



Clinical risk factors of long-term post-traumatic stress symptoms, anxiety, and depression in COVID-19 survivors

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Received: 16 April 2024 / Accepted: 20 November 2024 / Published online: 23 December 2024
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Abstract

The COVID-19 pandemic has a profound and lasting impact on the mental health of recovered individuals. To investigate the clinical risk factors associated with long-term post-traumatic stress symptoms (PTSS), anxiety, and depression in COVID-19 survivors, demographic information and medical records were collected during February 19 and March 20, 2020. Assessments of PTSS, anxiety, and depressive symptoms were conducted at two months (April to May 2020, Session 1) and two years (April to May 2022, Session 2) post-discharge. Session 1 included 127 survivors who were infected with the early strains of SARS-CoV-2, and 54 of these participants took part in Session 2. PTSS (median: Session 1 = 9, Session 2 = 7; $p = 0.522$) and depression (median: Session 1 = 5, Session 2 = 4; $p = 0.127$) remained unchanged over the two years following COVID-19 infection, while anxiety (median: Session 1 = 5, Session 2 = 2; $p < 0.001$) significantly decreased at the two-year mark. Severe COVID-19 symptoms were consistently identified as significant risk factors for depression at both time points (Session 1: dyspnea [$\beta = -0.268$, $p = 0.016$], nausea or vomiting [$\beta = 0.239$, $p = 0.031$]; Session 2: headache [$\beta = 0.414$, $p = 0.014$]). They also emerged as risk factors for PTSS and anxiety at the two-month mark (PTSS: cough [$\beta = -0.334$, $p = 0.002$]; anxiety: continued oxygen therapy [$\beta = 0.343$, $p = 0.002$], cough [$\beta = -0.267$, $p = 0.013$]). At the two-year mark, blood sample characteristics were identified as risk factors for PTSS (albumin: $\beta = 0.455$, $p = 0.010$), anxiety (total bilirubin: $\beta = 0.440$, $p = 0.013$), and depression (total bilirubin: $\beta = 0.386$, $p = 0.021$). Mann-Whitney U-tests showed that female survivors had higher anxiety ($p = 0.012$) and depression ($p = 0.046$) levels than males at the two-month mark. The sample size was relatively small, and further investigation is needed to determine whether our findings can be directly applied to other samples, including those involving different variants of SARS-CoV-2. Our study may highlight the differences between short-term and long-term clinical risk factors for PTSS, anxiety, and depression in COVID-19 survivors. The identified predictors could provide valuable insights for tailoring interventions to improve the PTSS, anxiety, and depression outcomes at different stages of recovery in COVID-19 survivors.

Keywords COVID-19 · Post-traumatic stress symptom · Anxiety · Depression · Risk factor

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a global health crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Alongside the physical challenges faced by individuals infected with COVID-19 [18], there is a significant burden of mental health problems, including post-traumatic stress symptoms (PTSS), anxiety, and depression [10, 23]. Research indicates that these mental health issues can persist for months to years even after recovering from COVID-19 [4, 11, 17, 28, 29]. While the severity of these issues may decrease over time following acute COVID-19, a significant proportion of

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survivors continue to experience a high burden of physical or mental sequelae for at least 12 months [29, 32]. In particular, female survivors have been found to exhibit higher levels of PTSS and depression compared to female controls for up to two years [4]. This underscores the critical need to identify risk factors associated with PTSS, anxiety, and depression in COVID-19 patients at different stages of recovery. Identifying these factors not only aids in developing effective interventions to mitigate the psychological risk associated with COVID-19 but also provides valuable guidance for addressing similar mental health problems in future disease outbreaks.

Several risk factors have been reported in relation to PTSS, anxiety, and depression due to COVID-19. These include demographic factors like age and sex, lifestyle habits like smoking and alcohol consumption, past traumatic experiences, COVID-19 severity (e.g., pulmonary inflammation, COVID-19-related symptoms, and treatments), and comorbidities (e.g., hypertension and diabetes) [4, 15, 26, 27, 30, 31]. However, since most studies have focused on risk factors within the first 12 months post-infection, there is a relative paucity of research on long-term risk factors (e.g., 2 years post-infection). Notably, the long-term risk factors may differ from the short-term risk factors.

To address this gap, we conducted a longitudinal cohort study to investigate the potential clinical risk factors associated with the long-term (> 2 years) PTSS, anxiety, and depression and compare them with the short-term (~2 months) risk factors following the acute phase of COVID-19 infection in discharged patients. The study enrolled individuals who had recovered from COVID-19 between February 29 and March 20, 2020. Demographic information and medical records during hospitalization (including vital signs, peripheral blood samples, physical health condition, diagnosis of pulmonary inflammation, the severity of COVID-19 symptoms, COVID-19-related symptoms and treatments, comorbidities, and hospitalization duration) were collected. Additionally, mental health status (i.e., PTSS, anxiety, and depression) and their clinical risk factors were assessed at two months and two years after discharge.

Methods

Subjects

All participants were COVID-19 survivors who had been discharged from the hospital between February 29 and March 20, 2020, in Wuhan, China. The study was approved by the Ethics Committee of the Institutional Review Board at the Guanggu Branch of Hubei Maternal and Child Health Care Hospital and was conducted in accordance with the

Declaration of Helsinki. Informed consent was obtained from all participants, and we assured participants that their personal information would remain confidential. The inclusion criteria were as follows: patients who survived for at least two months after hospital discharge, aged 18 years or older, and had been hospitalized for a minimum of 24 hours primarily due to COVID-19. Exclusion criteria included patients who were lost of follow-up within two months after discharge. Medical charts of patients were reviewed to ensure that they met the eligibility criteria.

Hospitalization

Demographics, vital signs, peripheral blood samples taken upon admission, physical conditions, severity of COVID-19 symptoms, symptoms experienced, treatments received, diagnosis based on chest computed tomography (CT) scans, comorbidities, and duration of hospitalization were collected from medical records during hospitalization (February 19 and March 20, 2020; Tables 1 and 2). The duration between hospital discharge and follow-up was recorded for each participant.

