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Latent Trajectories of Activities of Daily Living Disability and Associated Factors Among Adults with Post-Intensive Care Syndrome One Week After ICU Discharge

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Objective: To identify the latent trajectories of activities of daily living (ADL) disability and the influential factors among adults with post-intensive care syndrome (PICS).

Methods: We evaluated five-time longitudinal data about PICS diagnosed in 434 of 593 assessed patients (73.19%). Disability was measured by the Barthel index scale, which grades individuals according to how difficult it is to carry out ADL. We utilized the growth mixture model (GMM) to identify latent trajectories and associated factors.

Results: Two groups with distinct trajectories of ADL disability were identified, including the Severe Disability Sustained Group and the Disability Recovery Group. People who were of advanced age transferred to another hospital for treatment, or had cognitive impairment or depression were more likely to be classified into the Severe Disability Sustained Group ($P < 005$).

Conclusion: There are two potential trajectories of ADL disability in patients with PICS, which are the severe disability persistence group and the disability recovery group. Improvement in cognitive impairment or depression may contribute to recovery from disability, transfer to hospital or advanced age may not be conducive to recovery of ADL ability, and disability may last longer.

Keywords: activities of daily living, critical illness, disability, growth mixture model, post-intensive care syndrome

Introduction

Currently, in North America, up to 80% of critically ill patients survive Intensive Care Unit (ICU) treatment.[1] However, ICU survivors may experience a series of setbacks. Six months to 3 years after discharge, ICU survivors are more likely than patients treated in regular wards to develop cognitive impairment, mental disorders, fatigue, chronic pain, or Activities of Daily Living (ADL) disability.[2] In 2010, the Society of Critical Care Medicine (SCCM) named this collection of mental, cognitive and physical problems in ICU survivors "post-intensive care syndrome" (PICS).[3] More specifically, PICS was defined "as new onset or worsening of impairment(s) in physical, cognitive, and/or mental health that arose after the ICU and persisted beyond hospital discharge".[3] PICS can either develop or worsen after ICU treatment and can last for months to years after discharge, seriously affecting patients' long-term quality of life.[3] The incidence of PICS in China ranges from 24.8% to 53.6%.[4,5] Wang Ying et al[6] found that the incidence of PICS in Zunyi

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was 68.21%, which was higher than that in other regions of China. At present, most patients are not diagnosed and treated in time, which not only aggravates the patient ‘s primary disease but also poses a great threat to their prognosis and quality of life. PICS is significantly correlated with all-cause mortality, largely due to ADL disability.[7]

With the deepening study of PICS, the focus of research has gradually shifted from survival following ICU discharge to functional recovery after discharge. ADL, or self-care ability, is a key component of functional status and an important indicator of quality of life.[7,8] There is a high incidence of ADL disability in discharged ICU patients, Ma et al found that 75% of patients still had ADL disability at 6 months after they were transferred out of ICU.[9] Van et al found that 67% of patients had full ADL disability at 1 week after they were transferred out of ICU.[10] Another study found that 47% of patients had new ADL disability at 2 months after they were transferred out of ICU.[11] ADL disability is associated with an increased risk of unplanned readmission, increased health expenditure and increased mortality.[12,13] Thus, improving ADL is the key to promote the rehabilitation of ICU patients and improving their quality of life.[14] Some studies showed different patterns of ADL disability development in older populations.[15,16] However, whether there are different development trajectories of ADL disability in PICS population has not been confirmed by relevant studies. In order to further understand the heterogeneity of ADL disability development in PICS population, it is necessary to identify its potential development trajectory and influencing factors. In addition, studies have shown that patients with physiological impairment may take 1 year or even longer to fully recover, suggesting that PICS, especially post-ICU physiological dysfunction, should be paid enough attention to.[17] Clinical medical staff should take relevant measures as early as possible, such as early functional exercise to prevent the occurrence of related damage, and identify and intervene as early as possible after ICU patients are transferred out to promote the rehabilitation of patients. Therefore, early identification of the occurrence of ADLs in the PICS population is essential, and through this study it is possible to provide reference information for early intervention of ADLs, thereby improving quality of life.

As a statistical method commonly used to evaluate the development trajectory of longitudinal health data, traditional growth modeling is to characterize the average development trajectory of the population under the premise that the overall internal development trajectory is homogeneous, including multilevel modeling (MLM) and latent growth curve modeling (LGCM).[18] However, the overall development trajectory may have non-negligible heterogeneity characteristics, that is, there may be mutually exclusive groups in the overall population, and the development trajectory in the population is homogeneous, while there are differences between groups, so in order to explore the heterogeneous health trajectory, growth mixture modeling (GMM) has been widely concerned and applied.[18] GMM is a statistical model that introduces the concept of latent class on the basis of LGCM and is used to deal with the heterogeneity of overall development trajectory. The basic analysis process can be understood as: dividing the heterogeneous population into different potential trajectory categories and depicting the development trajectory of each type through LGCM, and naming according to the trajectory characteristics of each type.[18]

Therefore, the aim of this study was to identify potential trajectories of ADL disability and factors influencing trajectories using growth mixed models (GMM). In addition, by identifying the latent trajectories, our study’s aim also to provide more valuable information about the development of ADL disability after ICU stay.

