Prevalence of Post Intensive Care Syndrome Among Japanese Intensive Care Unit Patients: A Prospective, Multicenter, Observational J-PICS Study

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Research

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Abstract

Background

Many studies have compared quality of life of post-intensive care syndrome (PICS) patients with age-matched population-based controls, instead of baseline quality of life. Furthermore, many studies on PICS used the 36-item Short Form (SF-36) health survey questionnaire version 2 but lack the data for SF-36 values before and after intensive care unit (ICU) admission. Thus, the clinically important changes in the parameters of SF-36 are unknown. Therefore, we determined the frequency of co-occurrence of PICS impairments at 6 months after ICU admission. We also evaluated the changes in SF-36 health survey questionnaire subscales and interpreted the patients' subjective significance of impairment.

Methods

A prospective, multicenter, observational cohort study was conducted in 16 ICUs across 14 Japanese hospitals. Adult ICU patients expected to receive mechanical ventilation for > 48 hours were enrolled and their 6-month outcome was assessed using the questionnaires. PICS definition was based on the physical status, change in SF-36 physical component score (PCS) ≥ 10 points; mental status, change in SF-36 mental component score ≥ 10 points; cognitive function, Short-Memory Questionnaire (SMQ) score worsened and SMQ score at 6 months < 40. Multivariate logistic regression model was used to identify the factors associated with PICS occurrence. The patients' subjective significance of physical and mental symptoms was assessed using the 7-scale Global Assessment Rating.

Results

Among 192 patients, 48 (29.6%) died at 6 months. Among the survivors at 6 months, 96 patients responded to the questionnaire; ≥1 PICS impairment occurred in 61 (63.5%) patients, and ≥ 2 occurred in 19 (19.9%) patients. Physical, mental, and cognitive impairments occurred in 33.3%, 14.6%, and 37.5% patients, respectively. Low education level was associated with PICS occurrence (Odds ratio: 3.8, 95% confidence interval: 1.1–17.9, P=0.036). Based on the patients' subjective assessment, a 10-point change in PCS indicated moderate negative change.

Conclusions

Among the survivors who received mechanical ventilation, 64% had PICS at 6 months; co-occurrence of PICS impairments occurred in 20%. PICS occurrence was associated with low educational level. Future studies elucidating the minimal clinically important difference of SF-36 scores among the ICU patients and standardizing the PICS definition are required.

Trial registration

UMIN000034072

Background

Recent improvement in intensive care unit (ICU) mortality rate has resulted in numerous ICU survivors. Most ICU survivors experience long-term impairment in their quality of life, known as post-intensive care syndrome (PICS). PICS is defined as a new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalization for critical illness [1]. Globally, many observational studies have been conducted for each PICS parameter among ICU patients [2–5]. These studies have several limitations. First, most studies focused on only one or two aspects of PICS (i.e., only cognitive function, or only physical and mental status). Only a few studies focusing on the co-occurrence of PICS symptoms in individual patients have been conducted [6, 7]. Second, limited data regarding PICS after implementation of PICS prophylaxis strategy are available, especially for Asian populations with different cultural backgrounds and races from Western countries [8–11]. Growing awareness about PICS; many guidelines and bundle strategies; clinical practice guidelines for the prevention and management of pain, agitation, sedation, delirium, immobility, and sleep disruption in adult patients in the ICU [12]; guidelines for family centered care in the neonatal, pediatric, and adult ICU [13]; and ABCDEFGH bundle [14] have been published and implemented to decrease the occurrence of PICS. ABCDEFGH stands for Airway management, Breathing trials, Coordination of care and Communication, Delirium assessment, Early mobility, Family involvement, Follow-up referrals and Functional reconciliation, Good handoff communication, and Handout materials on PICS and post-intensive care syndrome-family. The Japanese PICS survey conducted in 2019 revealed that PICS was identified in more than 60% patients, and early rehabilitation was provided in more than 90% cases [15]. Third, ICU patients often report lower health-related quality of life (HRQOL) than the general population before ICU admission. However, many studies have compared quality of life of PICS patients with age-matched population-based controls, instead of baseline quality of life [16]. Furthermore, many studies on PICS used the 36-item Short Form (SF-36) health survey questionnaire version 2, which is the most popular HRQOL scale for the outcome measure, among ICU survivors [17]; however, these studies lack the data for SF-36 values before and after ICU admission. Thus, the clinically important changes in the parameters of SF-36 in these studies is unknown.

