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Trajectories of Short-Term Post-Traumatic Stress Disorder Symptoms in Patients with Post-Intensive Care Syndrome: A Longitudinal Observational Study

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Purpose: Post-traumatic stress disorder (PTSD) is a major psychiatric health issue among intensive care unit (ICU) survivors with post-intensive care syndrome (PICS). Although early PTSD intervention has been demonstrated to decrease the risk of progression from acute to chronic PTSD, information on the progression trajectory of short-term PTSD symptoms and modifiable risk factors in PICS patients is limited. This study aimed to explore the clinical progression trajectories of short-term PTSD symptoms and the associated factors in PICS patients by conducting a prospective longitudinal observational study.

Patients and Methods: This study was conducted at a tertiary hospital in China. The impact of event scale-revised was used to collect data on the PTSD symptoms of patients at 1, 2, 3, and 4 months post-discharge from the ICU. The latent growth mixture model was used to construct trajectory models for PTSD symptoms and multivariate logistic regression was used to determine the factors associated with the trajectories.

Results: A total of 130 ICU survivors with PICS completed the 4-month short-term follow-up. Our results showed that PTSD symptoms in PICS patients manifested as three trajectories, namely, moderate chronic (n = 17, 13.1%), recovery (n = 25, 19.2%), and resilience (n = 88, 67.7%). Compared with the resilience trajectory, age and female were identified as risk factors for the moderate chronic trajectory, while prolonged ICU stay was a risk factor for the recovery trajectory.

Conclusion: Our study showed that short-term PTSD symptoms in PICS patients manifested as moderate chronic, recovery, and resilience trajectories. Additionally, our results showed that PTSD screening should be conducted for critically ill patients, especially younger, female, or long-term ICU patients, immediately after their discharge from the ICU.

Keywords: post-traumatic stress disorder, latent growth mixture model, longitudinal study, post-intensive care syndrome

Introduction

The rapid development in critical care diagnosis and treatment techniques in recent years has led to a significant decrease in the mortality rate of intensive care unit (ICU) patients and a subsequent increase in the number of patients discharged from the ICU. The post-discharge physical and mental health of such patients has attracted increasing research attention worldwide.[1] The term "post-intensive care syndrome (PICS)" was first proposed by the Society of Critical Care Medicine in 2010 to describe new or worsening cognitive, physical, or psychological impairment in critically ill patients and their family members after discharge from the ICU.[2] Previous studies have reported that the incidence of PICS and psychological disorders is 49.6–95.7% and 14.6–50%, respectively, after ICU discharge.[3–7] Post-traumatic stress disorder (PTSD) is a primary psychiatric disorder in PICS, with a prevalence of 4–62% among ICU survivors.[8] Its psychological

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symptoms can last for over a month post-discharge, thus negatively affecting the health-related quality-of-life of ICU survivors.[9] Despite having similar experiences, PTSD progression and its symptoms among ICU patients may vary due to various factors.[10] Previous studies on PTSD in ICU survivors were primarily cross-sectional[11,12] or longitudinal in design and used traditional data analysis methods, which do not fully capture the heterogeneity in symptom progression.[13] For instance, there has been one reported retrospective observational study analyzing the PTSD trajectory and associated factors in sepsis survivors; however, the sample was from a previous interventional study, which may have affected the results.[14] Although a handful of studies have explored PTSD trajectories in ICU survivors (including those with sepsis, acute lung injury, and chronic critical illness, and pediatric ICU patients), these studies primarily focus on long-term PTSD trajectories.[14–17] The trajectory of short-term PTSD symptoms in ICU survivors remains poorly understood. Several studies demonstrated that early intervention can reduce the progression of PTSD from acute to chronic PTSD.[18–20] Determining the progression trajectories of short-term PTSD symptoms and potentially modifiable risk factors in PICS patients is significant for early intervention and prevention of chronic PTSD. Therefore, in this study, we used the latent growth mixture model (LGMM)[21] to examine the trajectories of short-term PTSD symptom progression in PICS patients. Additionally, we analyzed trajectory-related sociodemographic, diagnostic, and therapeutic characteristics to provide a clinical basis for the early prevention, intervention, and management of PTSD symptoms in PICS patients.

Materials and Methods

Study Design

To better evaluate and analyze PTSD trajectories over time, this study used a prospective, longitudinal, observational design, and it was conducted from January 2023 to June 2024.