Study Subjects and Methods

Study Subjects

From June 2020 to April 2021, all patients admitted to a 58-bed general ICU in a tertiary university hospital in Guizhou, China, were eligible. This Study was a prospective observational study. Data on all population characteristics were collected prospectively. This study was approved by the Ethics Committee of Jinsha County People’s Hospital (KLL Y-2020-150), and was carried out in accordance with the ethical principles as set out in the Declaration of Helsinki, verbal informed consent process was acceptable and approved by the ethics committee. Verbal was obtained before commencement of the survey. The participants or their relatives were assured that their responses would be confidential and anonymous; they reviewed a comprehensive brochure that explained the purpose of the registry and the intended use of the data.

We collected a group of patients aged >18 years old who stayed in the general ICU for at least 24 hours. All patients were screened and evaluated by a postgraduate majoring in critical care nursing, and patients who presented PICS 1 week after ICU were included. The exclusion criteria were as follows: (a) craniocerebral trauma, toxic encephalopathy and other diseases that can cause cognitive impairment; (b) preexisting ADL disability; (c) preexisting cognitive impairment; (d) severe hearing or vision impairment completing the scale test; (e) unconscious or dead within a week of leaving the ICU; and (f) traffic accident or severe trauma. Patients with cognitive impairment or ADL disability due to other causes, as well as patients who could not complete the full trial, were excluded by the above criteria to avoid these factors affecting the trial results.

Data Collection

The following demographic and hospital data were collected: Acute Physiology and Chronic Health Evaluation (APACHE) II score, type of diagnosis at admission, mental status at admission, maximum C-reactive protein (CRP) during hospitalization, delirium, medical expenses, leave ICU direction (refers to the medical results after the patient is transferred out of ICU, including discharge and transfer therapy), duration of mechanical ventilation (MV), length of ICU stay, hospital length of stay (LOS), tracheotomy, operation, restraints, continuous renal replacement therapy (CRRT), types and doses of sedatives and analgesics, and demographic variables such as age, sex, years of education, marital status, medical expenses payment method, occupation, body mass index (BMI), history of smoking and alcohol intake. BMI was divided into lean (<18.5 kg/m^2), normal (18.5 to 23.9 kg/m^2), overweight (24 to 27.9 kg/m^2), and obese (≥28 kg/m^2) groups.

This study aims to identify subgroup of homogeneous subgroup based on the evolutionary profiles. Two trained research nurses, using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), screened all patients for delirium at 8:00 daily.[19] PICS symptom assessment scales, such as the Chinese version of the Blessed Dementia Rating Scale (BDRS), were completed by relatives and used to assess the cognitive status of patients before admission to the ICU. A score >4 indicated that patients had cognitive impairment.[20] It is not convenient to evaluate the cognitive status of patients before ICU admission, so BDRS is used.[21] Previous studies[22,23] have found that BDRS is highly effective, with a sensitivity of 90.5% and specificity of 98.1% in cognitive status from healthy controls, and despite changes in participants' characteristics, BDRS has shown overall stability in the assessment of cognitive status over nearly 30 years. The Chinese version of the Mini-mental State Examination (MMSE®), which is a scale that includes composition items and computing ability,[24] Hospital Anxiety and Depression Scale (HADS),[25] Barthel Index (BI),[26] Pittsburgh Sleep Quality Index (PSQI),[27] and a severity subscale of fatigue assessment instrument (FAI)[28] assessed cognitive impairment, anxiety and depressive symptoms, ADL ability, sleep disorders and fatigue degree of patients at 1 week (time 0) after transfer from the ICU. Patients diagnosed with PICS continued to use the BI to assess their ADL scores at 1 month (time 1), 3 months (time 2), 6 months (time 3) and 9 months (time 4) after transfer from the ICU. The patients completed the scales individually when they were in the general ward, and the scales were completed by the patients individually or the researcher during home visits, video follow-up or outpatient follow-up when patients were discharged. Among them, (1) MMSE® score < 24,[29] (2) BI score < 100,[26] (3) HADS score ≥ 8,[25] (4) PSQI score ≥ 8,[27] and (6) FAI subscale score ≥ 4 indicated the existence of symptoms.[27] At least one symptom was required for a diagnosis of PICS. All of these scales were available in Chinese and are commonly used in Chinese studies, with high reliability and validity. The MMSE® is easy to administer and is therefore commonly used in the ICU population;[30] the HADS is the questionnaire most commonly used to measure anxiety and depressive symptoms in ICU survivals;[30] the PSQI is a widely used scale commonly used to follow long-term sleep in critically ill ICU patients;[30] and the FAI was developed by Schwart et al, of the American Psychological and Behavioral Sciences Laboratory, in 1993, mainly to assess the fatigue status of daily activities in patients transferred out of the ICU.[28]

The Barthel Index (BI) is a self-care ability scale, which measures 10 areas of eating, bathing, decorating, dressing, controlling stool, controlling urine, toileting, bed and chair transfer, walking on the ground, and going up and down stairs. Each item is rated 0,5,10, and 15 points according to whether it needs help and the degree of disability. The total score is 0–100 points, and less than 100 points are ADL disability. 0~20 is divided into very severe disability, 25~45 is divided into severe disability, 50~70 is divided into moderate disability, 75~95 is divided into mild disability. It can be

used to evaluate the functional status of patients before and after treatment, and can also predict the therapeutic effect. It is the most widely used and studied ADL evaluation method.[26]