Psychological assessments

At two months (April to May 2020, Session 1) and two years (April to May 2022, Session 2) after hospital discharge, patients were contacted via telephone by interviewers and asked to complete a series of online self-reported questionnaires assessing their PTSS, anxiety, and depressive symptoms. Specifically, PTSS was measured using a post-traumatic stress disorder checklist for DSM-5 (PCL-5) [5], consisting of 20 questions rated on a 5-point Likert scale [0–4], with a cutoff value of ≥ 31 indicating the presence of post-traumatic stress disorder symptoms. Anxiety was assessed using the General Anxiety Disorder-7 (GAD-7) [24], comprising 7 items rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). Cutoff scores of 5, 10, and 15 were used to indicate mild, moderate, and severe anxiety, respectively. Depression was evaluated using the Patient Health Questionnaire-9 (PHQ-9) [14], which includes 9 questions rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). Cutoff scores of 5, 10, 15, and 20 were used to indicate mild, moderate, moderately severe, and severe depression, respectively.

Statistical analysis

The normality of the data was assessed using Shapiro-Wilk tests. For variables with skewed distributions, nonparametric methods such as Mann-Whitney U-tests and Spearman

Table 1 Baseline characteristics of COVID-19 survivors who completed the two-month and two-year follow-up assessments

	Session 1 (<i>n</i> = 127)	Session 2 (<i>n</i> = 54)
Demographics		
Age at discharge, y	53 (44–64)	49 (35–57)
Sex		
Women	87 (68.5)	34 (63.0)
Men	40 (31.5)	20 (37.0)
Weight, mean (SD), kg	61 (55–70)	62 (56–72)
Height, cm	162 (158–164)	163 (159–164.75)
Vital Sign Records at admission		
Body temperature, °C	36.4 (36.2–36.8)	36.5 (36.3–36.8)
Peak body temperature during hospitalization, °C	37.1 (36.9–37.4)	37.1 (36.9–37.2)
≤ 37.2	88 (69.3)	42 (77.8)
37.3–38.0	35 (27.6)	10 (18.5)
38.1–39.0	1 (0.8)	1 (1.9)
≥ 39.1	3 (2.4)	1 (1.9)
Number of days with a body temperature greater than 37.2 °C, d	0 (0–1)	0 (0–0)
Heart rate, bpm	86 (78–98)	86.5 (78–100)
Respiratory frequency, times/min	20 (18–20)	20 (18–20)
Blood oxygen saturation, %	98 (97–98.75)	98 (97–99)
Systolic pressure, mmHg	132 (120–141)	128.5 (115–139)
Diastolic pressure, mmHg	83 (76–91)	83 (76–90)
Usual Physical Condition before admission		
Excellent	11 (8.7)	8 (14.8)
General	115 (90.5)	45 (83.3)
Poor	1 (0.8)	1 (1.9)
Severity of COVID-19 during hospital stay		
Asymptomatic or presymptomatic infection	0 (0)	0 (0)
Mild illness	1 (0.8)	0 (0)
Moderate illness	115 (90.5)	52 (96.3)
Severe illness	11 (8.7)	2 (3.7)
Critical illness	0 (0)	0 (0)
Symptoms at admission		
Cough	89 (70.1)	41 (75.9)
Fever	84 (66.1)	36 (66.7)
Insomnia	67 (52.8)	27 (50.0)
Low vitality	66 (52.0)	29 (53.7)
Loss of appetite	65 (51.2)	27 (50.0)
Fatigue	64 (50.4)	29 (53.7)
Dyspnea	52 (41.0)	21 (38.9)
Muscle soreness	47 (37.0)	22 (40.7)
Expectoration	24 (18.9)	11 (20.4)
Chest pain	12 (9.4)	6 (11.1)
Headache	7 (5.5)	2 (3.7)
Nausea or vomiting	3 (2.4)	2 (3.7)
Diarrhea	8 (6.3)	3 (5.6)
Hemoptysis	2 (1.6)	2 (3.7)
Incontinence	1 (0.8)	0 (0)
Chest CT scan during hospital stay		
Abnormality in lung CT scan	121 (95.3)	51 (94.4)
Persistent ground-glass opacities	27 (21.3)	12 (22.2)
Pleural thickening	23 (18.1)	4 (7.4)
Lung fibrotic lesions	9 (7.1)	2 (3.7)
Treatments received during hospital stay		
Arbidol hydrochloride tablets	83 (65.4)	33 (61.1)
Continued oxygen therapy	38 (29.9)	15 (27.8)
Comorbidities at admission		

Table 1 (continued)

	Session 1 (<i>n</i> = 127)	Session 2 (<i>n</i> = 54)
Demographics		
Hypertension	32 (25.2)	9 (16.7)
Diabetes mellitus	13 (10.2)	2 (3.7)
Coronary heart disease	7 (5.5)	1 (1.9)
Respiratory disease	7 (5.5)	1 (1.9)
Thyroiditis	4 (3.1)	0 (0)
Reproductive system disease	3 (2.4)	2 (3.7)
Digestive Disorder	3 (2.4)	2 (3.7)
Cancer	1 (0.8)	0 (0)
Cerebral infarction	1 (0.8)	0 (0)
Total duration of hospitalization, median (IQR), d	13 (9–17)	11.5 (9–17)
Time from hospital discharge to follow-up, median (IQR), d	53 (39–62)	758 (750–763)

Data are median (IQR) and *n*/total (%)

Table 2 Post-traumatic stress symptoms, anxiety, and depression in COVID-19 survivors

