



Long-term post-traumatic stress symptoms in COVID-19 survivors and its risk factors: a two-year longitudinal cohort study

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ABSTRACT

The COVID-19 pandemic has led to widespread mental health problems, necessitating the investigation of longitudinal mental health changes, associated risk factors, and neural mechanisms in survivors. We recorded demographics, mental health, social support, and potential exposures in survivors at 3 months ($n = 189$), 6 months ($n = 47$), and 2 years ($n = 69$) post-discharge and collected brain imaging data at the second timepoint. Control groups included non-COVID-19 locals (3 months: $n = 188$, 6 months: $n = 42$, 2 years: $n = 71$). Results indicated that female survivors exhibited higher post-traumatic stress symptoms (PTSS) and depression levels than female controls for up to 2 years, along with higher anxiety level for up to 6 months. Male survivors had higher PTSS, depression, and anxiety levels than male controls at 2 months. Moreover, COVID-related trauma and low social support were risk factors for PTSS and negative emotions in survivors. Neuroimaging revealed increased amygdala activity in male survivors and correlations between hippocampus activity and depression symptoms as well as between right hippocampus activity and social support. Our study emphasized the importance of monitoring mental wellness in COVID-19 survivors and underscored the crucial role of social support in mitigating mental health problems.

1. Introduction

With the ongoing COVID-19 pandemic, there have been about 762 million confirmed cases globally, including about 7 million deaths (<https://covid19.who.int/>). With the increasing number of patients recovered from the disease, there is growing concern among the public about the long-term consequences after acute COVID-19 recovery (Evans et al., 2021), which could have significant medical and socioeconomic implications (Crook et al., 2021; Sudre et al., 2021). The 2023 trends report from the American Psychological Association highlighted that venture capitalists are shifting their investments towards mental health, due to the soaring mental health needs during and after the COVID-19 pandemic (<https://www.apa.org/>). Growing epidemiological and clinical evidence found that a proportion of survivors are experiencing ongoing mental health problems, including post-traumatic stress symptoms (PTSS), anxiety, and depression (Huang et al., 2022; Jiang et al., 2021). However, the longitudinal changes in mental health status over time in COVID-19 survivors remain largely unknown. Thus, there is

an urgent need for ongoing longitudinal follow-up studies to better characterize the natural history of mental health state for COVID-19 survivors and to establish when full recovery can be expected.

PTSS can develop after an individual experiences one or multiple traumatic events, such as being seriously injured, witnessing someone's death or injury, or being exposed to aversive details in traumatic scenes (O'Donnell et al., 2021; Pitman et al., 2012). Various risk factors can determine the development of PTSS, including age, sex, trauma exposure, and social support (Contractor et al., 2013; Gerber et al., 2018; Nisar et al., 2020). For example, women and younger adults are more likely to report mental health problems after experiencing a traumatic event (Tu et al., 2021). Moreover, strategies implemented to prevent the spread of COVID-19, such as physical distancing and remote work and school, may have resulted in social isolation and a sense of loneliness during the pandemic, which have impeded people's ability to seek social support that may increase the risk of mental health problems (Groarke et al., 2020; Hall et al., 2023; Lakey and Orehek, 2011). In addition to these possible risk factors for PTSS, previous neuroimaging studies also

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investigated brain structural and functional abnormalities in COVID-19 survivors (Liu et al., 2022; Tu et al., 2021), and highlighted the significant role of amygdala and hippocampus in their PTSS (Tu et al., 2021). However, the risk factors contributing to the development of PTSS and the associated negative emotions, including anxiety and depression, in individuals who have survived COVID-19 have remained largely unexplored. Moreover, the sex difference in brain activity within the amygdala and hippocampus among COVID-19 survivors and their relationship with the mental health status and social support remain unclear.

To address these issues, we performed a longitudinal cohort study on individuals who had recovered from COVID-19 between February 21st and March 20th, 2020. Demographics, mental health status, perceived social support, and potential exposures during the pandemic were collected at three timepoints: 3 months, 6 months, and 2 years after discharge from the hospital. Brain structural and functional magnetic resonance imaging (MRI) data were also collected at 6 months after hospital discharge. Age- and sex-matched controls who had not been infected with COVID-19 were included to determine the recovery progress of COVID-19 survivors.

2. Methods

The research was approved by the Institutional Review Board of the local ethics committee. All procedures were performed in accordance with the Declaration of Helsinki. All participants provided informed consent and were paid for their participation, receiving 30 Chinese Yuan (CNY) for the first and third assessments each and 80 CNY for the second assessment.

2.1. Study design and participants

A longitudinal cohort study was conducted on individuals who had been survived from COVID-19 between February 21st and March 20th, 2020, in Wuhan, China, which was the epicenter of the outbreak at the beginning of 2020. Demographics, mental health status, perceived social support, and potential exposures during the pandemic were assessed at three different timepoints: 3 months (April to May, 2020), 6 months (August 2020), and two years (April to May, 2022) after their discharge from the hospital. In total, 213 COVID-19 survivors and 230 age- and sex-matched controls without COVID-19 infection were included in the study. Specifically, at the first time point, 189 COVID-19 survivors and 188 controls completed the assessments. At the second time point, 47 COVID-19 survivors and 42 controls completed the assessments, along with brain structural and functional MRI data collection. At the third time point, 69 COVID-19 survivors and 71 controls completed the assessments.

2.2. Self-reported psychological scales

PTSS, anxiety, depression, and perceived social support were evaluated using Chinese versions of validated measurement tools. Specifically, PTSS was measured using post-traumatic stress disorder checklist for DSM-5 (PCL-5) (Blevins et al., 2015), 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. The severity of anxiety symptom was assessed using the General Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006), 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. The severity of depression symptom was evaluated using the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001), 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. Perceived social support was assessed using the

12-item Perceived Social Support Scale (PSSS) (Zimet et al., 1988), which is a measure of how an individual perceives the social support level from family, friends, and significant others. PSSS consists of 12 questions rated on a 7-point Likert scale (1–7) with a higher score indicating higher perceived social support. The Cronbach's alpha coefficients of PCL-5, GAD-7, PHQ-9, and PSSS were 0.91 (Cheng et al., 2020), 0.898 (He et al., 2010), 0.854 (Zhang et al., 2013), and 0.923 (Zhao et al., 2022), respectively, which indicates a high reliability of these Chinese version scales.

2.3. Potential exposures in COVID-19 survivors

The potential exposures during the pandemic were only recorded from COVID-19 survivors, which included the severity of COVID-19 symptoms and COVID-related trauma during the pandemic. According to the COVID-19 Treatment Guidelines from NIH, the severity of COVID-19 symptoms was grouped into the following five categories: asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness, and critical illness (<https://www.covid19treatmentguidelines.nih.gov/>). COVID-related trauma included receiving emergency treatment, witnessing someone's death, and witnessing someone receiving emergency treatment (American Psychiatric Association and Association, 2013).

2.4. MRI data acquisition

At the second time point, MRI data were collected using a 3.0-Tesla MRI system equipped with a standard birdcage head coil (Discovery MR 750; General Electric Healthcare; Milwaukee; Wisc.). A high-resolution brain structural image was acquired using the T1-weighted fast-spoiled gradient echo sequence (repetition time = 8.16 ms, echo time = 3.18 ms, flip angle = 12°, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, and field of view [FOV] = $256 \times 256 \text{ mm}^2$). Resting-state functional data were acquired using an echo-planar-imaging sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, FOV = $64 \times 64 \text{ mm}^2$, in-plane resolution = $3.5 \times 3.5 \text{ mm}^2$, slice thickness = 3.5 mm, and 38 slices). During the acquisition of resting-state fMRI data, participants were instructed to remain still with their eyes open, not to fall asleep, and not to think about anything.