Statistical Analysis

The latent trajectories were identified with Mplus version 7.4 software, and a missing value in follow-up was replaced by "999"; when the study data had missing values, Mplus software used the full information maximum likelihood (FIML) estimator to fit the model. It assumes that the missing values in the follow-up data are random missing values and avoids its influence on the fitting results under the premise of allowing the missing data to exist. SPSS version 26.0 was used for data input and analysis. The counting data were expressed as frequency (n) and percentage (%) and compared by chi-square test. With patient demographic variables, clinical variables, and PCS-related symptoms as independent variables and covariables, and GMM classification results as the dependent variable, univariate analysis and multinomial logistic regression were used to investigate the factors influencing potential categories of symptom characteristics in patients with PICS. Two-tailed $p< 0.05$ was the significance level for the logistic regression.

Three types of indices were used to select the optimal model: 1) information criteria (Akaike Information Criterion, AIC; Bayesian Information Criterion, BIC; and Sample-size Adjusted Bayesian Information Criterion, aBIC).[31,32] 2) Likelihood ratio test (Lo-Mendell-Rubin, LMR; Bootstrapped Likelihood Ratio Test, BLRT).[33] 3) The smaller the AIC, BIC and aBIC were, the better the model fit; an entropy ≥0.8 indicates that the classification accuracy of the model reached 90%. When the P values corresponding to LMR and BLRT reached the significance level ($P < 0.05$), the k class model fit the data better.[34]

Results

A total of 653 subjects were initially included in the study according to the inclusion and exclusion criteria. A total of 593 patients were included 1 week after ICU discharge, including 434 patients with PICS (73.19%) and 159 patients with Non-PICS (26.81%). The flow chart of subject screening and enrolment is shown in Figure 1. The baseline socio-demographic characteristics of the patients are shown in Table 1. The baseline clinical characteristics of the patients are shown in Table 2. The PICS-related symptoms of the patients are shown in Table 3. Patients had a mean age of admission of 54.57 years (SD, 16.28 years). Male patients predominated (60.37%), and most patients were admitted to the ICU due to digestive system diseases (29.03%).

Latent Trajectories of ADL Disability in Patients with PICS

This study starts with a 1-class latent trajectory, increases the number of classes (c) and fits 4-class latent trajectories (Table 4). With the increase in classes, AIC, BIC and aBIC decreased, while entropy value increased. When 3 classes

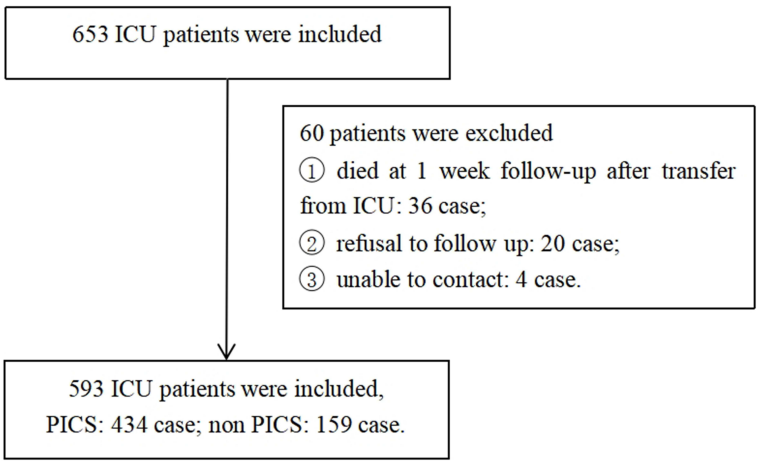

Figure 1 To explore the latent trajectories and influencing factors of ADL disability in PICS patients, the flow for screening PICS patients.

Table 1 Sociodemographic Characteristics of the Patients

Variables		Severe Disability Sustained Group (n=90), n (%)	Disability Recovery Group (n=344), n (%)	χ^2 value	*P* value
Sex	Male	59(65.56)	203(59.01)	1.277	0.258
	Female	31(34.44)	141(40.99)		
Age(years)	18~44	6(6.67)	110(31.98)	26.973	<0.001
	45~59	33(36.67)	118(34.30)		
	≥60	51(56.67)	116(33.72)		
Marital status	Divorced/Widowed/ Unmarried	2(2.22)	14(4.07)	0.264	0.607
	Married	88(97.78)	330(95.93)		
Years of education (years)	≤6	47(52.22)	158(45.93)	2.081	0.353
	7~9	27(30.00)	101(29.36)		
	≥10	16(17.78)	85(24.71)		
Occupation	Unemployed	13(14.44)	39(11.34)	5.665	0.340
	Worker	9(10.00)	29(8.43)		
	Farmer	26(28.89)	116(33.72)		
	Staff	3(3.33)	32(9.30)		
	Retired	25(27.78)	74(21.51)		
	Others	14(15.56)	54(15.70)		
BMI(kg/m^2)	18.5~23.9	45(50.00)	142(41.28)	4.630	0.201
	<18.5	16(17.78)	62(18.02)		
	24~27.9	22(24.44)	85(24.71)		
	≥28	7(7.78)	55(15.99)		
Addiction	None	57(63.33)	210(61.05)	1.743	0.639
	Smoking	15(16.67)	45(13.08)		
	Drinking	3(3.33)	15(4.36)		
	Smoking and Drinking	15(16.67)	74(21.51)		
Medical expenses payment methods	Own expense	4(4.44)	11(3.20)	0.064	0.801
	Medical insurance	86(95.56)	333(96.80)		