	Session 1 (<i>n</i> = 127)	Session 1 (<i>n</i> = 54) ^a	Ses- sion 2 (<i>n</i> = 54) ^a	<i>p</i> value
PTSS				
PCL-5 scores	9 (3.25–15.75)	8.5 (3–13)	7 (3–14)	0.522 ^b
≥ 31	8 (6.3)	3 (5.6)	2 (3.7)	1.000 ^c
Anxiety				
GAD-7 scores	5 (1–7)	4.5 (1–7)	2 (0–5)	<0.001 ^b
0–4 (none)	60 (47.2)	27 (50.0)	37 (68.5)	0.031 ^c
5–9 (mild)	47 (37.0)	21 (38.9)	16 (29.6)	0.359 ^c
10–14 (moderate)	15 (11.8)	4 (7.4)	1 (1.9)	0.375 ^c
15–21 (severe)	5 (3.9)	2 (3.7)	0 (0)	
Depression				
PHQ-9 scores	5 (2–9)	5 (2–8)	4 (1–8)	0.127 ^b
0–4 (none)	57 (44.9)	23 (42.6)	28 (51.9)	0.383 ^c
5–9 (mild)	42 (33.1)	22 (40.7)	18 (33.3)	0.541 ^c
10–14 (moderate)	20 (15.7)	7 (13.0)	6 (11.1)	1.000 ^c
15–19 (moderately severe)	6 (4.7)	1 (1.9)	2 (3.7)	1.000 ^c
≥ 20 (severe)	2 (1.6)	1 (1.9)	0 (0)	

^a Fifty-four patients completed all assessments during both the two-month and two-year follow-up periods. ^b Paired-sample *t*-tests were conducted to analyze changes in PTSS, anxiety, and depression over time, as assessed by the total scores of the PCL-5, GAD-7, and PHQ-9 in 54 patients. ^c McNemar's tests were employed to examine the differences in PTSS, anxiety, and depression across different severity levels between two time points in 54 patients. Data are median (IQR) or *n* (%), where *n* is the total number of patients with available data. Abbreviations: PTSS, post-traumatic stress symptom; PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9

rank correlation analyses were employed. Parametric methods, including independent-samples *t*-tests, Welch's *t*-tests, and Pearson correlation analyses, were utilized for normally distributed variables. The results indicated that PCL-5, GAD-7, and PHQ-9 scores exhibited skewed distributions (all $p < 0.001$). Therefore, Mann-Whitney *U*-tests were

employed to examine the impact of sex, physical conditions, lung CT scan abnormalities, COVID-19-related symptoms, treatments, and comorbidities on PTSS, anxiety, and depression. Spearman rank correlation analyses were performed to assess the association between PTSS, anxiety, and depression (i.e., PCL-5, GAD-7, and PHQ-9 scores) and each potential independent variable recorded during hospitalization (e.g., age, weight, height, vital signs, blood sample variables, hospitalization duration, and time between hospital discharge and follow-up) for each session. Paired-sample *t*-tests were conducted to evaluate changes in PTSS, anxiety, and depression over time, as assessed by the total scores of the PCL-5, GAD-7, and PHQ-9 in 54 patients. Additionally, McNemar's tests were employed to examine differences in PTSS, anxiety, and depression across different severity levels between the two time points in these patients. All statistical analyses were performed using R statistical package version 4.2.1 (R Foundation for Statistical Computing).

Multiple linear regression analyses

To explore the potential risk factors of PTSS, anxiety, and depression, we conducted multiple linear regression analyses at each time point. These analyses assessed the impact of all collected variables—including demographic information, medical records during hospitalization, and the time elapsed between hospital discharge and follow-up—on the PCL-5, GAD-7, and PHQ-9 scores among COVID-19 survivors. Please note that activated partial thromboplastin time and fasting blood glucose were excluded from the regression analyses due to excessive missing values (> 25% of the total sample) at both time points. The regression analyses were carried out in SPSS 25.0 (SPSS Inc., New York, USA).

Results

Participants and follow-up information

A total of 1144 patients diagnosed with COVID-19 were discharged from hospital in Wuhan, China between February 29 and March 20, 2020. Out of these patients, 127 patients completed the assessment at the two-month follow-up (i.e., Session 1), while 54 patients completed the assessment at the two-year follow-up (i.e., Session 2) (Fig. 1). The demographic and clinical characteristics of these patients are shown in Table 1. The median duration of follow-up after hospital discharge was 53 days (interquartile range [IQR], 39 to 62) for the two-month assessment and 758 days (IQR, 750 to 763) for the two-year assessment. The median duration of hospitalization was 13 days (IQR, 9 to 17) for the participants assessed at two months and 11.5 days (IQR, 9 to 17) for those assessed at two years.

Blood sample characteristics

Upon admission, the blood counts of certain patients in both session 1 and session 2 exhibited abnormalities, including lower white blood cells, reduced Lymphopenia, elevated levels of Aspartate aminotransferase levels, and higher Hypersensitive troponin I. The majority of patients exhibited normal serum levels for other blood immune indexes (Supplementary Table 1).

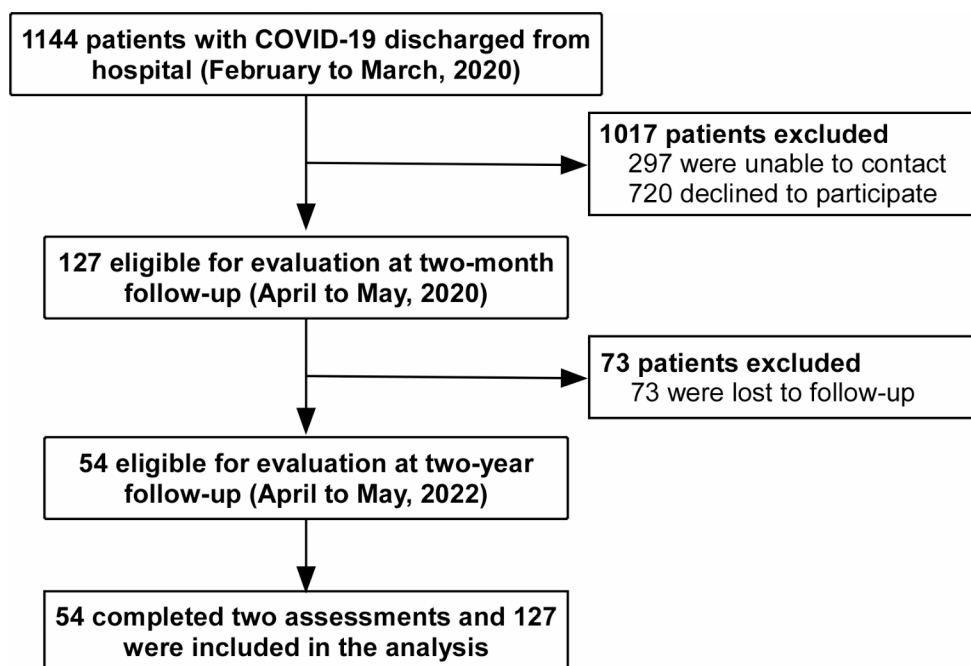
COVID-19 severity, symptoms, and treatments