2.5. MRI data analysis

Functional MRI data were analyzed using Data Processing and Analysis for (Resting-State) Brain Imaging (DPABI) software (DPABI_V5.1_201201, <http://rfmri.org/dpabi>) (Yan et al., 2016). The pre-processing steps included the following steps: remove the first ten volumes, slice timing correction, spatially realign, co-register structural images to their corresponding functional space, segment structural images into gray matter, white matter, and cerebrospinal fluid, nuisance covariates (i.e., white matter signal, cerebrospinal fluid signal, and Friston's-24 motion parameters) regression, normalize to the Montreal Neurological Institute (MNI) space (resampling voxel size = $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$), spatially smooth using a Gaussian kernel of 5-mm full width at half maximum (FWHM), and detrend to remove the linear drifts. After preprocessing, the amplitude of low-frequency fluctuation (ALFF) analysis was performed to quantify the intensity of regional spontaneous brain activity by calculating the mean square root of the power spectrum density over the low frequency band (0.01–0.08 Hz). The resultant ALFF values were transformed into z values using Fisher's r-to-z transformation.

2.6. Statistical analyses

The current study assessed three distinct mental health states: PTSS, anxiety, and depression at three time points, all of which are designed to capture negative emotional states. Therefore, we employed principal

component analysis (PCA) to perform dimension reduction.

To test the changes in self-reported mental health states (i.e., PTSS, anxiety, depression, negative emotions, and perceived social support) over time for females and males in both COVID-19 survivors and controls, we performed a series of Linear Mixed Effects (LME) model analyses with two between-subject factors ("group": COVID-19 survivors and controls, "sex": females and males) and one within-subject factor ("time": three time points) on PCL-5, GAD-7, PHQ-9, principal component (PC), and PSSS scores. To assess the self-reported score differences between groups for each sex group at each time point, the self-reported score differences between sex for each group at each time point, and the self-reported score differences between different time points for each sex group, a series of post-hoc paired-sample t-tests were performed.

To explore the relationship among PTSS (i.e., PCL-5), anxiety (i.e., GAD-7), depression (i.e., PHQ-9), negative emotions (i.e., PC), and social support (i.e., PSSS) in COVID-19 survivors, a series of Pearson correlation analyses were performed on these variables at each time point.

Since the severity of COVID-19 symptoms was a categorical variable, we performed Spearman correlation analyses between the severity of COVID-19 symptoms and PCL-5 scores as well as PC scores in COVID-19 survivors to assess the impact of the severity of COVID-19 symptoms on PTSS and negative emotions at each time point. To investigate the influence of COVID-related trauma (i.e., witnessing someone's death and witnessing someone receiving emergency treatment) on PTSS and negative emotions in COVID-19 survivors, we performed a series of LME model analyses with one between-subject factor ("COVID-related trauma": yes or no) and one within-subject factor ("time": three time points) on the PCL-5 and PC scores, respectively. Independent-sample t-tests were then performed to assess the influence of COVID-related trauma on PTSS and negative emotions at each time point. Please note that the number of COVID-19 survivors exposed to COVID-related trauma at the second time point and the number of COVID-19 survivors receiving emergency treatment at all three time points were relatively small (as shown in Table 1), and therefore these data were not included in the LME model analysis.

To explore the possible risk factors of PTSS and negative emotions, we evaluate the potential impact of age, sex, severity of COVID-19 symptoms, COVID-related trauma, and perceived social support on the PCL-5 and PC scores for COVID-19 survivors using multiple linear regression analyses at each time point, respectively. Please note that to estimate different levels of COVID-related trauma, the total score of all three items of COVID-related trauma was calculated and was then used in the regression analysis.

Since previous studies showed that COVID-19 survivors with PTSS exhibited gray matter volume abnormalities in bilateral amygdala and hippocampus (Besteher et al., 2022; Del Casale et al., 2022; Tu et al., 2021), we selected these four brain areas as regions-of-interest and extracted the average z values of ALFF using masks based on the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002). To determine whether the regional activities in these brain areas could be associated with the sex of COVID-19 survivors and controls, we performed an analysis of variance (ANOVA) with two between-subject factors ("group": COVID-19 survivors and controls, "sex": male and female) for each brain area. When there was a significant interaction, post-hoc paired-sample t-tests were performed. Furthermore, to assess the associations between regional activities and self-reported mental health status (i.e., PTSS, anxiety, depression, negative emotions, and perceived social support), we performed a series of Pearson correlation analyses between ALFF z values in bilateral amygdala and hippocampus and the mental health scores of all participants at the second time point.

Please note that some subjects participated in the assessment at different time points, thus we employed LME model analyses to examine the changes in self-reported mental health scores and investigate the impact of COVID-related trauma on PTSS and negative emotions. The use of LME models allowed for the inclusion of repeated measures within

Table 1

Demographics, psychological scores, and potential exposures during the pandemic of participants at three time points.

	1 st time point	2 nd time point	3 rd time point
Participants (n)			
COVID-19 survivor (female, male)	189 (125F, 64M)	47 (33F, 14M)	69 (42F, 27M)
Control (female, male)	188 (118F, 70M)	42 (30F, 12M)	71 (45F, 26M)
PCL-5 score			
COVID-19 survivor	12.201 ± 0.859	15.128 ± 1.730	10.507 ± 1.284
Female	13.048 ± 1.085	17.879 ± 2.136	11.595 ± 6.756
Male	10.547 ± 1.381	8.643 ± 2.119	8.815 ± 2.319
Control	5.686 ± 0.490	7.000 ± 0.873	6.535 ± 0.757
Female	6.466 ± 0.691	7.300 ± 1.066	6.756 ± 0.913
Male	4.371 ± 0.584	6.250 ± 1.543	6.154 ± 1.353
GAD-7 score			
COVID-19 survivor	5.355 ± 0.329	5.617 ± 0.745	3.130 ± 0.425
Female	5.768 ± 0.420	6.879 ± 0.928	3.857 ± 0.571
Male	4.547 ± 0.507	2.643 ± 0.796	2.000 ± 0.570
Control	2.707 ± 0.214	2.500 ± 0.418	2.761 ± 0.425
Female	3.229 ± 0.287	2.600 ± 0.479	2.867 ± 0.526
Male	1.829 ± 0.286	2.250 ± 0.871	2.577 ± 0.734
PHQ-9 score			
COVID-19 survivor	6.370 ± 0.390	7.745 ± 0.820	5.348 ± 0.566
Female	6.888 ± 0.498	9.000 ± 1.038	6.191 ± 0.758
Male	5.359 ± 0.602	4.786 ± 0.884	4.037 ± 0.791
Control	2.915 ± 0.231	3.595 ± 0.539	2.944 ± 0.400
Female	3.314 ± 0.312	3.700 ± 0.661	3.289 ± 0.525
Male	2.243 ± 0.316	3.333 ± 0.948	2.346 ± 0.602
PSSS score			
COVID-19 survivor	61.905 ± 0.897	58.362 ± 1.795	62.406 ± 1.414
Female	61.192 ± 1.122	57.818 ± 2.287	60.714 ± 1.844
Male	63.297 ± 1.486	59.643 ± 2.785	65.037 ± 2.142
Control	63.947 ± 0.813	64.643 ± 1.755	61.662 ± 1.231
Female	65.332 ± 0.981	65.733 ± 2.214	63.111 ± 1.442
Male	61.629 ± 1.390	61.917 ± 2.633	59.154 ± 2.205
Severity of COVID-19 symptoms of COVID-19 survivors (n)			
Asymptomatic or presymptomatic infection	4	1	5
Mild illness	27	9	30
Moderate illness	88	21	30
Severe illness	10	3	3
Critical illness	1	0	1
COVID-related trauma of COVID-19 survivors (n)			