Notes: BMI: Body Mass Index= weight (kg) / height (m) ^{2}; BMI was divided into lean (< 18.5 kg/m^2), normal (18.5 to 23.9 kg/m^2), overweight (24 to 27.9 kg/m^2), and obese (≥ 28 kg/m^2) groups.

Table 2 Clinical Characteristics of the Patients

Variables		Severe Disability Sustained Group (n=90), n (%)	Disability Recovery Group (n=344), n (%)	χ^2 value	*P* value
Main diagnosis admission ICU	Respiratory disease	12(13.33)	42(12.21)	4.897	0.673
	Digestive system disease	21(23.33)	105(30.52)		
	Poisoning/trauma	3(3.33)	21(6.10)		
	Obstetrics and gynaecology disease	4(4.44)	22(6.40)		
	Circulatory system disease	9(10.00)	31(9.01)		
	Urinary system disease	7(7.78)	18(5.23)		
	Immune system disease	4(4.44)	13(3.78)		
	Others	30(33.33)	92(26.74)		
Consciousness at admission*	Sober	44(48.89)	168(48.84)	0.202	1.000
	Lethargy	1(1.11)	5(1.45)		

(*Continued*)

Table 2 (Continued).

Variables		Severe Disability Sustained Group (n=90), n (%)	Disability Recovery Group (n=344), n (%)	χ^2 value	*P* value
	Drowsiness	9(10.00)	35(10.17)		
	Confusion	4(4.44)	14(4.07)		
	Coma	32(35.56)	122(35.47)		
APACHE II score	≤15	18(20.00)	123(35.76)	8.252	0.016
	15~20	30(33.33)	98(28.49)		
	>20	42(46.67)	123(35.76)		
CRP (mg/L)	≤30	8(8.89)	50(14.53)	4.849	0.089
	30~150	52(57.78)	156(45.35)		
	>150	30(33.33)	138(40.12)		
Delirium	Yes	43(47.78)	149(43.31)	0.576	0.448
ICU LOS (day)	≤5	39(43.33)	159(46.22)	0.860	0.651
	5~10	25(27.78)	102(29.65)		
	>10	26(28.89)	83(24.13)		
Hospital LOS(day)	≤10	15(16.67)	66(19.19)	13.061	0.001
	10~30	43(47.78)	216(62.79)		
	>30	32(35.56)	62(18.02)		
Medical expenses (million yuan)	≤5	14(15.56)	93(27.03)	9.641	0.008
	5~10	25(27.78)	116(33.72)		
	>10	51(56.67)	135(39.24)		
Leave ICU direction	Transferred treatment	66(73.33)	294(85.47)	7.482	0.017
	Discharge	20(22.22)	43(12.50)		
	Hospital transfer treatment	4(4.44)	7(2.03)		
Tracheotomy	Yes	17(18.89)	47(13.66)	1.550	0.213
Invasive MV (h)	0	29(32.22)	121(35.17)	2.358	0.308
	1~96	26(28.89)	118(34.30)		
	≥97	35(38.89)	105(30.52)		
Noninvasive MV (h)	0	67(74.44)	267(77.62)	1.912	0.384
	1~96	19(21.11)	54(15.70)		
	≥97	4(4.44)	23(6.69)		
Operation[#]	Yes	49(54.44)	196(56.98)	0.186	0.666
Restraints	Yes	51(56.67)	185(53.78)	0.240	0.624
CRRT[$]	Yes	15(16.67)	69(20.06)	0.526	0.468
Dexmetomidine hydrochloride (mg)	0	27(30.00)	118(34.30)	1.475	0.688
	0~1	29(32.22)	111(32.27)		
	1~3	19(21.11)	73(21.22)		
	>3	15(16.67)	42(12.21)		
Propofol (g)	0	45(50.00)	173(50.29)	4.412	0.220
	0~1	31(34.44)	92(26.74)		
	1~3	10(11.11)	43(12.50)		
	>3	4(4.44)	36(10.47)		
Midazolam (mg)	0	32(35.56)	113(32.85)	3.019	0.389
	0~50	21(23.33)	68(19.77)		
	50~200	18(20.00)	59(17.15)		
	>200	19(21.11)	104(30.23)		
Nabufine hydrochloride(mg)	0	60(66.67)	189(54.94)	6.088	0.107
	0~100	12(13.33)	41(11.92)		

(*Continued*)

Table 2 (Continued).