Table 1 displays the categorization of COVID-19 patients based on the severity of their symptoms, ranging from mild to moderate and severe illness. The predominant symptoms associated with COVID-19 comprised cough, fever, insomnia, low vitality, loss of appetite, fatigue, and dyspnea. Less commonly reported symptoms included muscle soreness, expectoration, chest pain, headache, nausea or vomiting, diarrhea, hemoptysis, and incontinence. Chest CT scans revealed lung abnormalities, including ground-glass opacities, pleural thickening, fibrotic lesions, and other manifestations. In terms of treatment, patients underwent antiviral therapy (i.e., arbidol hydrochloride tablets) and/or received oxygen therapy. Notably, a considerable number of patients presented comorbid conditions, such as hypertension, diabetes mellitus, coronary heart disease, respiratory diseases, and others.

PTSS, anxiety, and Depression Changes over Time

No significant differences in PCL-5 and PHQ-9 scores were observed between sessions (Table 2; Fig. 2). However, GAD-7 scores exhibited a notable reduction in Session 2 compared to Session 1 (Table 2; Fig. 2). Concerning post-traumatic stress disorder symptoms, 8 (6.3%) out of 127 patients experienced such symptoms in Session 1, with this proportion slightly decreasing to 2 (3.7%) out of 54 patients in Session 2 ($p=1.000$). Regarding anxiety symptoms, 67 (52.8%) out of 127 patients reported mild to severe anxiety symptoms in Session 1, and this proportion decreased to 17 (31.5%) out of 54 patients in Session 2 ($p=0.031$). In terms

Fig. 1 Study flowchart. Out of 1144 patients with COVID-19 discharged from the hospital between February 29 and March 20, 2020, 127 patients completed the assessment at the two-month follow-up, while 54 patients completed the assessment at the two-year follow-up



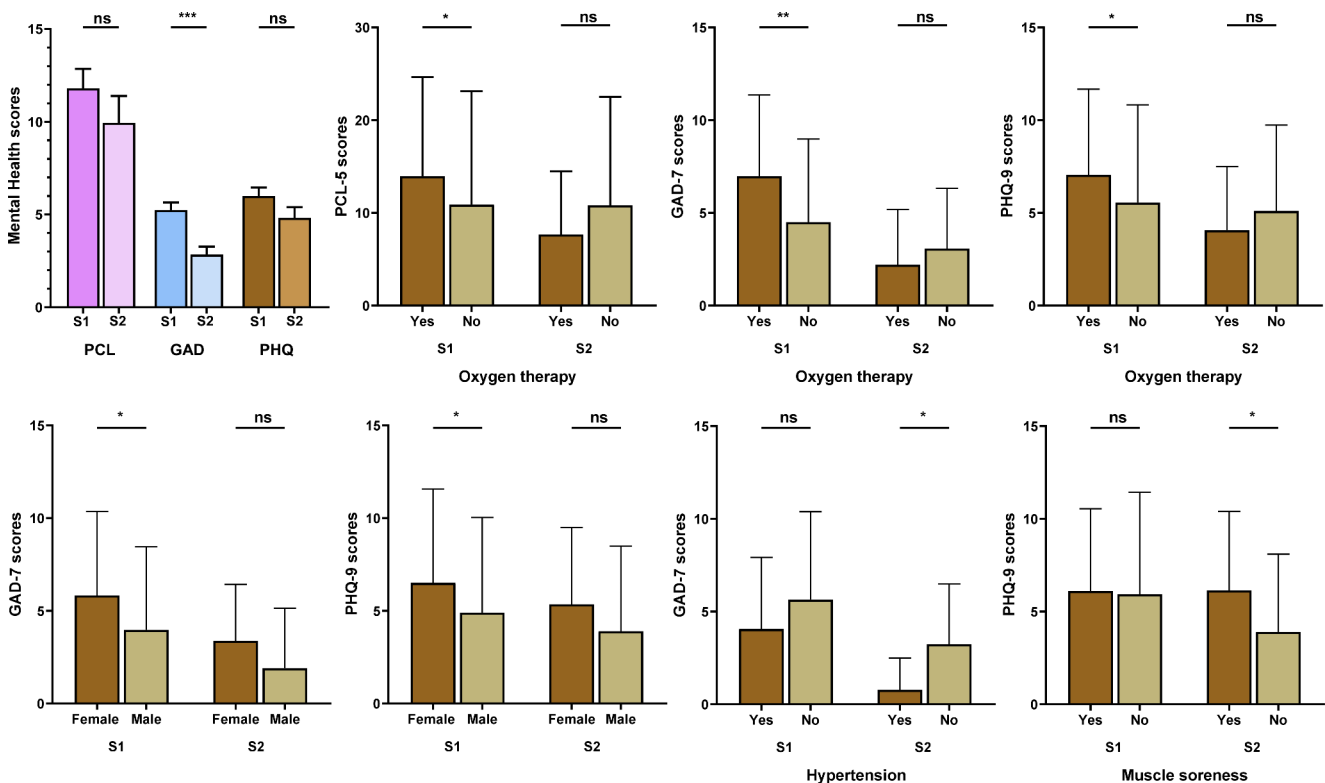


Fig. 2 Results for Mann-Whitney U-tests. PTSS and depression scores remained unchanged within two years after acute COVID-19 infection, while anxiety scores decreased at the two-year mark after discharge. At two months post-hospital discharge (i.e., S1), survivors who received oxygen therapy reported higher levels of PTSS (i.e., PCL-5), anxiety (i.e., GAD-7), and depression (i.e., PHQ-9) than patients who did not receive oxygen therapy. Females had higher levels of anxiety

of depression symptoms, 70 (55.1%) out of 127 patients exhibited mild to severe depression symptoms in Session 1, and this proportion decreased slightly to 26 (48.1%) out of 54 patients in Session 2 ($p=0.383$; Table 2).