(continued on next page)

Table 1 (continued)

	1 st time point	2 nd time point	3 rd time point
Receiving emergency treatment (yes, no)	189 (17, 172)	34 (2, 32)	69 (5, 64)
Witnessing someone's death (yes, no)	189 (54, 135)	34 (14, 20)	69 (24, 45)
Witnessing someone receiving emergency treatment (yes, no)	189 (68, 121)	34 (14, 20)	69 (30, 39)

Data were reported as mean $\pm$ standard error of mean unless otherwise indicated. Abbreviations: PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale.

each subject, thus enabling a more comprehensive understanding of the longitudinal trends and individual differences in the study variables. To account for multiple comparisons in the post-hoc paired-sample t-tests, correlation analyses, and multiple linear regression analyses, Bonferroni correction was adopted to adjust the *p*-values separately for each of these analyses. In the post-hoc t-tests, missing data were handled using listwise deletion. All statistical analyses were carried out in SPSS 25.0 (SPSS Inc., New York, USA).

3. Results

3.1. Demographics

At three time points, no significant differences in age (1st time point: $t_{375} = -0.355$, $p = 0.723$; 2nd time point: $t_{87} = 0.166$, $p = 0.869$; 3rd time point: $t_{138} = -1.911$, $p = 0.058$) were observed between COVID-19 survivors (mean $\pm$ standard deviation [SD], 1st time point: 51.519 $\pm$ 13.565 years; 2nd time point: 51.128 $\pm$ 11.180 years; 3rd time point: 48.826 $\pm$ 13.798 years) and controls (mean $\pm$ SD, 1st time point: 52.011 $\pm$ 13.344 years; 2nd time point: 50.690 $\pm$ 13.650 years; 3rd time point: 52.958 $\pm$ 11.721 years). Chi-Square tests revealed no significant differences in sex between COVID-19 survivors and controls (1st time point: $\chi^2 = 0.468$, $p = 0.494$; 2nd time point: $\chi^2 = 0.016$, $p = 0.900$; 3rd time point: $\chi^2 = 0.094$, $p = 0.759$; Table 1).

3.2. PCA results for self-reported psychological scales

Both the Kaiser-Meyer-Olkin measure (1st time point: value = 0.756; 2nd time point: value = 0.762; 3rd time point: value = 0.756) and Bartlett's test of sphericity ($p < 0.001$) indicated the suitability of the data for PCA. One PC was identified, explaining 86.875%, 86.607%, and 85.115% of the total variance at the first, second, and third time points, respectively. Subsequently, we extracted this PC and applied it in the LME model analyses, correlation analyses, and multiple linear regression analyses.

3.3. LME model results for PTSS and negative emotions

3.3.1. Interaction effect

As indicated in Table 2, the LME model analysis revealed a significant interaction effect between "group" and "sex" for PTSS (PCL-5 scores) and perceived social support (PSSS scores). No other significant interaction effects were detected. Please note that the results of LME model analyses and post-hoc paired-sample t-tests related to anxiety, depression, and perceived social support can be found in Supplementary materials.

3.3.2. Main effect of group

Significant main effects of "group" were observed in PTSS and negative emotions. Post-hoc paired-sample t-tests (Fig. 1) revealed that female COVID-19 survivors exhibited significantly higher levels of PTSS and negative emotions compared to female controls at all three time

Table 2

LME model analysis to assess the effects of "group", "sex", and "time" on the post-traumatic stress symptom (PTSS), anxiety, depression, negative emotions, and social support.

Factors	F value	df	<i>p</i> value ^a
PCL-5 score			
Group	34.642	(1, 542.459)	<0.001
Sex	12.852	(1, 542.459)	<0.001
Time	0.705	(2, 256.290)	0.495
Group $\times$ Sex	4.310	(1, 542.459)	0.038
Group $\times$ Time	2.109	(2, 256.290)	0.123
Sex $\times$ Time	2.664	(2, 256.290)	0.072
Group $\times$ Sex $\times$ Time	2.076	(2, 256.290)	0.128
GAD-7 score			
Group	19.914	(1, 526.766)	<0.001
Sex	14.688	(1, 526.766)	<0.001
Time	7.866	(2, 296.542)	<0.001
Group $\times$ Sex	2.665	(1, 526.766)	0.103
Group $\times$ Time	6.672	(2, 296.542)	0.001
Sex $\times$ Time	2.671	(2, 296.542)	0.071
Group $\times$ Sex $\times$ Time	1.221	(2, 296.542)	0.296
PHQ-9 score			
Group	40.984	(1, 535.161)	<0.001
Sex	13.599	(1, 535.161)	<0.001
Time	2.336	(2, 273.568)	0.099
Group $\times$ Sex	2.588	(1, 535.161)	0.108
Group $\times$ Time	0.868	(2, 273.568)	0.421
Sex $\times$ Time	0.853	(2, 273.568)	0.427
Group $\times$ Sex $\times$ Time	1.036	(2, 273.568)	0.356
Negative emotions			
Group	36.862	(1, 542.451)	<0.001
Sex	16.203	(1, 542.451)	<0.001
Time	3.378	(2, 267.296)	0.036
Group $\times$ Sex	3.044	(1, 542.451)	0.082
Group $\times$ Time	2.325	(2, 267.296)	0.100
Sex $\times$ Time	1.914	(2, 267.296)	0.150
Group $\times$ Sex $\times$ Time	0.979	(2, 267.296)	0.377
PSSS score			
Group	1.544	(1, 513.013)	0.215
Sex	0.071	(1, 513.013)	0.790
Time	0.277	(2, 305.923)	0.758
Group $\times$ Sex	4.325	(1, 513.013)	0.038
Group $\times$ Time	2.741	(2, 305.923)	0.066
Sex $\times$ Time	0.137	(2, 305.923)	0.872
Group $\times$ Sex $\times$ Time	0.222	(2, 305.923)	0.801

Please note that the principal component scores obtained in the principal component analysis were used to represent negative emotions.

^a *p* value of less than 0.05 was considered significant. Abbreviations: PCL-5, post-traumatic stress disorder (PTSD) checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale.

points (1st time point: all $p < 0.001$; 2nd time point: $p = 0.011$ for PTSS and $p = 0.010$ for negative emotions; 3rd time point: all $p < 0.001$). As for male COVID-19 survivors, they had significantly higher levels of PTSS and negative emotions than male controls at the first time point (all $p < 0.001$).