Variables		Severe Disability Sustained Group (n=90), n (%)	Disability Recovery Group (n=344), n (%)	χ^2 value	*P* value
	100~300	8(8.89)	43(12.50)		
	>300	10(11.11)	71(20.64)		
Remifentanil hydrochloride (mg)	0	38(42.22)	148(43.02)	6.186	0.103
	0~3	15(16.67)	94(27.33)		
	3~10	19(21.11)	51(14.83)		
	>10	18(20.00)	51(14.83)		
Sufentanil citrate (ug)	0	46(51.11)	169(49.13)	2.572	0.462
	0~50	25(27.78)	80(23.26)		
	50~200	10(11.11)	61(17.73)		
	>200	9(10.00)	34(9.88)		

Notes: *Admission consciousness was assessed by the responsible nurse using the Glasgow Coma Score; #Any operation experienced during this treatment is defined as yes, $experienced CRRT during this treatment is defined as yes. "Discharge from ICU direction" refers to the medical outcome after the patient is transferred out of ICU, including discharge, and transfer therapy; Transferred treatment: the patient's vital signs were stable, and his condition was stable and transferred from ICU to general condition. Discharge: patients were discharged for various reasons (getting better, refusing treatment). Hospital transfer treatment: patients with aggravating conditions were transferred to a higher level hospital for further treatment or their condition improved and transferred to a local hospital for treatment. The doses of sedatives and analgesics in the table refer to the total doses used in ICU; the cumulative use time needs to be recorded when invasive mechanical ventilation is used, and the recording method is bounded by 96 hours, which is divided into greater than 96 hours and less than 96 hours, so it is classified as 96 hours.

Abbreviations: APACHE II: Acute physiology and chronic health evaluation II; CRP: C-reactive protein; ICU LOS: length of ICU stay; Hospital LOS: length of Hospital stay; CRRT: continuous renal replacement therapy.

Table 3 Post-Intensive Care Syndrome-Related Symptoms of the Patients

Variables		Severe Disability Sustained Group (n=90), n (%)	Disability Recovery Group (n=344), n (%)	χ^2 value	*P* value
Cognitive impairment	Yes	45(50.00)	76(22.09)	27.630	<0.001
Anxiety	Yes	72(80.00)	203(59.01)	13.537	<0.001
Depression	Yes	78(86.67)	222(64.53)	16.372	<0.001
Sleep disorders	Yes	71(78.89)	238(69.19)	3.275	0.070
Fatigue	Yes	65(72.22)	236(68.60)	0.439	0.507

Notes: The evaluation tools and scoring criteria for variables are as follows: Cognitive impairment: MMSE (MMSE score <24); Anxiety: HADS (HADS score≥8); Depression: HADS (HADS score≥8); Sleep disorders: PSQI (PSQI score≥8); Fatigue: FAI (FAI subscale score≥4).

Table 4 Activities of Daily Living Disability Latent Trajectories Fitting Indices for Growth Mixture Model with 1 to 4 Classes

Number of Classes	AIC	BIC	aBIC	Entropy	LMR(*P*)	BLRT(*P*)
1	16,154.609	16,211.631	16,167.203	—	—	—
2	15,916.744	15,985.986	15,932.037	0.882	0.009	<0.001
3	15,754.763	15,836.224	15,772.755	0.891	0.050	<0.001
4	15,642.205	15,735.885	15,662.896	0.888	0.162	<0.001

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, Adjusted Bayesian Information Criterion; LMR, Lo-Mendell-Rubin; BLRT, Bootstrapped Likelihood Ratio Test.

were retained, LMR did not reach a significant level; entropy decreased, and LMR did not reach a significant level when 4 classes were retained; and LMR reached a significant level when 2 classes were retained, BLRT reached a significant level ($P < 0.05$), and entropy >0.8; so, 2 classes (c1, c2) were comprehensively considered (Table 4).

Latent Trajectories of ADL Disability in Patients with PICS

Terms were assigned to each trajectory group according to the changing trends and characteristics of each: ① class 1 (c1): During the period of T0, the ADL scores showed severe disability (intercept = 36.513), and the degree of ADL disability of the patients remained at a high level during the follow-up period (slope = 0.388, P = 0.139); this group was named "Severe Disability Sustained Group". There were 90 cases (20.74%) in this group. ② class 2 (c2): The ADL scores at T0 showed moderate disability (intercept = 69.399), and the degree of ADL disability decreased during the follow-up period (slope = 1.751, P < 0.001). This group was named the "Disability Recovery Group" and had a total of 344 patients (79.26%) (Figure 2).

Univariate Analysis of Latent Trajectories of ADL in Patients with PICS

According to univariate analysis, age, APACHE II score (Acute Physiology And Chronic Health Evaluation II score), hospital LOS (length of stay), medical expenses, leave ICU direction, cognitive impairment, anxiety or depression, which were related to ADL, were grouped (P < 0.05) (Tables 1–3).

Multivariate Analysis of Latent Trajectories of ADL in Patients with PICS

Statistically significant variables in univariate analysis, such as age, APACHEII score, direction of ICU discharge, hospital LOS, medical costs, cognitive impairment, anxiety and depression, were used as independent variables, and the results of latent class analysis were used as dependent variables, followed by binary logistic regression analysis. c1 was selected as the reference category and independent variables were screened using stepwise entry.