Variables Associated with PTSS, anxiety, and depression

For PTSS, Mann-Whitney U-tests showed that COVID-19 patients who received oxygen therapy reported higher PCL-5 scores than patients who did not receive oxygen therapy in Session 1 ($U(N_{\text{receive}}=38, N_{\text{non-receive}}=89)=1260.5$, $z=-2.27$, $p=0.023$; Fig. 2). Correlation results showed that the PCL-5 scores were significantly positively correlated with the duration between discharge and the date of participating in Session 1 ($r(127)=0.276$, $p=0.002$; Fig. 3). For anxiety, Mann-Whitney U-tests showed that females and patients who received oxygen therapy had higher levels of GAD-7 scores than males ($U(N_{\text{female}}=87, N_{\text{male}}=40)=1259.0$, $z=-2.51$, $p=0.012$) and patients who did not receive oxygen therapy ($U(N_{\text{receive}}=38, N_{\text{non-receive}}=89)=1105.5$, $z=-3.10$, $p=0.002$) respectively in Session

and depression than males. At two years post-hospital discharge (i.e., S2), survivors with hypertension had lower anxiety scores. Having COVID-19-related symptom (i.e., muscle soreness) was associated with higher PHQ-9 scores. Abbreviations: PTSS, post-traumatic stress symptom; PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

1. Patients with hypertension had lower anxiety scores than those without hypertension in Session 2 ($U(N_{\text{hypertension}}=9, N_{\text{non-hypertension}}=45)=109.5$, $z=-2.27$, $p=0.024$; Fig. 2). Correlation results showed that activated partial thromboplastin time ($r(31)=-0.365$, $p=0.044$), total ($r(50)=0.349$, $p=0.013$) and direct bilirubin levels ($r(50)=0.281$, $p=0.048$) were significantly correlated with GAD-7 scores in Session 2 (Fig. 3). For depression, Mann-Whitney U-tests showed that females and patients who received oxygen therapy had higher depression scores in Session 1 than males ($U(N_{\text{female}}=87, N_{\text{male}}=40)=1357.5$, $z=-1.99$, $p=0.046$) and patients who did not receive oxygen therapy ($U(N_{\text{receive}}=38, N_{\text{non-receive}}=89)=1315.0$, $z=-1.99$, $p=0.047$), respectively (Fig. 2). Having COVID-19-related symptom (i.e., muscle soreness) were associated with higher PHQ-9 scores in Session 2 ($U(N_{\text{muscle soreness}}=22, N_{\text{non-muscle soreness}}=32)=238.5$, $z=-2.01$, $p=0.044$; Fig. 2). Correlation results showed that total ($r(50)=0.369$, $p=0.008$) and direct bilirubin levels ($r(50)=0.346$, $p=0.014$) were significantly positively correlated with PHQ-9 scores in Session 2 (Fig. 3).

At two months post-hospital discharge (Table 3), multiple linear regression results indicated that the time from

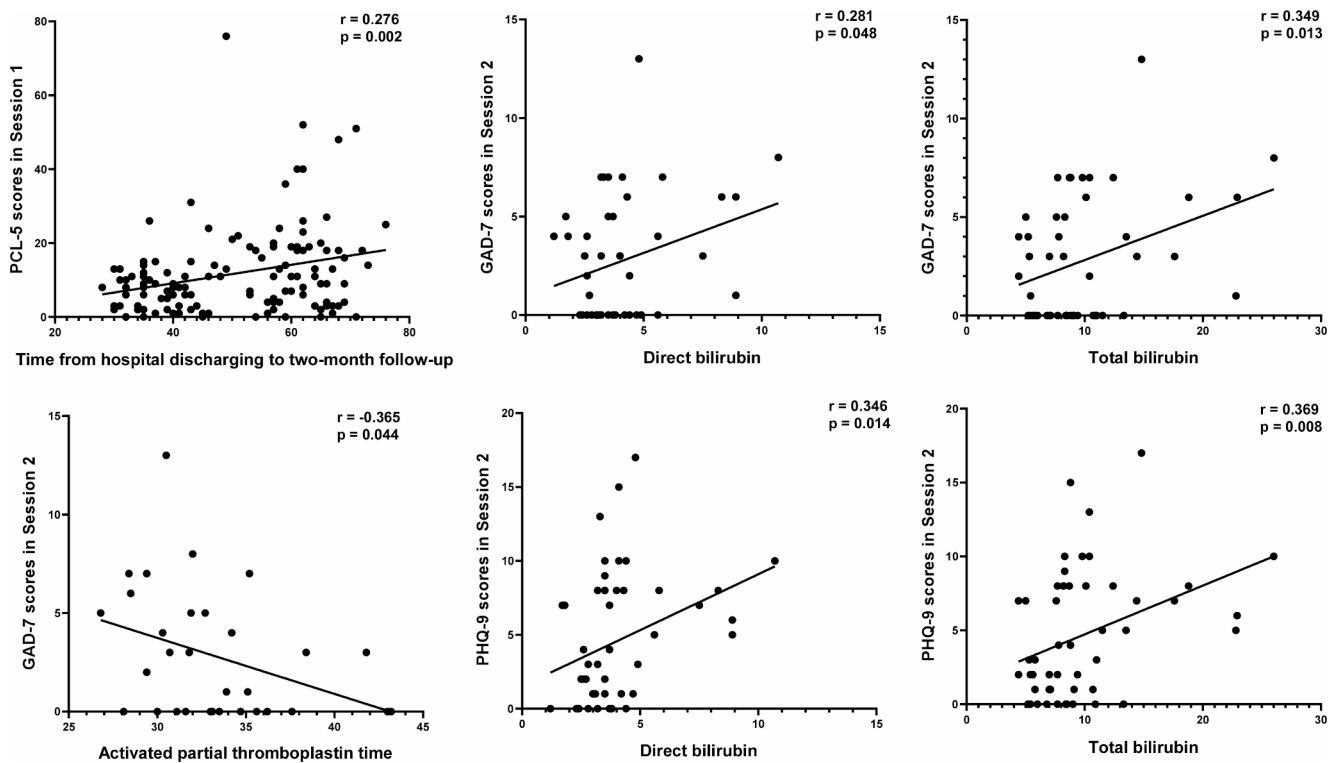


Fig. 3 Correlation results. At two months post-hospital discharge (i.e., Session 1), PTSS (i.e., PCL-5) were significantly positively correlated with the time from hospital discharge to two-month follow-up. At two years post-hospital discharge (i.e., Session 2), total and direct bilirubin levels were positively correlated with anxiety (i.e., GAD-7) and