Therefore, the Japanese PICS (J-PICS) study aimed to evaluate the co-occurrence of PICS symptoms, along with the assessment of baseline HRQOL, in Japanese patients admitted to multicenter ICUs, after publication of several guidelines and bundles about PICS prophylaxis. Additionally, we evaluated the subjective significance of changes in SF-36 parameters before and after ICU admission among the patients.

Methods

Study design and setting

The J-PICS study was a prospective, multicenter, observational cohort study of mechanically ventilated patients, conducted in 16 ICUs across 14 hospitals of Japan. Five of the 16 ICUs were university-affiliated

hospitals and the others were tertiary teaching hospitals. The median number of ICU beds was 10 [interquartile range (IQR), 8–15]. All ICUs were mixed ICUs and were managed by intensivists. The study protocol was approved by the Kobe City Medical Center General Hospital (KCGH) ethics committee and the ethics committees of all participating hospitals (KCGH approval number: Zn181008). Written informed consent was obtained from all patients or authorized surrogates. The J-PICS study has been registered at UMIN-CTR (registration number: UMIN000034072).

Study population and eligibility criteria

All consecutive adult ICU patients who were expected to receive mechanical ventilation for more than 48 hours between April 01, 2019 and September 30, 2019 were recruited in the study. The patients who received noninvasive mechanical ventilation were also enrolled. Eligibility criteria were assessed next morning at 8:00 am after admission in the ICUs. The patients with the following conditions were excluded from the study: 1) patients who had primary brain injury that was likely to result in conscious or cognitive disorder (e.g., traumatic brain injury, subarachnoid hemorrhage, acute stroke, post cardiac arrest, meningitis, and encephalitis); 2) patients with pre-admission diagnosis of dementia; 3) patients who received home ventilation prior to admission; 4) patients with end-stage cancer; 5) patients with withdraw/withhold status; 6) expected death within 24 h; 7) second or subsequent readmission to ICU during the study period; 8) patients who had no family members; 9) patients who did not speak Japanese; and 10) the patients who could not be followed-up (e.g., did not live in Japan and/or homeless).

Variables and measurements

The following demographic and hospital data of the patients were collected: age, sex, body mass index, Charlson comorbidity index (CCI) [18], clinical frailty scale [19], do not attempt resuscitation code status at the time of ICU admission, educational level, employment status, marital status, patient's residential living status before admission, history of treatment with benzodiazepines and steroids, source of admission to ICU, and primary diagnosis at the time of ICU admission. The number of patients with sepsis and acute respiratory distress syndrome (ARDS) was also recorded. Sepsis and ARDS were diagnosed on the basis of Sepsis-3 [20] and Berlin definition [21], respectively. The severity of illness was measured using the Acute Physiology and Chronic Health Evaluation (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score [22] within 24 hours of ICU admission. The management data in the ICU, including the use of inotropes or vasopressors, paralytic agents except during intubation, renal replacement therapy, extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pumping, and tracheostomy were also collected. The data for the use of inotropes, vasopressors, and paralytic agents were collected during the first four days of ICU admission. The data on patient outcomes, including ICU mortality; in-hospital mortality; length of stay in ICU; length of stay in hospital; duration of mechanical ventilation; occurrence of delirium, diagnosed by the Confusion Assessment Method for the Intensive Care Unit [23] for the first four days; and discharge status among survivors were collected.

Patient-reported outcomes

Six months after ICU admission, the authors sent the questionnaires by post to all patients except those who died. Patient-reported data were collected centrally by mail. If the participants did not revert, the lead author asked each participating institution to attempt a contact via telephone to return the questionnaire.