3.3.3. Main effect of sex

Significant main effects of "sex" were observed in PTSS and negative emotions (Table 2). Post-hoc paired-sample t-tests (Fig. 1) revealed that at the second time point, female COVID-19 survivors had significantly higher levels of PTSS ($p = 0.002$) and negative emotions ($p = 0.001$) in comparison to male COVID-19 survivors. Additionally, female COVID-19 survivors exhibited higher levels of negative emotions than male COVID-19 survivors at the first ($p = 0.029$) and third ($p = 0.046$) time points. At the first time point, female controls also showed significantly higher level of negative emotions compared to male controls ($p =$

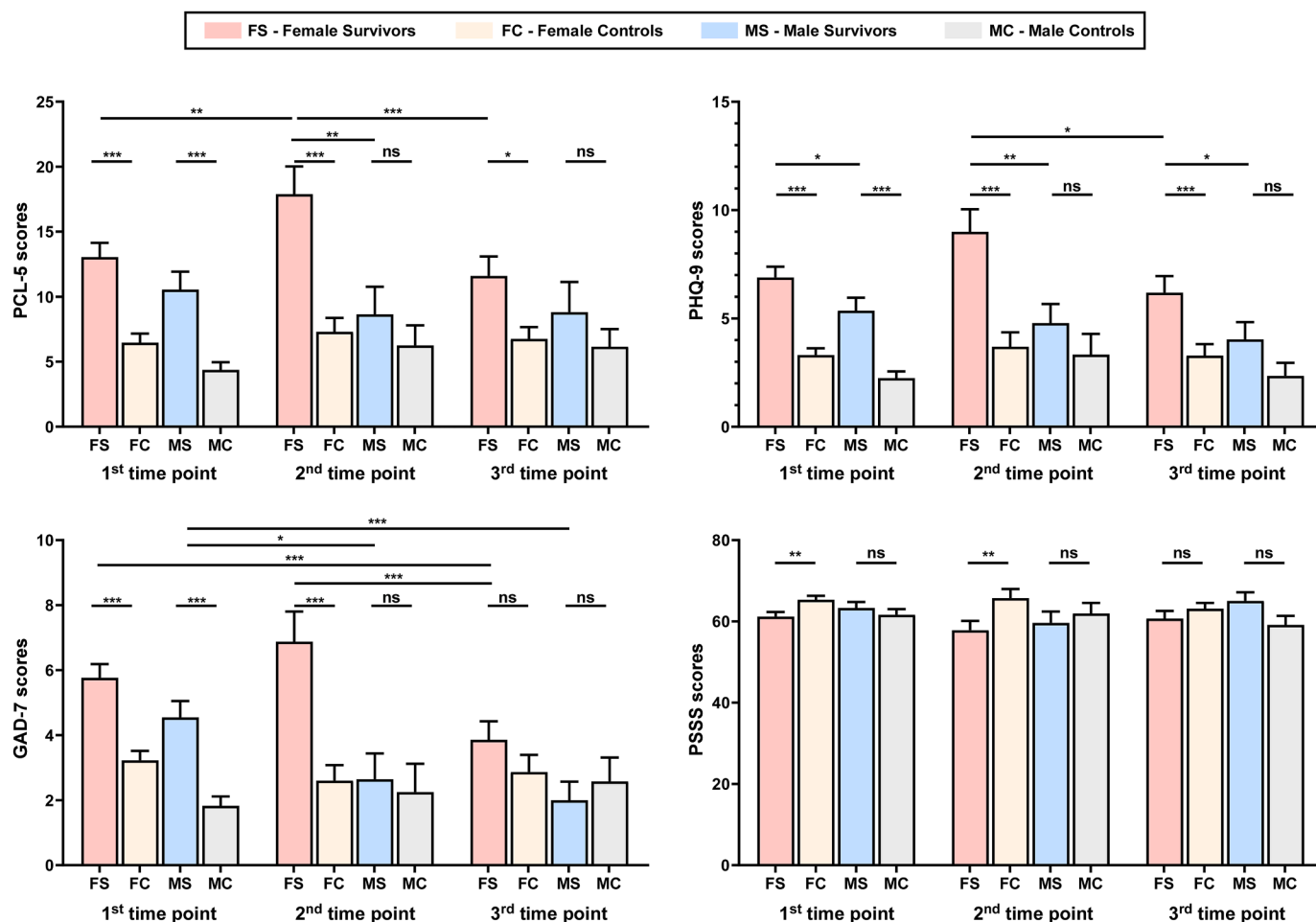


Fig. 1. Longitudinal changes in mental health scores and perceived social support for female and male COVID-19 survivors and controls. Self-reported psychological scores were collected at three time points: April to May 2020 (1st time point), August 2020 (2nd time point), and April to May 2022 (3rd time point). Female survivors had higher levels of PTSS and depression than female controls for up to 2 years, along with higher levels of anxiety for up to 6 months after the recovery from acute infection. Male survivors had higher levels of PTSS, depression, and anxiety than male controls at 2 months after the recovery, and then returned to control group level. PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale. *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$, ns not significant.

0.046).

3.3.4. Main effect of time

Significant main effect of “time” was observed in negative emotions but not in PTSS (Table 2). Post-hoc paired-sample t-tests revealed several significant findings (Fig. 1). Female COVID-19 survivors exhibited significantly higher level of PTSS at the second time point compared to both the first ($p = 0.002$) and third time points ($p = 0.001$). For male COVID-19 survivors, they had a higher level of negative emotions at the first time point compared to the second time point ($p = 0.004$). In contrast, male controls exhibited significantly lower level of negative emotions at the second time point compared to third time point ($p = 0.038$). No other statistically significant results were observed.

3.4. Correlations between self-reported psychological scales

Significantly positive correlations were consistently observed at all three time points between PTSS, anxiety, and depression (all $r \geq 0.729$, $p < 0.001$; Table 3). Moreover, perceived social support were significantly and negatively correlated with PTSS, anxiety, depression, and negative emotions at all three time points (all $r \leq -0.328$, $p < 0.001$; Table 3 and Fig. 2; for negative emotions: 1st time point: $r = -0.378$; 2nd time point: $r = -0.624$; 3rd time point: $r = -0.480$). After applying Bonferroni correction at each time point ($p < 0.05/7$), all these correlations remain

Table 3

Correlation results between different psychological scores at three time points.

	PCL-5	GAD-7	PHQ-9	PSSS
1st time point				
PCL-5	1	0.775***	0.741***	-0.328***
GAD-7		1	0.832***	-0.351***
PHQ-9			1	-0.369***
PSSS				1
2nd time point				
PCL-5	1	0.815***	0.772***	-0.552***
GAD-7		1	0.824***	-0.575***
PHQ-9			1	-0.622***
PSSS				1
3rd time point				
PCL-5	1	0.815***	0.729***	-0.396***
GAD-7		1	0.855***	-0.438***
PHQ-9			1	-0.509***
PSSS				1

All p values less than 0.05 are marked with asterisks. Abbreviations: PCL-5, post-traumatic stress disorder (PTSD) checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale.