depression (i.e., PHQ-9). Activated partial thromboplastin time was negatively correlated with anxiety. Abbreviations: PTSS, post-traumatic stress symptom; PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9

hospital discharge to follow-up, cough, and Immunoglobulin G were significant risk factors for PCL-5 scores, explaining 19.6% of the variance (adjusted $R^2=0.196$, $F(3, 76)=7.185$, $p<0.001$). For GAD-7 scores, continued oxygen therapy and cough were identified as significant risk factors, accounting for 16.5% of the variance (adjusted $R^2=0.165$, $F(2, 76)=8.527$, $p<0.001$). Dyspnea and nausea or vomiting were significant risk factors for PHQ-9 scores, explaining 10.3% of the variance (adjusted $R^2=0.103$, $F(2, 76)=5.373$, $p=0.007$).

At two years post-hospital discharge (Table 3), multiple linear regression results revealed that albumin was a significant risk factor for PCL-5 scores, explaining 17.9% of the variance (adjusted $R^2=0.179$, $F(1, 30)=7.556$, $p=0.010$). Total bilirubin was a significant risk factor for GAD-7 scores, accounting for 16.6% of the variance (adjusted $R^2=0.166$, $F(1, 30)=6.982$, $p=0.013$). For PHQ-9 scores, headache and total bilirubin were significant risk factors, explaining 25.6% of the variance (adjusted $R^2=0.256$, $F(2, 30)=6.153$, $p=0.006$).

Discussion

In the present study, we evaluated the longitudinal changes in PTSS, anxiety, and depression among COVID-19 survivors and examined their potential clinical risk factors. We observed that the scores for PTSS and depression did not change significantly within two years after acute COVID-19 infection, while anxiety scores decreased significantly at the two-year mark after discharge. Notably, the experience of severe COVID-19 symptoms consistently emerged as significant risk factors for depression at both two months and two years after hospital discharge, and for PTSS and anxiety at the two-month mark. Additionally, blood sample characteristics were identified as risk factors for PTSS, anxiety, and depression at the two-year post-hospital discharge point. These findings highlighted the differences of short-term and long-term clinical risk factors of PTSS, anxiety, and depression in COVID-19 survivors.

Previous studies have reported that individuals who survived COVID-19 experienced higher levels of PTSS, anxiety, and depression compared to those who were not infected with COVID-19 at the two-month mark following the acute infection [25]. Moreover, a positive correlation between PTSS scores and the time between discharge and

Table 3 Significant variables included in the multiple linear regression analyses for predicting PCL-5, GAD-7, and PHQ-9 scores across two sessions

Sessions				
Model		Beta	<i>p</i> value	<i>R</i> ²
Session 1				
PCL-5	Constant		0.609	0.196^{***}
	Time from hospital discharge to follow-up	0.307	0.005	
	Cough	-0.334	0.002	
	Immunoglobulin G	0.253	0.017	
GAD-7	Constant		<0.001	0.165^{***}
	Continued oxygen therapy	0.343	0.002	
	Cough	-0.267	0.013	
PHQ-9	Constant		<0.001	0.103^{**}
	Dyspnea	-0.268	0.016	
	Nausea or vomiting	0.239	0.031	
Session 2				
PCL-5	Constant		0.028	0.179^{**}
	Albumin	0.455	0.010	
GAD-7	Constant		0.999	0.166[*]
	Total bilirubin	0.440	0.013	
PHQ-9	Constant		0.484	0.256^{**}
	Headache	0.414	0.014	
	Total bilirubin	0.386	0.021	

Beta values represent standardized betas. R² values represent adjusted R² values, which explained the variance expressed by the model. *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$

the two-month follow-up has been reported, suggesting that the immediate period after recovering from COVID-19 may be a critical time for triggering PTSS. Our findings indicate that the COVID-19 survivors continue to experience elevated levels of PTSS and depression over the two years after acute COVID-19 infection. Interestingly, we observed that female survivors had higher anxiety and depression levels than males at two months post-discharge. This observation aligns with previous studies extensively reporting higher self-reported levels of mental health issues, including stress, anxiety, and depression, among females [9, 22]. Therefore, it is crucial to pay attention to the mental well-being of COVID-19 survivors post-discharge, especially female survivors in the early stages following their discharge, as this will yield long-term benefits [12].

In exploring the risk factors associated with the PTSS, anxiety, and depression of COVID-19 survivors, we observed the following findings. First, factors such as COVID-19 severity, higher Immunoglobulin G levels, and time elapsed since discharge were predictive of PTSS two months after discharge. Additionally, blood sample characteristics (i.e., higher albumin level) were predictive of PTSS two years post-discharge. Second, COVID-19 severity (i.e., continued oxygen therapy and cough) was a predictor of anxiety two months after discharge. Higher total bilirubin level in blood samples was predictive of anxiety

two years post-discharge. Third, COVID-19 severity was a predictor of depression both two months and two years after discharge, with higher total bilirubin levels also predicting depression at the two-year mark. Collectively, experiencing severe COVID-19 symptoms emerged as a key risk factor for PTSS, anxiety, and depression at two months after hospital discharge. In contrast, blood sample characteristics were prominent risk factors for these conditions two years post-discharge. These findings suggest a dynamic evolution in the factors influencing this mental health status over the long term. This dynamic nature emphasizes the importance of considering evolving factors in the development of targeted interventions for mental health in individuals recovering from COVID-19.