The patient-reported outcome survey evaluated the physical and mental functions of patients through the assessment of HRQOL and cognitive functions. HRQOL was assessed using the SF-36 questionnaire [24–26], which is available in the Japanese language [27,28]. At the time of enrolment in the study after ICU admission, the patients' baseline SF-36 questionnaire was completed by a proxy (4-week recall assessment before the patients' current acute illness). At 6 months after ICU admission, SF-36 questionnaire was obtained by mail from the patient or proxy. The SF-36 questionnaire has established acceptability, reliability, and validity in critically ill patient populations and as a surrogate-completed proxy measure [29–36]. SF-36 questionnaire is a comprehensive 36-item survey of HRQOL with two summary scales, physical component scale (PCS) and mental component scale (MCS), with scores ranging from 0 to 100. A higher score indicates better physical and mental functions. Both scales were transformed to a normalized scale using norm-based scoring (NBS) with 50 as the population mean and 10 points representing one standard deviation. The scores were calculated based on the standard methods [37]. The missing data were treated using the standard methods. If a patient answered more than half of the items on the subscale, the missing data were replaced with the mean of the subscale. In contrast, if a patient answered less than half items on the subscale, the data of the answered questions were excluded [37].

Cognitive functioning was assessed using the Short-Memory Questionnaire (SMQ) [38]. The SMQ was to be completed by a proxy, similar to the Informant Questionnaire on Cognitive Decline in the Elderly [39]. The SMQ is the only questionnaire filled by a proxy that has been translated and established in the Japanese language [40]. The SMQ is a 12-item questionnaire with scores ranging from 4 to 46. A score less than 40 indicates cognitive dysfunction.

The primary outcome was the occurrence of PICS 6 months after ICU admission. The definition of PICS was any of the following criteria: 1) decline in physical status, indicated by PCS score decrease of $\geq$ 10 points; 2) decline in mental status, indicated by MCS score decrease of $\geq$ 10 points; or 3) cognitive function impairment, indicated by decline in SMQ score and SMQ score < 40 at 6 months after ICU admission. A 10-point change was considered clinically important in a previous study in the ICU setting [36,41]. For the assessment of subjective significance of SF-36 score change, participants also answered anchor questions on whether their physical and mental status had improved, worsened, or unchanged on a 7-point Likert scale (from large negative change to large positive change) [42–44] at 6 months. The questions related to patients' employment status at 6 months were also asked.

Statistical analyses

Since the analyses focused on patient-reported outcomes at 6 months, participants who were lost to follow-up and who died before 6 months were excluded from the final analysis. Continuous variables are presented as median and interquartile range. Categorical variables are presented as absolute value and

percentage. A univariate analysis was performed using the Wilcoxon signed-rank test for continuous variables, and the chi-squared test or Fisher's exact test, if the number was less than 10, was used for categorical variables. Multivariate logistic regression model was used to identify the factors associated with the occurrence of PICS. Multivariate analysis included the following variables as confounding factors: age, APACHE II score, CCI, and educational status [7, 45–47]. The risk of PICS is expressed as odds ratio (OR) with 95% confidence interval (CI). The number of missing data have been reported, and no assumptions have been made except for SF-36 questionnaire data. The changes in SF-36 PCS, MCS, and SMQ scores between baseline and 6 months after ICU admission were compared using the Wilcoxon signed-rank test. The subjective significance of change in SF-36 PCS and MCS was assessed by an anchor-based question with a Global Assessment Rating as large negative change, moderate negative change, small negative change, no change, small positive change, moderate positive change, and large positive change in physical and mental status. Each Global Assessment Rating change is expressed as median and IQR change in SF-36 PCS or MCS scores.

Further, we conducted a sensitivity analysis, wherein, we did not use the baseline PCS, MCS, and SMQ data. We compared PCS and MCS scores at 6 months to NBS. In this analysis, the definition of PICS was any of the following criteria: 1) physical status; PCS score < 10; 2) mental status; MCS score < 50; or 3) cognitive function; SMQ score at 6 months < 40.

