news/documents/2021-04/wef_-_expectations_about_when_life_will_return_to_pre-covid_normal_-final.pdf.
91. Antiporta DA, Cutipé YL, Mendoza M, Celentano DD, Stuart EA, Bruni A. Depressive symptoms among Peruvian adult residents amidst a National Lockdown during the COVID-19 pandemic. BMC Psychiatry. 2021;21:111.
92. Kim J, Seo YE, Sung HK, Park HY, Han MH, Lee SH. Predictors of the Development of Mental Disorders in Hospitalized COVID-19 Patients without Previous Psychiatric History: A Single-Center Retrospective Study in South Korea. Int J Environ Res Public Health. 2022;19:1092.
93. Kim J-W, Stewart R, Kang S-J, Jung S-I, Kim S-W, Kim J-M. Telephone based Interventions for Psychological Problems in Hospital Isolated Patients with COVID-19. Clin Psychopharmacol Neurosci. 2020;18:616–20.
94. Tausch A, e Souza RO, Viciana CM, Cayetano C, Barbosa J, Hennis AJ. Strengthening mental health responses to COVID-19 in the Americas: A health policy analysis and recommendations. Lancet Reg Health - Am. 2022;5:100118.
95. Freyhofer S, Ziegler N, de Jong EM, Schippers MC. Depression and Anxiety in Times of COVID-19: How Coping Strategies and Loneliness Relate to Mental Health Outcomes and Academic Performance. Front Psychol. 2021;12:682684.
96. Ouanes S, Al-Amin H, Hussein NB, Khan F, Al Shahrani A, David P, et al. Physical and Psychosocial Well-Being of Hospitalized and Non-Hospitalized Patients With COVID-19 Compared to the General Population in Qatar. Front Psychiatry. 2021;12:792058.

Figures

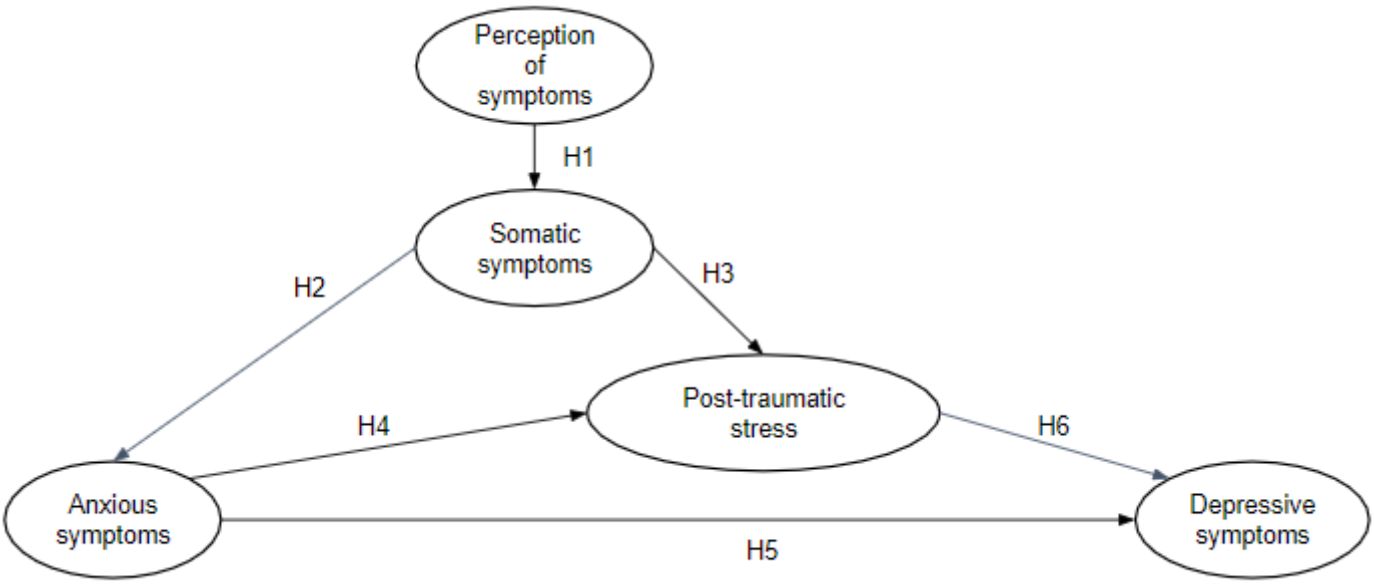

Figure 1

Model tested using structural equation modeling (SEM).