In line with previous studies [19], our findings indicate that the severity of COVID-19 symptoms is primarily predictive of PTSS, anxiety, and depression at two months post-discharge among survivors. Common symptoms reported by COVID-19 survivors included cough, headache, fever, insomnia, low vitality, loss of appetite, and fatigue [6, 8]. When examining the association between COVID-19 symptoms and PTSS, anxiety, and depression, we found that the severity of cough was a predictor for PTSS and anxiety at the two-month follow-up. Additionally, survivors who experienced nausea or vomiting had higher depression scores two months post-discharge, while those who had headaches showed elevated depression scores at the two-year follow-up. Muscle soreness during their hospitalization was also associated with higher depression scores at two-year follow-up. Notably, our study revealed that survivors who received treatments (i.e., oxygen therapy) exhibited elevated levels of PTSS, anxiety, and depression at two months post-discharge. This finding aligns with prior research suggesting that COVID-19 patients who underwent treatments like orotracheal intubation or were admitted to intensive care units were more susceptible to developing PTSD, anxiety, and depression [2]. These results suggest that individuals with more severe COVID-19 symptoms, who normally required more treatments during their hospital stay, were at a higher risk of developing long-term mental health problems.

We observed that the blood sample characteristics recorded during their hospital stay were linked to PTSS at both the two-month and two-year follow-ups, as well as with anxiety and depression of COVID-19 survivors two years after discharge. For example, higher levels of Immunoglobulin G were identified as risk factors for PTSS, while higher levels of total bilirubin were identified as risk factors for depression and anxiety. Immunoglobulin G, the primary antibody produced in response to a new infection, plays a key role in the body's immune response to COVID-19 [3]. Therefore, the level of Immunoglobulin G to some extent represents the functionality of the immune system and its

ability to combat viruses [21]. The observed association between PTSS and Immunoglobulin G suggests that short-term PTSS might be closely related to individual immune function [7]. Additionally, bilirubin plays a crucial role in hemoglobin metabolism and anti-inflammatory processes. Consistent with previous studies [1, 7, 13, 16, 20], both correlation and regression analyses revealed that higher bilirubin levels were significantly associated with depression and anxiety. This suggests that long-term depression and anxiety might be closely related to the body's metabolism and anti-inflammatory capacity.

In summary, mental health problems such as PTSS and depression can persist for up to two years following acute COVID-19 infection in survivors. It is crucial to prioritize the mental well-being of female survivors, especially during the early stages after discharge. In the short term, individual immune function and individuals who experienced severe COVID-19 symptoms are at a heightened risk of developing PTSS, anxiety, and depression. Over the long term, individual metabolism and anti-inflammatory capacity are closely linked to anxiety and depression. This study highlights the risk factors of PTSS, anxiety, and depression in COVID-19 patients at different time points after hospital discharge and provides essential insights for developing different interventions to mitigate the risk of short-term and long-term mental health problems. However, our study exclusively involved participants from Wuhan, who were infected with the earlier strains of SARS-CoV-2. Given the differences in disease severity and physical and mental health issues caused by various types of the SARS-CoV-2 virus, as well as the relatively small sample size in our study, it remains unclear whether our findings, based on participants infected with the wild-type SARS-CoV-2, can be directly applied to other samples, including those affected by different variants.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00406-024-01947-0>.

Author contributions Yian Xiao: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing - original draft, Writing - review & editing. Libo Zhang: Formal analysis, Writing - review & editing. Quanqi Yang: Formal analysis. Xinyu Pan: Data curation. Zhijie Lu: Data curation. Yanzhi Bi: Conceptualization, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. Li Hu: Conceptualization, Methodology, Writing - review & editing, Funding acquisition.

Funding This work was supported by the National Natural Science Foundation of China (No. 32071061) and Beijing Natural Science Foundation (JQ22018).

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare that they have no conflicts of interest.

References

- Alavian SM, Tavallaii SA, Farahani MAA, Khoddami-Vishteh HR, Lankarani KB (2007) Evaluation of the severity of depression and anxiety in hepatitis B and hepatitis C patients: a case control study. *Archives Clin Infect Dis* 2:113–119
- Alemanno F, Houdayer E, Parma A, Spina A, Del Forno A, Scatolini A, Angelone S, Brugliera L, Tettamanti A, Beretta L, Iannaccone S (2021) Covid-19 cognitive deficits after respiratory assistance in the subacute phase: a covid-rehabilitation unit experience. *PLoS ONE* 16:e0246590
- Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggemann MC, O'Mahony L, Gao Y, Nadeau K, Akdis CA (2020) Immune response to sars-cov-2 and mechanisms of immunopathological changes in covid-19. *Allergy* 75:1564–1581
- Bi Y, Xiao Y, Pan X, Zhang Y, Yang Q, Hu L (2023) Long-term post-traumatic stress symptoms in covid-19 survivors and its risk factors: a two-year longitudinal cohort study. *Psychiatry Res* 329:115523
- Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL (2015) The posttraumatic stress disorder checklist for dsm-5 (pcl-5): development and initial psychometric evaluation. *J Trauma Stress* 28:489–498
- Carfi A, Bernabei R, Landi F (2020) Persistent symptoms in patients after acute covid-19. *JAMA* 324:603–605
- Estrada BD, Angulo B, Navarro ME, Jarero I, Sánchez-Armass O (2019) Ptsd, immunoglobulins, and cortisol changes after the provision of the emdr-precis to females patients with cancer-related ptsd diagnosis. *Am J Appl Psychol* 8:64–71
- Fu R, Zhang Y (2020) Case report of a patient with suspected covid-19 with depression and fever in an epidemic stress environment. *Gen Psychiatr* 33:e100218
- González-Sanguino C, Ausín B, Castellanos M, Saiz J, López-Gómez A, Ugidos C, Muñoz M (2020) Mental health consequences during the initial stage of the 2020 coronavirus pandemic (covid-19) in Spain. *Brain Behav Immun* 87:172–176
- Hossain MM, Tasnim S, Sultana A, Faizah F, Mazumder H, Zou L, McKyer ELJ, Ahmed HU, Ma P (2020) Epidemiology of mental health problems in covid-19: a review. *F1000Res* 9:636
- Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, Liu M, Wang Y, Cui D, Wang Y, Zhang X, Shang L, Zhong J, Wang X, Wang J, Cao B (2022) Health outcomes in people 2 years after surviving hospitalisation with covid-19: a longitudinal cohort study. *Lancet Respir Med* 10:863–876
- Huang X, Liu L, Eli B, Wang J, Chen Y, Liu Z (2022) Mental health of covid-19 survivors at 6 and 12 months postdiagnosis: a cohort study. *Front Psychiatry* 13:863698
- Jayanti S, Moretti R, Tiribelli C, Gazzin S (2020) Bilirubin and inflammation in neurodegenerative and other neurological diseases. *Neuroimmunol Neuroinflammation* 2020:92–108
- Kroenke K, Spitzer RL, Williams JB (2001) The phq-9: validity of a brief depression severity measure. *J Gen Intern Med* 16:606–613
- Liu D, Baumeister RF, Veilleux JC, Chen C, Liu W, Yue Y, Zhang S (2020) Risk factors associated with mental illness in hospital discharged patients infected with covid-19 in Wuhan, China. *Psychiatry Res* 292:113297