The results showed that age, direction of ICU discharge, cognitive impairment and depression were independent factors affecting the latent type of ADL trajectory in PICS patients. Compared with patients aged 18–44 years, patients aged 45–59 years and ≥60 years had 0.232-fold [OR = 0.232, 95% CI (0.088, 0.609), P = 0.003] and 0.186-fold [OR = 0.186, 95% CI (0.071, 0.490), P = 0.001] higher risk of being assigned to C1, indicating that older patients were more likely to be classified as c1. Patients receiving transfer therapy had 0.157-fold higher risk of being assigned to c1 compared to those not receiving transfer therapy [OR = 0.157, 95% CI (0.034, 0.728), P = 0.018], indicating that patients receiving transfer therapy after ICU admission were more likely to be classified as c1. Compared with patients without cognitive impairment, patients with cognitive impairment had a 0.318-fold higher risk of being assigned to c1 [OR = 0.318, 95% CI (0.181, 0.560), P < 0.001], indicating that patients with cognitive impairment were more likely to be classified as c1. Compared with patients without depressive symptoms, patients with depressive symptoms had 0.363 times higher risk of being assigned to c1 [OR = 0.363, 95% CI (0.151, 0.875), P = 0.024], indicating that patients with depressive symptoms were more likely to be classified as c1 (Table 5).

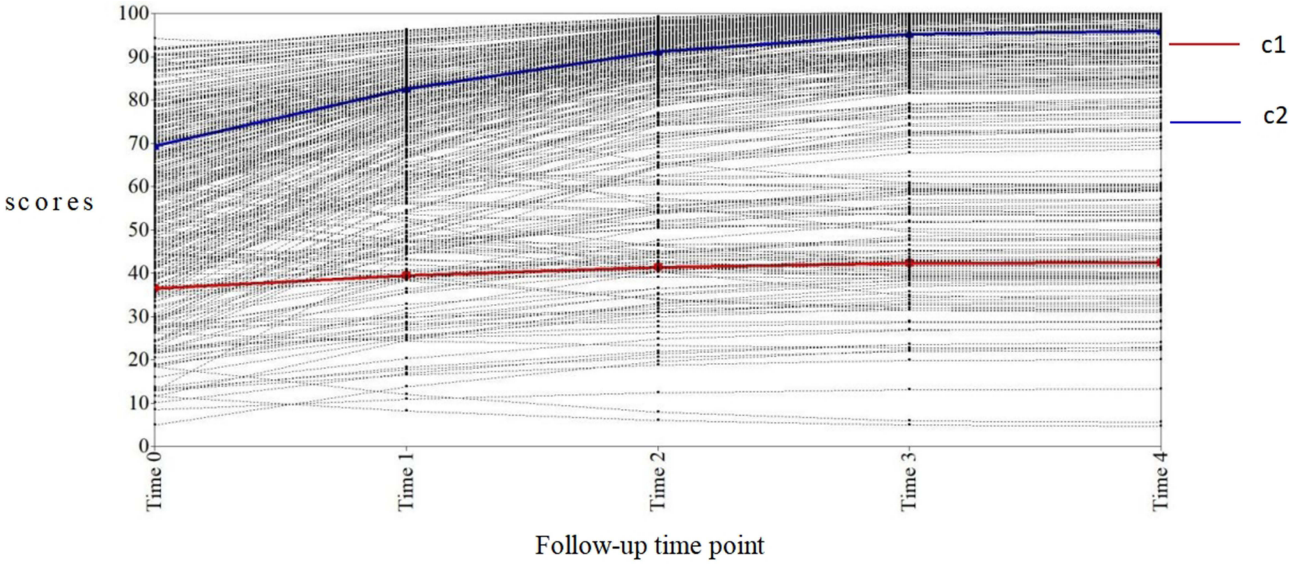

Figure 2 Development trends of activities of daily living disability.

Table 5 Multivariate Analysis of Latent Trajectories of Activities of Daily Living in Patients with Post-Intensive Care Syndrome

Variables	Regression Coefficients	Standard Error	*Wald* χ^2 value	*P* value	*OR* value	95% CI
Age(year)						
18~44	*Reference*					
45~59	−1.463	0.493	8.805	0.003	0.232	(0.088, 0.609)
≥60	−1.681	0.494	11.576	0.001	0.186	(0.071, 0.490)
APACHE II score						
≤15	*Reference*					
15~20	−0.135	0.369	0.728	0.394	0.730	(0.354, 1.505)
>20	−0.053	0.356	0.022	0.881	0.948	(0.472, 1.905)
Leave ICU direction						
Transferred treatment	*Reference*					
Discharge	−0.657	0.359	3.347	0.067	0.518	(0.257, 1.048)
Hospital transfer treatment	−1.853	0.783	5.598	0.018	0.157	(0.034, 0.728)
Hospital LOS (day)						
≤10	*Reference*					
10~30	0.001	0.457	<0.001	0.998	1.001	(0.409, 2.453)
>30	−0.525	0.530	0.980	0.322	0.592	(0.210, 1.672)
Medical expenses (million yuan)						
≤5	*Reference*					
5~10	−0.459	0.430	1.138	0.286	0.632	(0.272, 1.469)
>10	−0.630	0.453	1.933	0.164	0.533	(0.219, 1.294)
Cognitive impairment						
No	*Reference*					
Yes	−1.145	0.288	15.766	<0.001	0.318	(0.181, 0.560)
Anxiety						
No	*Reference*					
Yes	−0.449	0.377	1.421	0.233	0.638	(0.305, 1.335)
Depression						
No	*Reference*					
Yes	−1.012	0.449	5.094	0.024	0.363	(0.151, 0.875)