Site and Samples

The study was conducted at a tertiary hospital that had an 18-bed ICU. The inclusion criteria were as follows: patients aged ≥ 18 years; patients at 1-month post-discharge after receiving at least 24 hours of treatment during their first ICU admission; patients who met the diagnostic criteria for PICS (ie, new-onset or worsening cognitive impairment; psychological impairment, such as anxiety, depression, or PTSD; or physical impairment);[2] and patients who provided informed consent and were willing to participate in the study. The exclusion criteria were as follows: patients with a history of anxiety, depression, or other psychiatric disorders or cognitive impairment; patients with auditory or expression disorders (who were unable to understand the questionnaire); patients with a history of cranial trauma, dementia, epilepsy, stroke, Alzheimer's disease, or other diseases that could cause cognitive impairment; patients who were disabled, incompetent, or unable to perform self-care before ICU admission; or patients with a physical disease that would prevent participation in the study. A study by Mara and Carle showed that a sample size of > 100 patients and at least 4 repeated measurements met the sample size requirements for LGMM studies.[22] A total of 221 critically ill patients were initially included in the study, of which only 130 met the inclusion criteria. Among these, 6 and 7 patients failed to show up for the 2nd and 3rd follow-ups, respectively. The mean age of patients was 62.35 ± 17.45 years, with 56.9% being male, and 43.1% female. The vast majority of patients (93.1%) were married. The data of 130 PICS patients were included in the final analysis and the detailed information of each follow-up is shown in Figure 1.

Data Collection

Researchers who underwent unified training assisted patients in completing the surveys. All patients were screened after 1-month post-discharge (T1) from the ICU to determine if they met the diagnostic criteria for PICS. Those who met the PICS criteria were then screened at 2 (T2, first follow-up), 3 (T3, second follow-up), and 4 (T4, third follow-up) months post-discharge to reevaluate the PTSD symptoms. During this study, we conducted face-to-face interviews with patients if they were transferred to an ordinary ward or conducted a telephone follow-up if they were discharged. The integrity of the data was examined immediately after the surveys were completed. The patients were allowed to withdraw anytime from the study.