16. Liu X, Zhao W, Hu F, Hao Q, Hou L, Sun X, Zhang G, Yue J, Dong B (2022) Comorbid anxiety and depression, depression, and anxiety in comparison in multi-ethnic community of west China: prevalence, metabolic profile, and related factors. *J Affect Disord* 298:381–387
17. Liu X, Zhu M, Zhang R, Zhang J, Zhang C, Liu P, Feng Z, Chen Z (2021) Public mental health problems during covid-19 pandemic: a large-scale meta-analysis of the evidence. *Transl Psychiatry* 11:384
18. Mansfield KE, Mathur R, Tazare J, Henderson AD, Mulick AR, Carreira H, Matthews AA, Bidulka P, Gayle A, Forbes H, Cook S, Wong AYS, Strongman H, Wing K, Warren-Gash C, Cadogan SL, Smeeth L, Hayes JF, Quint JK, McKee M, Langan SM (2021) Indirect acute effects of the covid-19 pandemic on physical and mental health in the UK: a population-based study. *Lancet Digit Health* 3:e217–e230
19. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, Melloni EMT, Furlan R, Ciceri F, Rovere-Querini P, Benedetti F (2020) Anxiety and depression in covid-19 survivors: role of inflammatory and clinical predictors. *Brain Behav Immun* 89:594–600
20. Mei Z, Wu X, Zhang X, Zheng X, Li W, Fan R, Yu H, Zhang S, Gu Y, Wang X, Xia Y, Meng G, Shen J, Niu K (2022) The occurrence and risk factors associated with post-traumatic stress disorder among discharged covid-19 patients in tianjin, China. *Brain Behav* 12:e2492
21. Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock IM (2020) The immune response and immunopathology of covid-19. *Front Immunol* 11:2037
22. Qi R, Chen W, Liu S, Thompson PM, Zhang LJ, Xia F, Cheng F, Hong A, Surento W, Luo S, Sun ZY, Zhou CS, Li L, Jiang X, Lu GM (2020) Psychological morbidities and fatigue in patients with confirmed covid-19 during disease outbreak: Prevalence and associated biopsychosocial risk factors. *medRxiv*
23. Shanbehzadeh S, Tavahomi M, Zanjari N, Ebrahimi-Takamjani I, Amiri-Arimi S (2021) Physical and mental health complications post-covid-19: scoping review. *J Psychosom Res* 147:110525
24. Spitzer RL, Kroenke K, Williams JB, Löwe B (2006) A brief measure for assessing generalized anxiety disorder: the gad-7. *Arch Intern Med* 166:1092–1097
25. Tu Y, Zhang Y, Li Y, Zhao Q, Bi Y, Lu X, Kong Y, Wang L, Lu Z, Hu L (2021) Post-traumatic stress symptoms in covid-19 survivors: a self-report and brain imaging follow-up study. *Mol Psychiatry* 26:7475–7480
26. Vindegaard N, Benros ME (2020) Covid-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav Immun* 89:531–542
27. Wade D, Hardy R, Howell D, Mythen M (2013) Identifying clinical and acute psychological risk factors for ptsd after critical care: a systematic review. *Minerva Anestesiol* 79:944–963
28. Xie Q, Fan F, Fan XP, Wang XJ, Chen MJ, Zhong BL, Chiu HF (2020) Covid-19 patients managed in psychiatric inpatient settings due to first-episode mental disorders in Wuhan, China: clinical characteristics, treatments, outcomes, and our experiences. *Transl Psychiatry* 10:337
29. Xie Q, Liu XB, Xu YM, Zhong BL (2021) Understanding the psychiatric symptoms of covid-19: a meta-analysis of studies assessing psychiatric symptoms in Chinese patients with and survivors of covid-19 and sars by using the symptom checklist-90-revised. *Transl Psychiatry* 11:290
30. Xiong LJ, Zhong BL, Cao XJ, Xiong HG, Huang M, Ding J, Li WT, Tong J, Shen HY, Xia JH, Hu Y (2021) Possible posttraumatic stress disorder in Chinese frontline healthcare workers who survived covid-19 6 months after the covid-19 outbreak: prevalence, correlates, and symptoms. *Transl Psychiatry* 11:374
31. Yuan B, Li W, Liu H, Cai X, Song S, Zhao J, Hu X, Li Z, Chen Y, Zhang K, Liu Z, Peng J, Wang C, Wang J, An Y (2020) Correlation between immune response and self-reported depression during convalescence from covid-19. *Brain Behav Immun* 88:39–43
32. Zeng N, Zhao YM, Yan W, Li C, Lu QD, Liu L, Ni SY, Mei H, Yuan K, Shi L, Li P, Fan TT, Yuan JL, Vitiello MV, Kosten T, Kondratiuk AL, Sun HQ, Tang XD, Liu MY, Lalvani A, Shi J, Bao YP, Lu L (2023) A systematic review and meta-analysis of long term physical and mental sequelae of covid-19 pandemic: call for research priority and action. *Mol Psychiatry* 28:423–433

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