Discussion

The results of this study found that PICS was observed in 73.19% of patients (434/593) at 1 week after ICU discharge, which was similar to the findings of Wang et al, who had an incidence of PICS of 68.21%.[6] There were different underlying trajectories of ADL disability in patients with PICS, which were severe disability persistence (ADL scores: severe disability) and disability recovery groups (ADL scores: moderate disability). Improvement in cognitive

impairment or depression is associated with recovery from disability, and transfer to hospital or advanced age is associated with unfavorable recovery from disability and may make disability serious and persistent.

In this study, two latent trajectories of ADL patients with PICS were identified by GMM, namely, "Severe Disability Sustained Group" and "Disability Recovery Group", indicating that there were differences in the development trends of ADL disability in patients with PICS during disease recovery. Kim et al[35] conducted a study of elderly people with an average age of 73.3 years in the community and found that over time, three different ADL trajectory groups were identified. Huang et al[15] conducted a 12-year longitudinal survey of people aged 65 and older using the GMM model. It was found that the ADL disability trajectories included two groups, the slightly increasing group and the quickly increasing group. It is suggested that there are different ADL subgroups in the same population. The reason for the difference between the conclusions of this study and Kim et al[34] and Huang et al[15] may be due to the differences in patients with PICS, follow-up time and evaluation scales.

The results of this study showed that 20.74% of patients with PICS were classified as "Severe Disability Sustained Group", and the degree of ADL dependence of these patients remained at a high level over time, suggesting that medical staff should identify such patients as soon as possible and take effective measures to restore or prevent patients' disability from progressing. Early exercise combined with nutritional therapy in the ICU may be beneficial to the recovery of ADL function in such patients. Studies have shown that proper exercise can maximize muscle protein synthesis, while early exercise can maintain or improve body functions (such as muscle strength, endurance, walking ability).[36–39] Van et al[40] pointed out that during and after ICU admission, the best nutritional treatment is very important to improve long-term outcomes. Individualized nutritional therapy should correspond to different nutritional goals at different stages of rehabilitation after critical illness. Therefore, when formulating strategies to promote the recovery of patients' ADL ability, individualized early rehabilitation and optimal nutritional therapy should be combined to maximize the recovery of ADL function.

A total of 79.26% of patients with PICS belonged to the "Disability Recovery Group", indicating that this group of patients will have a certain degree of ADL disability in the early stage of serious illness but with treatment and rehabilitation, ADL disability will gradually improve. Even without special intervention, patients will gradually adapt to the damage caused by the disease so that ADL ability will gradually recover. This finding is similar to the conclusion that Shima et al[41] found that ADL disability in ICU patients improved after 1 year. For such patients, during the ICU period, nurses can help patients perform some simple rehabilitation exercise training; after discharge, involve family members in rehabilitation programs, including respiratory training techniques, muscle stretching techniques, exercise therapy and resistance training, which can enhance the strength of limbs and respiratory muscles and help improve ADL ability, and are recommended to last for 6 weeks, twice a week.[42–44]

In this study, older PICS patients were found to be more likely to be classified as members of the "severe disability persistence group". Older patients were more likely to have ADL disability after ICU transfer. Brummel et al[45] found that patients of all ages have a certain degree of disability after severe diseases, but most of them are elderly patients because of their poor acute stress response to critical diseases, poor adaptability to disease and treatment environment, and normal ageing, resulting in skeletal muscle loss and osteoporosis. In addition, during critical illness, inflammation changes the signalling pathway in skeletal muscle, leading to acute muscle atrophy within a few days of onset and an imbalance between muscle destruction and recovery, which cannot be offset in ageing muscles; in addition, due to the ageing population and the susceptibility of elderly individuals to disease, most patients with critical diseases are elderly individuals. Cognitive decline in elderly survivors of critical illness leads to a higher rate of ADL disability than in hospitalized, noncritically ill and community-based elderly patients. Another study also found that the older the patients were transferred from the ICU, the lower their self-care ability.[9,46] Therefore, for older patients, attention should be paid to the recovery of ADL function after transfer from the ICU, follow-up within a period of time after discharge, dynamic attention to the development of ADL in patients, and timely and effective measures, such as nutritional support, physical therapy, and functional exercise, to improve the quality of life of patients.

This study found that patients with PICS who were hospital transfers for treatment were more likely to be classified into the "Severe Disability Sustained Group". The possible reason is that after the patients transferred into the new medical facility, the unfamiliar environment and medical personnel made patients feel fearful, anxious and distrustful,

and they lost confidence in self-rehabilitation exercise and disease rehabilitation, which adversely affected the recovery of ADL function. Therefore, in the transitional stage between hospitals, it is necessary to do a good job of disease handover, strengthen communication with patients, do a good job of psychological nursing, improve nursing skills, enhance the trust between patients and medical personnel, and improve and promote the recovery of ADL function of patients as an important clinical outcome indicator.