*** $p < 0.001$.

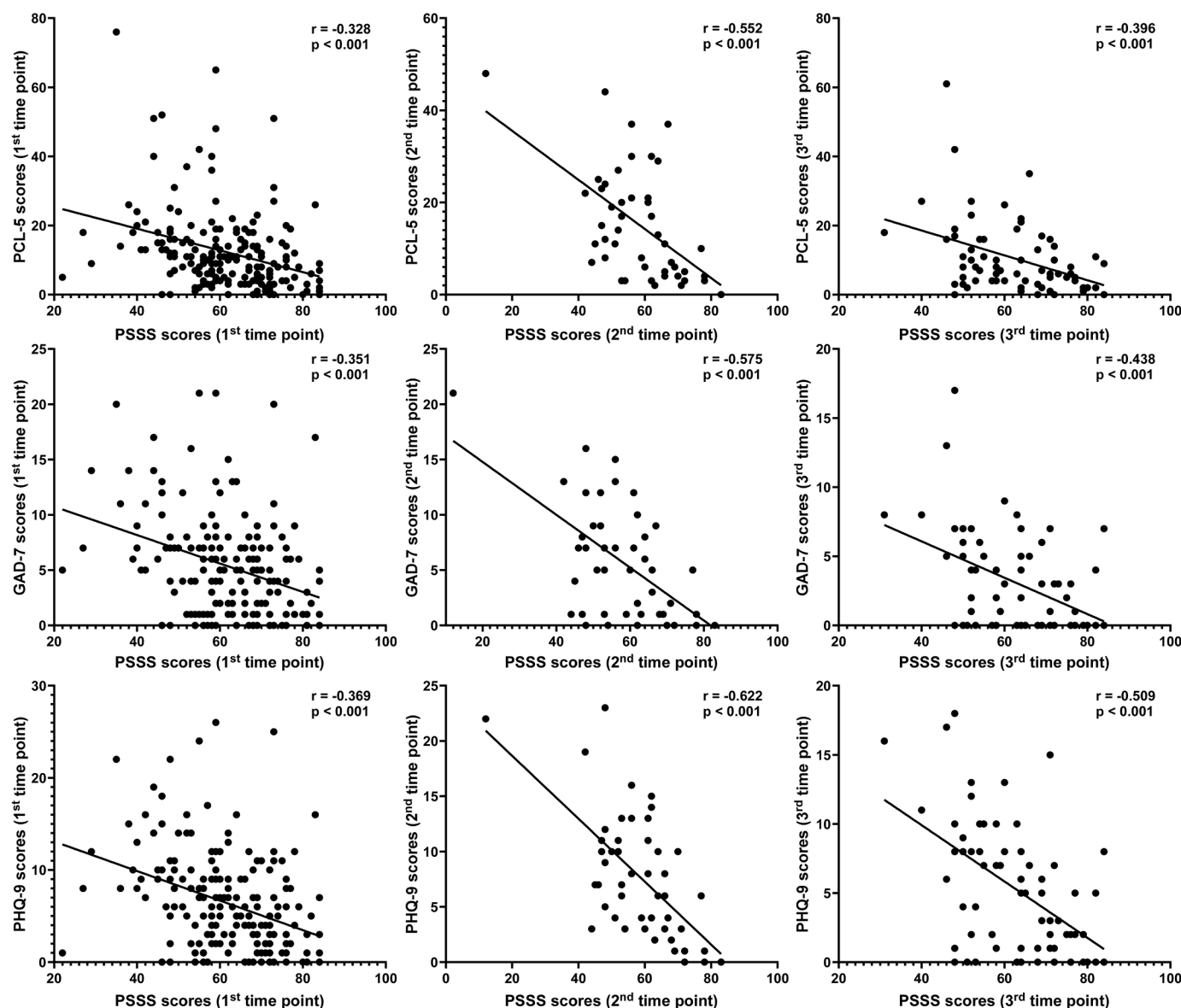


Fig. 2. Correlations between perceived social support and other psychological scores for COVID-19 survivors. The perceived social support (i.e., PSSS) showed significant negative correlations with the post-traumatic stress symptom (i.e., PCL-5), anxiety (i.e., GAD-7), and depression (i.e., PHQ-9) scores at all three time points. PCL-5, post-traumatic stress disorder checklist for DSM-5; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale.

statistically significant.

3.5. The effect of COVID-19 severity and COVID-related trauma on PTSS and negative emotions

The severity levels of COVID-19 symptoms exhibited significantly positive correlations with PTSS at the first ($r = 0.189$, $p = 0.031$; Fig. 3A) and third time points ($r = 0.352$, $p = 0.003$; Fig. 3A), as well as with negative emotion scores at the third time point ($r = 0.264$, $p = 0.029$). However, such a correlation was not observed at the second time point (PTSS: $r = -0.027$, $p = 0.881$; negative emotions: $r = -0.002$, $p = 0.989$), which might be associated with the relatively small sample size and limited range of symptom levels at the second time point. After applying Bonferroni correction at each time point ($p < 0.05/2$), only correlation between the severity levels of COVID-19 symptoms and PTSS scores remain statistically significant.

LME model analysis revealed a significant main effect of “COVID-related trauma” on the PTSS and negative emotions. No significant main

effect of “time” and interaction effect between the two factors were detected (Table 4). Independent-sample t-tests showed that COVID-19 survivors with COVID-related trauma had significantly higher level of PTSS and negative emotions than those without COVID-related trauma mainly at the first time point (witnessing someone’s death: 1st time point, $p = 0.004$ for PTSS and $p = 0.006$ for negative emotions, 3rd time point, $p = 0.053$ for PTSS and $p = 0.008$ for negative emotions; witnessing someone receiving emergency treatment: 1st time point, $p = 0.001$ for PTSS and $p = 0.001$ for negative emotions, 3rd time point, $p = 0.054$ for PTSS and $p = 0.048$ for negative emotions; Fig. 3B).

3.6. Multiple linear regression models for predicting PTSS and negative emotions

For PTSS, multiple linear regression results indicated that the variables of age, sex, severity of COVID-19 symptoms, COVID-related trauma, and perceived social support explained 15.6%, 53.4%, and 20.3% of the variance in PCL-5 scores at the first (adjusted $R^2 = 0.156$, F