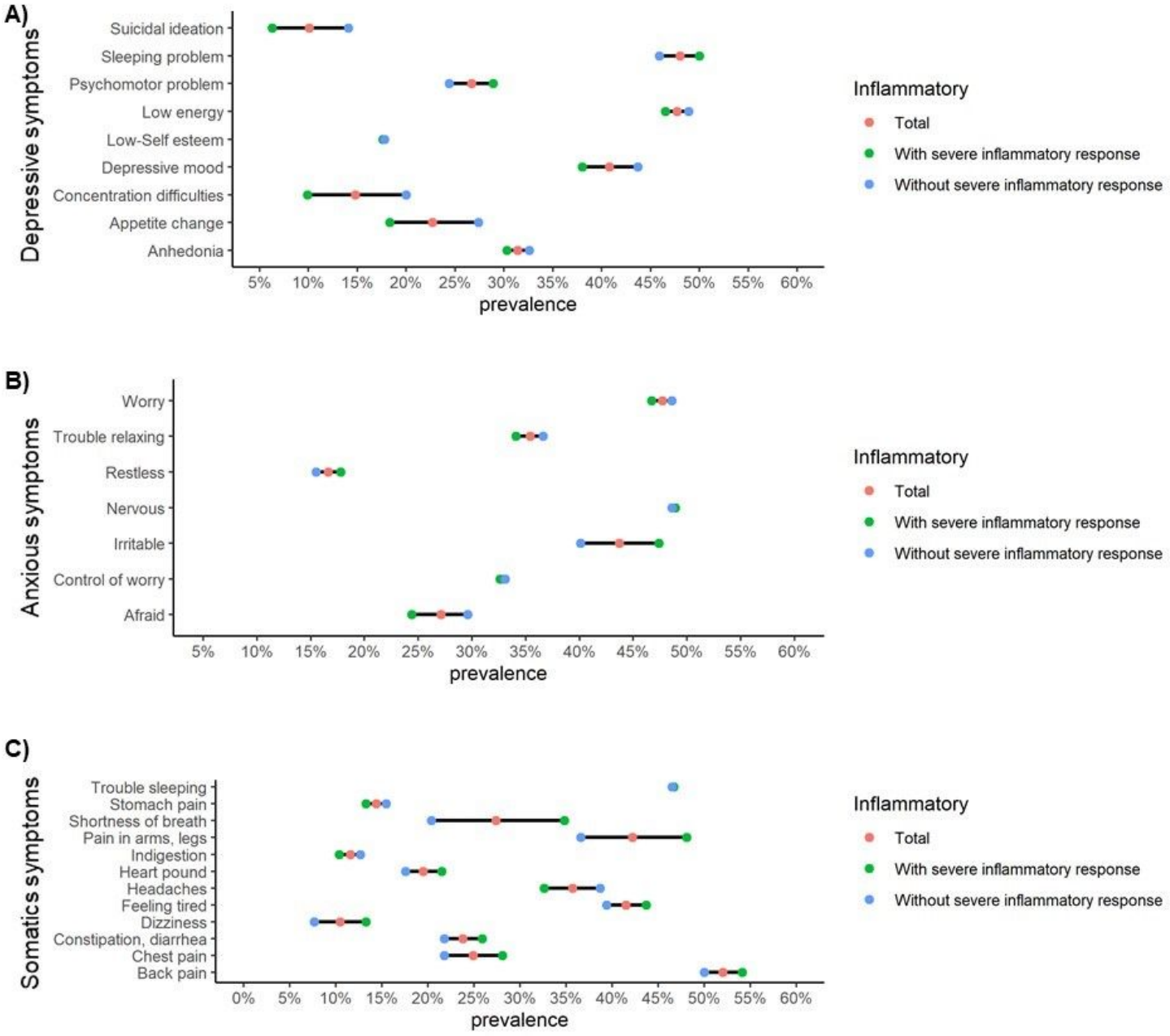

Figure 2

Prevalence of clinical indicators of depression, anxiety and psychosomatic symptoms.