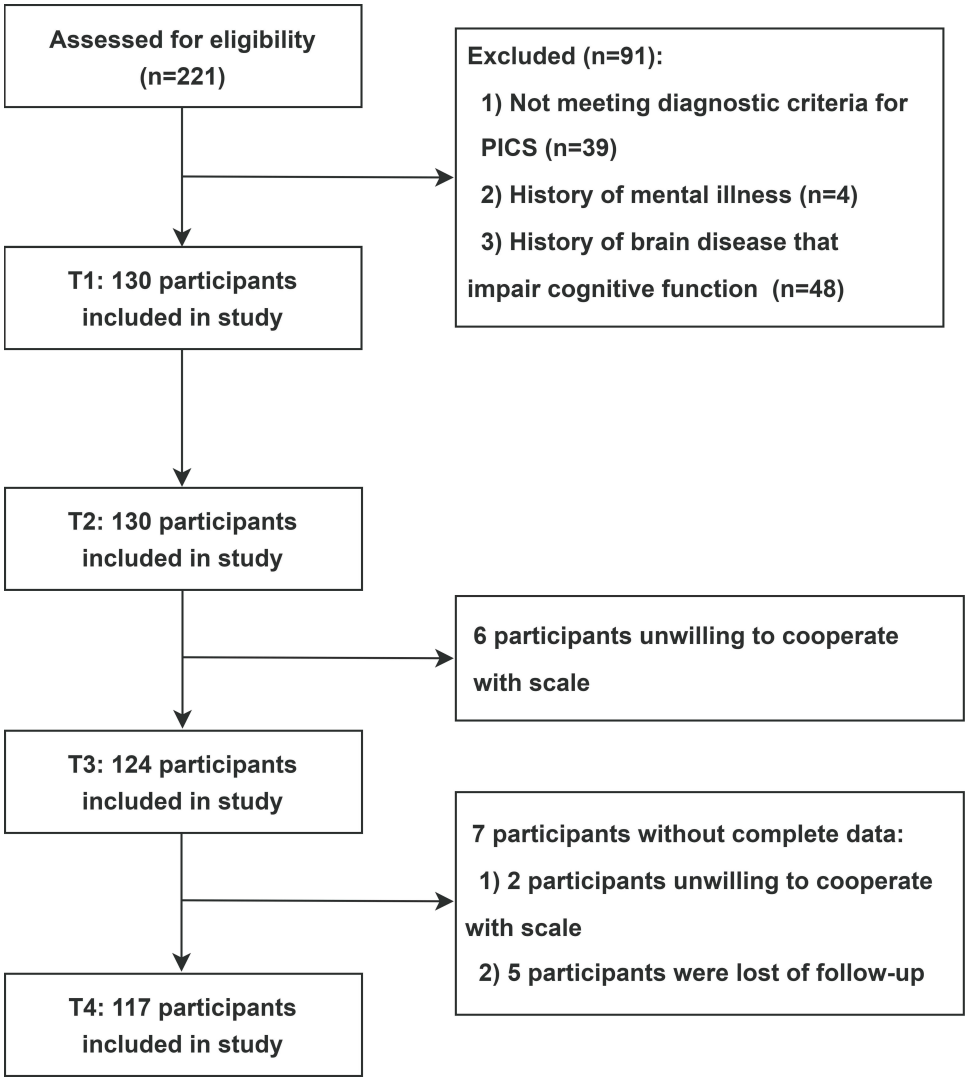

Figure 1 Participant flowchart.

Measurement

The researchers collected sociodemographic, clinical diagnostic, and treatment-related data of the patients, including age, gender, marital status, education level, past medical history (such as hypertension, diabetes mellitus), ICU admission route (emergency and non-emergency departments), Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[23] use of continuous renal replacement therapy (CRRT), surgery, mechanical ventilation and its duration, ICU sedative use, length of ICU stay, and length of hospitalization, from the institutional electronic medical record system.

Face-to-face PICS evaluation was conducted at 1-month post-discharge from the ICU. Due to the lack of PICS-specific evaluation tools, the patients were evaluated by mini-mental state examination (MMSE),[24] Barthel index (BI),[25] and Hospital Anxiety and Depression Scale (HADS)[26] for new or worsening cognitive, physical, and psychological impairments, respectively, based on the definition of PICS.[2,27] The MMSE is used to assess cognitive function, including orientation, memory, attention, calculation, recall, and language, on a scale of 0–30, with a score < 24 indicating cognitive impairment. The BI is used to evaluate daily activities on a scale of 0–100 points, with a higher score indicating greater independence in daily activities and a score of 100 indicating complete capability for self-care. The HADS is a 14-item scale used to evaluate anxiety and depression, with a score > 8 indicating the presence of anxiety or depression.[28] PTSD was evaluated using the impact of event scale-revised (IES-R),[29] which consisted of three core PTSD symptoms: intrusion, avoidance, and hyperarousal, with a score ≥ 1.6 indicating significant PTSD symptoms.[30]

Statistical Analysis

The missing covariate values (such as age) were first processed based on the mean sample value.

Thereafter, LGMM was used to examine the different progression trajectories of PTSD symptoms in PICS patients. The missing IES-R values of 6 (4.6%) and 13 (10%) patients at T3 and T4, were processed based on the default option in Mplus (full information maximum likelihood). Although the data not fully adhere to a normal distribution (Supplementary Material, Figure S1), the trajectory model estimated using maximum likelihood (default parametric estimation method for continuous variables in Mplus) was deemed acceptable, with absolute skewness and absolute kurtosis of < 2 and < 7, respectively.[31] Factor loadings were set as 0, 1, 2, and 3 to express the same interval for the 4 time points. First, the presence of a linear or non-linear trajectory model was confirmed. Briefly, the unconditional linear latent growth curve model (LGCM) or non-linear LGCM were fitted and the goodness-of-fit of the two models was detected using the root mean square error of approximation (RMSEA, ≤ 0.05–0.1), comparative fit index (CFI) and Tucker-Lewis index (TLI) (≥ 0.90–0.95), as well as the standardized root mean square residual (SRMR, ≤ 0.05–0.08).[32,33] Thereafter, the relative optimal model (the Mplus syntax can be found in the Supplementary Material) was confirmed. To select the optimal number of latent classes, the model started estimation from 1 latent class at the random start value set to 200. Thereafter, the number of classes was gradually increased until the proportion of one latent class was < 5%. The following criteria were used to determine the final number of latent classes: 1) lower Akaike information criterion (AIC),[34] Bayesian information criterion (BIC),[35] and sample size-adjusted BIC (aBIC),[36] indicating a better fit for the model; 2) entropy ≥ 0.80 (range from 0 to 1, the largest entropy indicating the highest classification accuracy);[37] and 3) $p < 0.05$ from Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) and bootstrap likelihood ratio test (BLRT) indicating that the model with k number of classes is better than that with k−1 number of classes.[22] Lastly, the actual significance and interpretability of the model were also taken into account. The model was constructed using Mplus v8.10 (Mplus, CA, USA; https://www.statmodel.com/index.shtml). Individuals were assigned to latent classes based on maximum posterior probability.