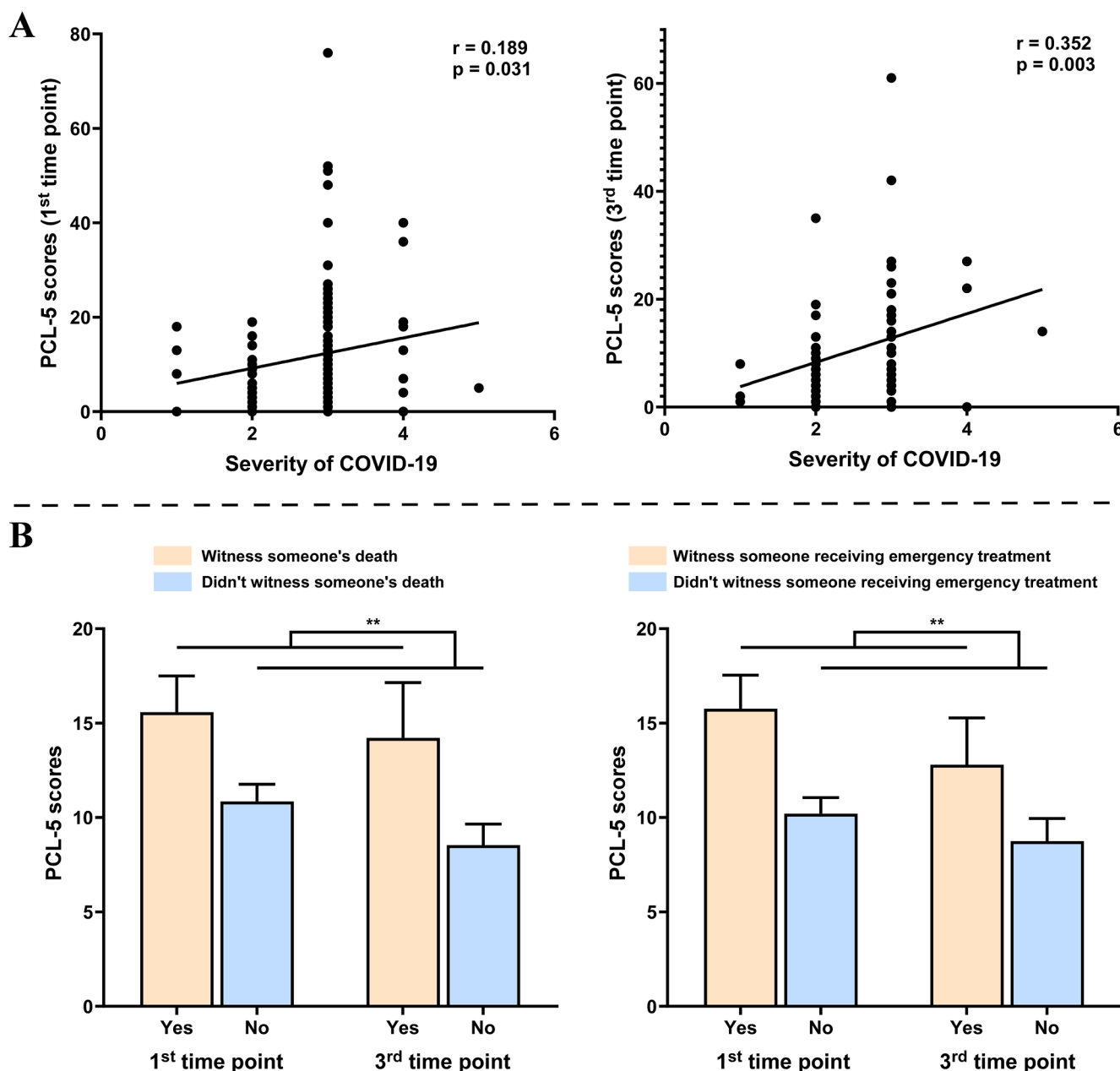


Fig. 3. The effect of COVID-19 severity and COVID-related trauma on post-traumatic stress symptoms for COVID-19 survivors. (A) The severity levels of COVID-19 symptoms showed significant positive correlations with the PCL-5 scores at the first and third time points. (B) Significant main effect of “COVID-related trauma” was detected on the PCL-5 scores. COVID-19 survivors with COVID-related trauma had significant higher PCL-5 scores than those without COVID-related trauma at the first time point. PCL-5, post-traumatic stress disorder checklist for DSM-5. ** $p < 0.01$.

(5, 124) = 5.758, $p < 0.001$), second (adjusted $R^2 = 0.534$, $F(5, 28) = 8.553$, $p < 0.001$), and third time points (adjusted $R^2 = 0.203$, $F(5, 63) = 4.473$, $p = 0.001$), respectively. As summarized in Table 5, COVID-related trauma ($\beta = 0.246$, $p = 0.005$) and perceived social support ($\beta = -0.267$, $p = 0.002$) were risk factors of PTSS as they significantly contributed to explaining PCL-5 scores at the first time point. At the second time point, only perceived social support ($\beta = -0.651$, $p < 0.001$) significantly contributed to explaining PCL-5 scores. At the third time point, the severity of COVID-19 symptom ($\beta = 0.239$, $p = 0.045$) and perceived social support ($\beta = -0.243$, $p = 0.049$) also significantly contributed to explaining PCL-5 scores. After applying Bonferroni correction at each time point ($p < 0.05/5$), the risk factors at the first and second time points remain statistically significant.

For negative emotions, multiple linear regression results indicated that the variables of age, sex, severity of COVID-19 symptoms, COVID-

related trauma, and perceived social support explained 18.0%, 58.4%, and 28.7% of the variance in PC scores at the first (adjusted $R^2 = 0.180$, $F(5, 124) = 6.657$, $p < 0.001$), second (adjusted $R^2 = 0.584$, $F(5, 28) = 10.260$, $p < 0.001$), and third time points (adjusted $R^2 = 0.287$, $F(5, 63) = 6.476$, $p < 0.001$), respectively. As summarized in Table 5, COVID-related trauma ($\beta = 0.226$, $p = 0.009$) and perceived social support ($\beta = -0.286$, $p = 0.001$) were risk factors of negative emotions as they significantly contributed to explaining PC scores at the first time point. At the second time point, only perceived social support ($\beta = -0.677$, $p < 0.001$) significantly contributed to explaining PC scores. At the third time point, sex ($\beta = 0.255$, $p = 0.028$) and perceived social support ($\beta = -0.326$, $p = 0.006$) also significantly contributed to explaining PC scores. After applying Bonferroni correction at each time point ($p < 0.05/5$), all risk factors remain statistically significant except for sex.

Table 4

LME model analysis to assess the effects of “COVID-related trauma” and “time” on post-traumatic stress symptoms (PTSS) and negative emotions.

Factors	PTSS			Negative emotions		
	df	F value	p value ^a	df	F value	p value ^a
Witnessing someone's death						
COVID-related trauma	(1, 222.464)	7.547	0.007	(1, 221.552)	10.063	0.002
Time	(1, 76.249)	1.248	0.267	(1, 77.974)	0.789	0.377
COVID-related trauma × Time	(1, 76.249)	0.076	0.784	(1, 77.974)	0.490	0.486
Witnessing someone receiving emergency treatment						
COVID-related trauma	(1, 226.203)	9.140	0.003	(1, 225.316)	8.787	0.003
Time	(1, 78.044)	1.478	0.228	(1, 79.082)	1.539	0.218
COVID-related trauma × Time	(1, 78.044)	0.489	0.486	(1, 79.082)	0.131	0.716

Please note that the principal component scores obtained in the principal component analysis were used to represent negative emotions.

^a p value of less than 0.05 was considered significant. Abbreviations: PCL-5, post-traumatic stress disorder (PTSD) checklist for DSM-5.

3.7. ANOVA results for ALFF in bilateral amygdala and hippocampus

For bilateral amygdala, ANOVA analysis revealed a significant interaction effect between “group” and “sex” on the ALFF z-values. No significant main effects were detected (Fig. 4A and Table 6). Post-hoc paired-sample t-tests showed that male COVID-19 survivors had significant higher ALFF z-values than female COVID-19 survivors (left amygdala: $p = 0.005$, right amygdala: $p = 0.005$) and male controls (left amygdala: $p = 0.026$, right amygdala: $p = 0.022$). For bilateral hippocampus, significant main effect of “sex” was only observed in the left hippocampus (Fig. 4A and Table 6). No other effects were detected (Table 6).

3.8. Correlations between ALFF and mental health scores and social support

The ALFF z-values of the left and right hippocampus were positively correlated with the depression scores (left hippocampus: $r = 0.211$, $p = 0.047$; right hippocampus: $r = 0.227$, $p = 0.032$). The ALFF z-values of the right hippocampus were negatively correlated with the perceived social support scores ($r = -0.223$, $p = 0.036$). Please note that two subjects had very small perceived social support scores (i.e., score of sub10: 12, score of sub87: 24), which were considered as outliers and were deleted when creating the correlation figure. The correlation between ALFF z-values of the right hippocampus and perceived social support scores after removing the two outliers was found to be much stronger ($r = -0.391$, $p = 0.003$; Fig. 4C). After applying Bonferroni correction ($p < 0.05/3$), only correlation between ALFF z-values of the right hippocampus and perceived social support scores remain statistically significant.