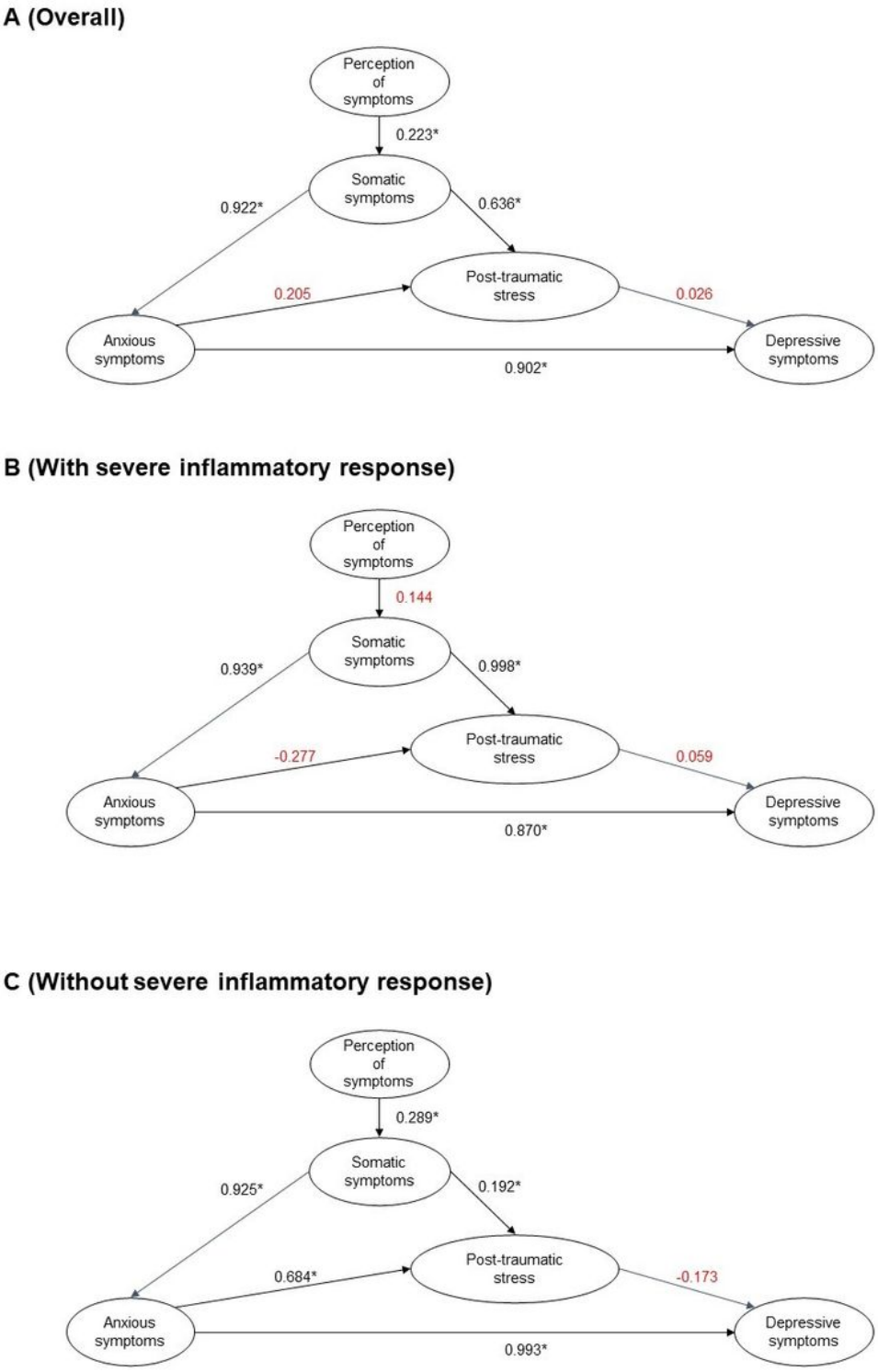

Figure 3

Path Analysis.

Note: A) Overall participant. B) Participants with severe inflammatory response. C) Participants without severe inflammatory response. The model was estimated with the WLSMV method. *p < 0.05. Values in red are not significant.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial1.pdf