The corresponding description method (mean ± standard deviation, median and quartiles, or number of subjects and percentage) and analysis methods (analysis of variance, Kruskal–Wallis *H*-test, or Chi-square test and Fisher's exact test) were selected based on the type of variable and normality of data distribution. Multivariate logistic regression analysis was used to analyze the effects of demographic data and disease-related data on the trajectory of PTSD symptoms. The R v.4.3.1 software (R Foundation for Statistical Computing; https://www.r-project.org/) was used to conduct statistical analysis and a P-value of < 0.05 was considered statistically significant.

Ethics Approval Details

This study was approved by the institutional ethics committee [KY-2022001] and was registered with the Chinese Clinical Trial Registry (ChiCTR2200067138). All subjects provided signed informed consent.

Results

The results showed that the goodness-of-fit of the unconditional linear LGCM was better than that of the non-linear LGCM (RMSEA: 0.098 vs 0.308), indicating that the trajectory of PTSD in PICS patients was closer to linearity (Supplementary Material, Table S1).

Table 1 shows the LGMM model fit indices. The 4-class estimation model was excluded as the p-value of BLRT was > 0.05, and one class in the model accounting for < 5%. The AIC, BIC, and aBIC decreased with the number of classes in four models. However, the 3-class estimation model was retained, as it had 0.949 entropy (higher than that for the 2-class estimation model) and statistically significant VLMR and BLRT ($p < 0.05$). The positive predictive value of the 3-class estimation model ranged between 0.950–0.998, which was considered to be acceptable (Supplementary Material, Table S2).[22]

The IES-R score (Y-axis) and time of discharge from ICU (X-axis) were used to plot the 3 latent class trajectories (Figure 2), and the trajectory intercepts and slopes are shown in Supplementary Material, Table S3. Based on the variation trend and characteristics of the trajectory curve, the three trajectories of PTSD symptom progression in PICS

Table 1 Fit Indices of the for the LGMM Models of the IES-R, for Increasing Number of Classes (1 to 4)

No. of Classes	Number of Free Parameters	AIC	BIC	aBIC	Entropy	VLMR	BLRT	N Per Class
1	4	230.689	242.159	229.508	–	–	–	130
2	9	−139.302	−113.494	−141.959	0.920	<0.001	<0.001	23/107
3	14	−196.438	−156.293	−200.572	0.949	0.013	<0.001	17/25/88
4	19	−193.721	−139.238	−199.331	0.933	0.373	1.000	18/5/24/83

Abbreviations: IES-R, impact of event scale-revised; LGMM, latent growth mixture modelling; AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, sample size-adjusted BIC; VLMR, Vuong-Lo-Mendell-Rubin test; BLRT, bootstrap likelihood ratio test.

patients could be interpreted as moderate chronic (n = 17, 13.1%), recovery (n = 25, 19.2%), and resilience (n = 88, 67.7%).

Univariate analysis showed significant differences in the age, female, and length of ICU stay among the trajectories ($p < 0.1$; Table 2). Further multivariate logistic regression analysis showed that compared with the resilience, age ($p = 0.017$) and female ($p = 0.009$) were the risk factors for the moderate chronic, while prolonged ICU stay ($p = 0.008$) was a risk factor for the recovery trajectory (Table 3).

Discussion

In this study, we explored the trajectories of short-term PTSD symptoms in PICS patients and determined their associated characteristics and factors. Our study showed that short-term PTSD symptoms manifested as three different trajectories, namely moderate chronic, recovery, and resilience. In this study, the majority of the PICS patients were classified within the resilience trajectory at 4 months post-discharge from the ICU (< 1.6 IES-R). Some patients had moderate PTSD symptoms at 1-month post-discharge from ICU, which were maintained at relatively comparable levels in the subsequent