4. Discussion

In the present study, we aimed to investigate the longitudinal changes in mental health status in COVID-19 survivors, with a focus on

Table 5

Results of multiple linear regression analyses for predicting post-traumatic stress symptoms (PTSS) and negative emotions at three time points.

Model	PTSS			Negative emotions		
	Beta	p value	R ²	Beta	p value	R ²
1st time point						
Constant		0.117	0.156***	0.496	0.180***	
Age	0.105	0.238		-0.005	0.959	
Sex	0.050	0.547		0.142	0.087	
Severity of COVID-19 symptom	0.105	0.225		0.126	0.142	
COVID-related trauma	0.246	0.005		0.226	0.009	
Perceived social support	-0.267	0.002		-0.286	0.001	
2nd time point						
Constant		0.006	0.534***	0.033	0.584***	
Age	0.254	0.081		0.157	0.246	
Sex	0.167	0.203		0.221	0.078	
Severity of COVID-19 symptom	-0.138	0.375		-0.067	0.645	
COVID-related trauma	0.167	0.240		0.185	0.169	
Perceived social support	-0.651	0.001		-0.677	0.001	
3rd time point						
Constant		0.260	0.203***	0.354	0.287***	
Age	-0.116	0.326		-0.171	0.128	
Sex	0.171	0.160		0.255	0.028	
Severity of COVID-19 symptom	0.239	0.045		0.186	0.097	
COVID-related trauma	0.195	0.117		0.190	0.106	
Perceived social support	-0.243	0.049		-0.326	0.006	

Please note that the principal component scores obtained in the principal component analysis were used to represent negative emotions. Beta values represent standardized betas. R² values represent adjusted R² values, which explained the variance expressed by the model.

*** $p < 0.001$.

exploring the risk factors and neural mechanisms associated with PTSS and related negative emotions. Our research yielded three main findings. First, female COVID-19 survivors had higher levels of PTSS and depression than female controls for up to 2 years, along with higher levels of anxiety for up to 6 months after their recovery from acute infection. Male COVID-19 survivors exhibited higher levels of PTSS, depression, and anxiety than male controls at 2 months, and then returned to control group level (Fig. 1). Second, COVID-related trauma and lower levels of social support were identified as key risk factors for PTSS and negative emotions in COVID-19 survivors. Finally, male COVID-19 survivors showed increased brain activity in bilateral amygdala than female COVID-19 survivors and controls (Fig. 4A). Whereas depression was positively correlated with hippocampus activity, and the perceived social support showed a negative correlation with right hippocampus activity (Fig. 4C).

Growing epidemiological and clinical evidence have revealed that a significant proportion of survivors reported ongoing mental health problems (Huang et al., 2022; Jiang et al., 2021). In the present study, we systematically explored the longitudinal changes of mental health outcomes over time in COVID-19 survivors and controls. We observed that female COVID-19 survivors exhibited a higher level of PTSS and

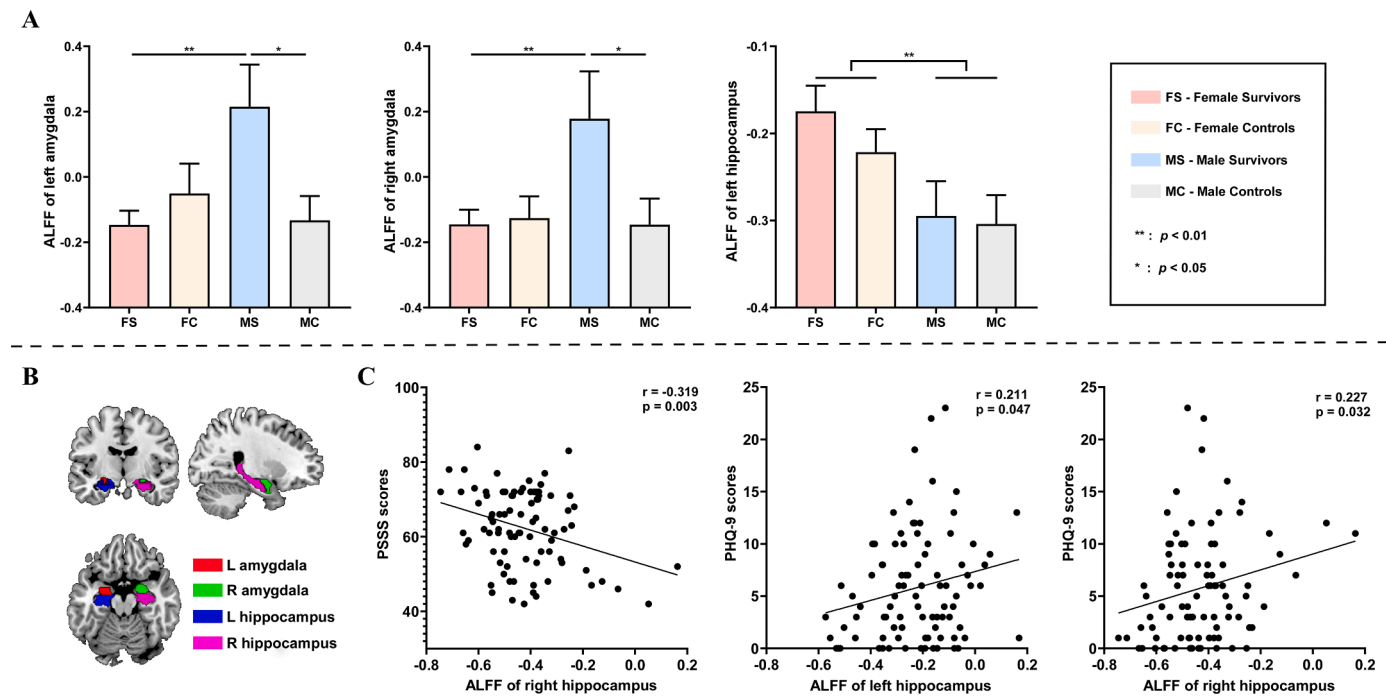


Fig. 4. Brain imaging results at the second time point. (A) Male COVID-19 survivors had significant higher ALFF z-values in bilateral amygdala than female COVID-19 survivors and male controls. Significant main effect of “sex” was observed in the left hippocampus. (B) Schematic representation of bilateral amygdala and hippocampus. (C) The ALFF z-values of bilateral hippocampus were positively correlated with PHQ-9 scores. The ALFF z-values of right hippocampus were negatively correlated with PSSS scores. PHQ-9, Patient Health Questionnaire-9; PSSS, Perceived Social Support Scale. ** $p < 0.01$, * $p < 0.05$.

Table 6

ANOVA results to assess the effects of “group” and “sex” on the ALFF z values.