We found that patients with PICS with cognitive impairment were more likely to be classified as "Severe Disability Sustained Group". A study has shown that any cognitive impairment (even mild cognitive impairment) before ICU admission is associated with increased ADL disability within 6 months after critical illness, and moderate cognitive impairment doubles the likelihood of elderly patients being admitted to nursing homes.[47] Another study pointed out that the cognitive decline in elderly patients who survive critically ill diseases leads to a higher rate of ADL disability than that of hospitalized, noncritically ill and community-resident elderly patients.[42] ADL disability is related to the sudden decline in cognitive function. Therefore, it is necessary to evaluate the change pattern of cognitive function after discharge and to explore the relationship between the recovery of ADL function and cognitive function. However, since most current studies evaluate cognitive function at a certain time after discharge, no study has found an impact of dynamic changes in cognitive function on ADL.[48]

We found that patients with PICS with depression were more likely to be classified into the "ADL Severe Dependence Persistence Group", which is consistent with the conclusion of Valenzuela et al.[49] These researchers pointed out that depression is an important determinant of new or worsening ADL disability. Changes in depressive symptoms are significantly correlated with changes in physical function, both at the group and individual levels.[50] Depressive symptoms are an important and potentially modifiable risk factor for physical injury, which is not only persistent in patients with ICU transfer but also an independent risk factor for impairment of physical function.[51] This may be because patients with depressive symptoms find it more difficult to receive physiotherapy, and physiotherapy is often essential for functional recovery. In addition, depressive symptoms affect patients' adherence to drug treatment, and depressive symptoms may affect physiological function through direct neurobiological pathways.[49] Therefore, early identification and treatment of a depressive state should be regarded as a potential intervention, and comprehensive and continuous depression assessment and active management of depressive symptoms should be carried out to improve ADL function and avoid persistent ADL disability.

According to the above influencing factors, it is recommended that multidisciplinary diagnosis and treatment (MDT) can be performed during the period when the patient is admitted to the ICU, and appropriate expert composition can be selected according to the patient's condition needs, including ICU doctors and nurses, psychological counselors, physiotherapists (rehabilitation nurses, etc), complete diagnosis of the patient's condition, early detection of problems from many aspects, and intervention to reduce the occurrence of PICS, improve ADL ability, and improve the quality of life. For example, if patients are diagnosed with depression during ICU, professional psychologists should be timely invited to intervene in patients, adjust psychological status, and actively cope with disease status, so as to reduce the possibility of ADL disability after ICU. Regular assessment of health status and timely adjustment of the intervention program are also required during the follow-up period after ICU discharge.

The strengths of the study include the following: 1) To our knowledge, this is the first study to present the latent trajectories of ADL disability and the influential factors in the PICS population from a person-centred viewpoint. 2) The current study used a scoring method that reflected the change in ADL disability levels in patients with PICS. 3) A novel longitudinal method, the GMM, was adopted to identify the latent trajectories of ADL disability. 4) The factors affecting the development of both trajectories were analyzed. However, this study has several limitations. First, due to the limitations of time and conditions, this study was a single-centre longitudinal survey with a small sample size, and the follow-up time was short. Second, the sample size lost (dropout rate: 9.19%) during follow-up and the subjects excluded because of illness (such as severe cognitive impairment, language disorder, inability to contact) meant that the scale could not be completed, and the evaluation may have a certain impact on the results of the study. Finally, some of the scales used in this study, such as the BDRS and MMSE®, have not been fully validated for their application in the ICU population, so there may be some unknown factors influencing the measurements. Therefore, in the future, longitudinal follow-up studies with multicentre sites and large samples can be carried out to dynamically observe the changes in ADL

function in patients with PICS and to observe whether the symptoms of PICS will continue to affect the ADL function of patients for a long time after transfer out of the ICU. Based on quantitative research and qualitative interviews, and the mixed research method was used to further explore the influencing factors of the latent subtypes of ADL in patients with PICS.

Conclusion

In this study, based on GMM to identify the latent trajectories of ADL in patients with PICS, two latent trajectories were obtained, namely, "Severe Disability Sustained Group" and "Disability Recovery Group". In addition, our findings suggest that improvement in cognitive impairment or depression may help prevent recovery from disability, and transfer to hospital or advanced age may not be conducive to recovery from disability. Case management with an interprofessional team may have positive impacts on ADL disability patients. Rehabilitation nurses should identify patients with high-risk ADL disabilities and should work with an interdisciplinary team to develop interventions to reshape the patients' ADL ability, facilitating their transition back to orthobiosis, if possible.

Declaration on the Use of MMSE-2 Scale

An unauthorized version of the Chinese MMSE was used by the study team without permission, which has been rectified. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without the written permission of PAR (www.parinc.com).

Ethical Approval Statement

This study was approved by the Ethics Committee of Jinsha County People's Hospital (KLL Y-2020-150), and was carried out in accordance with the ethical principles as set out in the Declaration of Helsinki. Verbal was obtained before commencement of the survey. The verbal informed consent process was approved by our institution's ethics committee.

Disclosure

The authors declare that they have no competing interests.

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