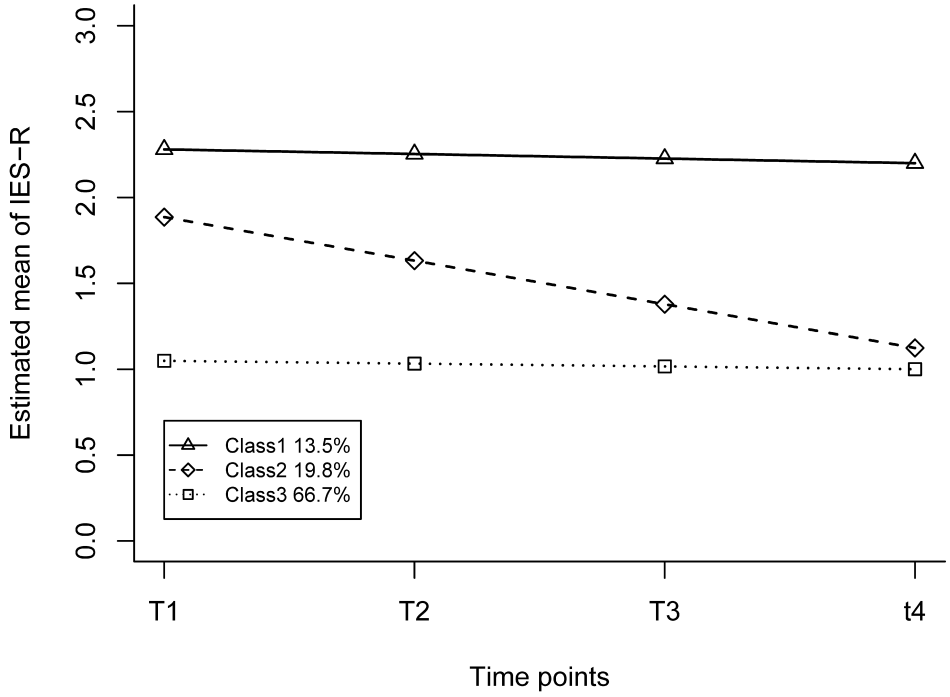

Figure 2 Estimated means for 3-class solution of IES-R (n = 130).
Notes: T1, T2, T3, and T4 represent the assessments at 1 month, 2 months, 3 months, and 4 months after patients were transferred out of the intensive care unit, respectively.
Abbreviations: IES-R, impact of event scale-revised.

Table 2 Univariate Analyses of Characteristics of Trajectory Classes

Variables	Moderate Chronic (n = 17)	Recovery (n = 25)	Resilience (n = 88)	*F*/x^2/*H*	*P* value
Age (y), mean (SD)	53.7 (20.9)	64.5 (15.4)	63.4 (17.0)	2.497	0.086[a]
Female, no. (%)	12 (70.6)	11 (44.0)	33 (37.5)	6.372	0.041[b]
Married, no. (%)	17 (100.0)	22 (88.0)	82 (93.2)	–	0.367[c]
Educational status > high school, no. (%)	4 (23.5)	3 (12.0)	14 (15.9)	–	0.623[c]
Hypertension, no. (%)	6 (35.3)	8 (32.0)	35 (39.8)	0.549	0.760[b]
Diabetes, no. (%)	5 (29.4)	9 (36.0)	22 (25.0)	1.205	0.547[b]
Emergency, no. (%)	7 (41.2)	9 (36.0)	29 (33.0)	0.452	0.798[b]
APACHE II scores, median (IQR)	19.0 (13.5)	23.0 (5.5)	18.0 (10.8)	3.345	0.188[d]
Use of CRRT, no. (%)	3 (17.6)	2 (8.0)	6 (6.8)	–	0.307[c]
Surgery, no. (%)	5 (29.4)	10 (40.0)	33 (37.5)	0.526	0.769[b]
Use of MV, no. (%)	9 (52.9)	19 (76.0)	49 (55.7)	3.649	0.161[b]
Duration of MV (h), median (IQR)	4.8 (121.5)	60.0 (127.8)	18.8 (89.2)	3.381	0.184[d]
Use of sedative, no. (%)	15 (88.2)	22 (88.0)	68 (77.3)	–	0.436[c]
Length of ICU stay (d), median (IQR)	5.0 (6.0)	7.0 (8.5)	5.0 (4.0)	7.886	0.019[d]
Length of hospitalization (d), median (IQR)	14.0 (22.0)	20.0 (31.0)	19.5 (18.8)	1.171	0.557[d]

Notes: [a] analysis of variance; [b] Chi-square analysis; [c] Fisher's exact test; [d] Kruskal–Wallis *H*-test.
Abbreviations: SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; ICU, intensive care unit.