Factors	F value	df	p value ^a	partial η^2
Left amygdala				
Group	1.894	(1, 85)	0.172	0.022
Sex	2.344	(1, 85)	0.129	0.027
Group $\times$ Sex	5.939	(1, 85)	0.017	0.065
Left hippocampus				
Group	0.623	(1, 85)	0.432	0.007
Sex	8.124	(1, 85)	0.005	0.087
Group $\times$ Sex	0.28	(1, 85)	0.598	0.003
Right amygdala				
Group	3.414	(1, 85)	0.068	0.039
Sex	3.37	(1, 85)	0.070	0.038
Group $\times$ Sex	4.309	(1, 85)	0.041	0.048
Right hippocampus				
Group	1.401	(1, 85)	0.240	0.016
Sex	2.392	(1, 85)	0.126	0.027
Group $\times$ Sex	0.791	(1, 85)	0.376	0.009

^a p value of less than 0.05 was considered significant.

depression than female controls for up to 2 years, along with a higher level of anxiety for up to 6 months after the recovery from acute infection (Fig. 1). Male COVID-19 survivors had a higher level of PTSS, depression, and anxiety than male controls at 2 months after the recovery from acute infection, and then returned to control group level. Consistent with previous studies suggesting that females were associated with higher self-reported levels of stress, anxiety, depression, and PTSS (Sun et al., 2021; Wang et al., 2020; Yuan et al., 2022), our findings also revealed that the mental health problems persisted for a longer duration among females. Considering that female COVID-19 survivors experienced remarkably lower mental health status for up to 2 years, it is crucial to pay special attention to the mental wellness of female

survivors.

The COVID-19 pandemic has exposed millions of people to trauma, such as witnessing someone's death or injury, almost losing their lives, and witnessing someone receiving emergency treatment. Previous studies showed that trauma exposure could be a significant risk factor for the development of PTSD in an individual (American Psychiatric Association and Association, 2013; Ehlers and Clark, 2000; Nisar et al., 2020). Interestingly, we found that COVID-19 survivors with severe COVID symptoms and COVID-related trauma reported a higher level of PTSS (Fig. 3), which possibly confirmed the crucial role of COVID-19-related trauma exposure in developing PTSD among COVID-19 survivors. Moreover, our regression model further revealed that COVID-related trauma could predict PTSS and negative emotions in the short term, whereas severity of COVID-19 symptoms could predict PTSS in the long term. On the contrary, maintaining close relationships and social connections can have a positive impact on an individual's mental health and well-being, especially in managing daily or chronic stress (Lakey and Orehek, 2011; Liu et al., 2020). However, during the COVID-19 pandemic, social distancing and self-isolation strategies may limit the availability and reception of social support as social boundaries are extended (Liu et al., 2020; Szkody et al., 2021). In the present study, we found that female COVID-19 survivors perceived significant lower levels of social support than female controls at 2 months and 6 months post-discharge (Fig. 1). This observation indicated that having COVID-19 infection may have an adverse effect on perceived social support in females, ultimately affecting their mental health state. Consistent with previous studies demonstrating the protective role of social support on mental health outcomes, including PTSD, anxiety, and depression (Dour et al., 2014; Liu et al., 2020; Shi et al., 2022; Wang et al., 2021; Zalta et al., 2021), we found significant negative correlations between perceived social support and PTSS, anxiety, depression, and negative emotions at all three time points (Fig. 2). Importantly, the regression model showed that the perceived social support could always predict the severity of PTSS and negative emotions at all three time points. Altogether, we identified that COVID-related trauma (short

term) and low social support (sustained) were risk factors for PTSS and negative emotions in COVID-19 survivors. Therefore, it is essential to prioritize provision of social support and other forms of assistance to promote the mental well-being of COVID-19 survivors, especially those who have endured severe symptoms and traumatic events. Interventions, such as support from family members, friends, peers, professionals, and social networks, as well as remote interventions via the internet or telephone, might be beneficial in improving individual's mental well-being. Importantly, fostering reciprocal support (e.g., both giving and receiving support) might be especially useful.

The amygdala and hippocampus are two important brain structures involved in PTSS (Fenster et al., 2018), emotion regulation (Phelps and LeDoux, 2005), and social support (Förster et al., 2021). Our previous study reported that COVID-19 survivors had larger grey matter volume and increased functional activity in bilateral hippocampus and amygdala, and that the volumes of these brain regions were significantly correlated with PTSS (Tu et al., 2021). In the present study, we investigated brain activity in the amygdala and hippocampus separately for females and males, and we found that male COVID-19 survivors had higher amygdala activity (Fig. 4A), which was accompanied with lower levels of PTSS, depression, and anxiety than female survivors. These results suggested that the amygdala was hyper-activated among male survivors, and the heightened brain activity could be a functional compensation to cope with the acute stress and the ongoing COVID-19 related trauma (Lu et al., 2020; Tu et al., 2021). Besides, the hippocampus plays a crucial role in trauma-related memory (Pitman et al., 2012), which may influence the trauma-related negative emotions (Mary et al., 2020), such as anxiety and depression. In the present study, we found that females had higher left hippocampus activity than males (Fig. 4A), which may be related to more trauma-related negative emotions. Notably, we also found positive correlations between bilateral hippocampus activities and depression symptoms in COVID-19 survivors (Fig. 4C), indicating a relationship between heighten hippocampus activity and increased depression symptoms. Furthermore, we detected a negative correlation between right hippocampus activity and perceived social support (Fig. 4C), suggesting that perceiving more social support has a protective effect on hippocampus function, which may in turn improve mental health state, such as depression. Overall, our findings suggested that the amygdala and hippocampus play vital roles in the mental health outcomes of COVID-19 survivors. Furthermore, our study underscored the significance of the hippocampus in relation to PTSS risk factors, such as lower levels of social support, which supported our behavioral observations and demonstrated the critical role of the hippocampus in the development of PTSS.

Several limitations of the present study should be acknowledged. Recent evidence has underscored the existence of persistent symptoms long after the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, now termed 'long COVID' (Sudre et al., 2021; The Lancet, 2020). Like acute COVID-19, long COVID encompasses a spectrum of multiorgan symptoms, spanning from cough and shortness of breath to fatigue, dyspnea, headache, muscle pain, cardiac abnormalities, sleep disturbances, cognitive impairment, and mental health problems (i.e., post-traumatic stress disorder, anxiety, and depression). In our study, we observed enduring mental health problems among COVID-19 survivors, especially among females. These conditions may be linked to the long COVID. Nevertheless, it is important to note that we solely collected mental health data during the post-epidemic periods and lacked a pre-epidemic baseline. Consequently, we cannot ascertain whether the mental health problems in COVID-19 survivors preexisted before the pandemic or resulted from COVID-19. Furthermore, our study did not encompass an assessment of other persistent symptoms in COVID-19 survivors, aside from their mental health status. Therefore, we cannot definitively determine whether the participants in our study experienced long COVID.

5. Conclusion

Our study highlights the possible impact of COVID-19 on mental health and emphasizes the importance of continued monitoring mental wellbeing of COVID-19 survivors, particularly for female survivors and individuals with severe COVID-19 symptoms and COVID-related trauma. Moreover, establishing a strong social support system during epidemics is crucial to improve mental health outcomes for COVID-19 survivors. Our results isolating risk factors for developing PTSS and negative emotions also provide valuable insights that can be leveraged to tailor mental health services to the needs of COVID-19 survivors and inform the development of effective interventions.

Data and code availability statements

Data in the present study can be requested from the corresponding author with clear research aims. The codes for analyzing MRI data can be found in the Data Processing & Analysis for Brain Imaging toolbox (DPABI_V5.1_201201, <http://rfmri.org/dpabi>). No customized codes were used in this study.

CRediT authorship contribution statement

Yanzhi Bi: Conceptualization, Methodology, Formal analysis, Investigation, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. **Yian Xiao:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft. **Xinyu Pan:** Investigation, Data curation. **Yuqi Zhang:** Investigation, Data curation. **Quanqi Yang:** Methodology, Formal analysis. **Li Hu:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2023.115523](https://doi.org/10.1016/j.psychres.2023.115523).

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