Table 3 Multivariate Logistic Regression of Trajectory Classes (Reference Class: Resilience)

Variables	Moderate Chronic (n = 25)			Recovery (n = 17)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	0.961	0.930–0.993	0.017	0.989	0.961–1.018	0.461
Female	4.891	1.498–15.968	0.009	1.674	0.638–4.389	0.295
Length of ICU stay	1.046	0.948–1.155	0.367	1.096	1.025–1.173	0.008

Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

evaluations. In the remaining patients, PTSD symptoms declined gradually with time, eventually reaching the asymptomatic state at the last follow-up.

Several studies demonstrated that PTSD due to natural disasters,[38] war,[39] violence,[40] and coronavirus disease 2019 (COVID-19)[41] manifests into different trajectories with time, indicating its heterogeneity. A meta-analysis of 54 PTSD trajectory-related studies showed that recovery, chronic, resilience, and delayed onset are the 4 most common PTSD trajectories,[42] with the resilience, chronic, and recovery trajectories accounting for 66%, 11%, and 21% of the mean prevalence, respectively, which is consistent with our findings (67.7%, 13.1%, and 19.2%, respectively). However, in our study, we did not detect the delayed onset trajectory, which may be attributed to our focus on short-term PTSD and the low prevalence of delayed onset trajectory. For instance, among 22 related studies, delayed onset trajectory was only observed in 41% of the studies.[42] Therefore, our results are generally consistent with previous reports on PTSD in non-ICU environments.

Limited studies have been conducted on the short-term PTSD symptom trajectories of ICU survivors. Among these, only 4 studies demonstrated the longitudinal changes in long-term PTSD symptoms of ICU survivors (with a follow-up duration of 6 months to 2 years). Of these, 2 studies conducted PTSD evaluations four times,[14,15] while 2 studies conducted PTSD evaluations twice (one of them included both children and their parents).[16,17] Schmidt et al[14] conducted a 2-year follow-up in sepsis survivors at 3-, 6-, 12-, and 24-months post-discharge and found 3 trajectories, namely stable low symptoms (ie, non-clinically significant symptoms, 59%), increasing symptoms (26%), and recovering from symptoms (15%), with the incidence of stable low symptoms and recovering from symptoms consistent with our

findings. Another study conducted a 2-year follow-up at 4 time points and found 4 trajectories, namely no symptoms (65%), maintainers (19%), remitters (11%), and relapsers (5%), with the incidence of the first 3 trajectories aligning with our findings.[15]

A previous study found that women are more prone to PTSD, owing to their testosterone, estradiol, and progesterone levels.[43] Consistently, a recent retrospective trajectory study demonstrated that the incidence of PTSD is higher in women compared to men.[14] A global epidemiology report on cross-national world health survey data showed that the risk of PTSD is higher among the younger population.[44] In addition, a systematic review of 23 critical care and PTSD-related studies showed that younger patients (< 50 years old) and patients with prolonged ICU stay had higher PTSD symptom scores in the follow-up.[45] These results were verified in a large-scale cohort study that found that the risk of subsequent psychiatric disorders was higher in patients with prolonged ICU stay,[46] which could have been due to the increase in intrusion score (a core characteristic of PTSD) with an increase in the length of ICU stay.[47] Our results found that young age, female sex, and prolonged ICU stay increase the risk of PTSD in PICS patients, consistent with the results of previous studies.

This study has a few limitations. First, this study is focused on short-term PTSD symptoms, and future studies may involve more measurements and longer follow-up duration to examine the differences in short-term and long-term PTSD symptom trajectories. Second, this study used IES-R for screening PTSD, without clinical diagnosis by a psychiatrist. Lastly, the sociodemographic and clinical information included in our study was not comprehensive, thus future studies should consider including other potential factors that were not measured in this analysis.

Conclusion

We employed LGMM to examine the growth trajectories of short-term PTSD and their associated factors in PICS patients post-discharge from the ICU. The results found that PICS patients who were younger, female, or had prolonged ICU stay were at an increased risk of developing PTSD symptoms post-discharge from the ICU. Future studies should consider evaluating PTSD symptoms in ICU survivors, immediately after their discharge from the ICU, in order to adopt corresponding preventative measures to stop its progression to chronic PTSD.

Data Sharing Statement

The data will be shared on reasonable request to the corresponding author.

Ethics Approval and Informed Consent

All procedures performed in this study adhered to the ethical standards of the Xiamen Haicang Hospital and the 1964 helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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