The differences with P value less than 0.05 (two-sided) were considered statistically significant. All data were analyzed using JMP 15.1.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

During the study period, 947 consecutive patients were registered in the J-PICS study, among whom, 755 patients were excluded from the study based on the exclusion criteria. Finally, 192 patients were included in the study. Among 192 patients, 30 (15.6%) patients did not return the questionnaire survey, 48 (25%) patients died before 6 months of follow-up, and 18 (9.4%) patients did not complete the questionnaires. Thus, in total, 96 (50%) patients were enrolled for the assessment of 6-month outcome (Fig. 1).

Overall characteristics of the patients, along with stratification based on the presence and absence of PICS, are shown in Table 1. In total, 61 (63.5%) patients were in the PICS group and 35 (36.5%) in the non-PICS group. The mean age of the patients was 74 [64–81] years, the proportion of men was 65%, mean APACHE II score was 23 [18–28], and mean SOFA score was 8 [6–11]. The main cause of ICU admission was acute respiratory failure. There were 35% and 41% patients with ARDS and sepsis, respectively. Patients with PICS had lower education level.

Table 1
Patients' characteristics: overall and stratified by the presence and absence of PICS

	non-PICS (N = 35)	PICS (N = 61)	P value	Overall (N = 192)
Age, years	75 [64–79]	74 [59–81.5]	0.77	74 [64–81]
Male, N (%)	25 (71.4)	43 (70.5)	0.92	125 (65.1)
BMI, kg/m^2	21.9 [19.5–24.4]	22.8 [19.7–25.3][a]	0.21	21.9 [19.5–25.0][b]
APACHE II score	21 [18–25]	20 [14.5–25]	0.14	23 [18–28]
SOFA score	7 [4–10]	8 [5–10]	0.21	8 [6–11]
Charlson comorbidity index	1 [0–2]	1 [0–2]	0.9	1 [0–3]
Clinical frailty scale	3 [2–4][a]	3 [2–4]	0.67	3 [3–4][a]
DNAR status at ICU admission, N (%)	1 (2.9)	2 (3.3)	1	15 (7.8)
Educational level, N (%)	N = 33*	N = 60*	0.098	N = 177
≤ 9 years	3 (9.1)	15 (25)		49 (27.7)
> 9 years	30 (91.0)	45 (75)		128 (72.3)
Employment status, N (%)	N = 34*	N = 61*	0.16	N = 188
Student	0 (0)	0 (0)		2 (1.1)
Employed or self-employed	11 (32.4)	23 (37.7)		60 (31.9)
Unemployed	3 (8.8)	11 (18)		41 (21.8)
Housework	2 (5.9)	8 (13.1)		21 (11.2)
Retired	18 (52.9)	19 (31.2)		64 (34.0)

Data are presented as median [interquartile range] or number (percentage).

Abbreviations: PICS: Post-intensive care syndrome, BMI: Body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, DNAR: Do not attempt resuscitation, ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome, ECMO: Extracorporeal membrane oxygenation, IABP: Intra-aortic balloon pumping

[a] one missing datum

[b] three missing data

* the education status or the employment status of the remaining persons were unknown

	non-PICS (N = 35)	PICS (N = 61)	P value	Overall (N = 192)
Marital status, N (%)			0.64	
Married	25 (71.4)	39 (63.9)		119 62.0)
Separated or divorced	1 (2.9)	6 (9.8)		16 (8.3)
Widowed	5 (14.3)	9 (15.8)		37 (19.3)
Unmarried	4 (11.4)	7 (11.5)		20 (10.4)
Patient's residential living status, N (%)			0.25	
Lived alone at home	3 (8.6)	12 (19.7)		33 (17.2)
Lived with someone else	32 (91.4)	48 (78.7)		152 (79.2)
Nursing home	0 (0)	1 (1.6)		7 (3.6)
History of treatment with benzodiazepines, N (%)	3 (8.6)	7 (11.5)	0.74	18 (9.4)
History of treatment with steroids, N (%)	2 (5.7)	4 (6.6)	1	35 (18.2)
Source of admission to ICU, N (%)			0.19	
Emergency department	20 (57.1)	23 (37.7)		95 (49.5)
Hospital floor	5 (14.3)	16 (26.2)		45 (23.4)
Another hospital	1 (2.9)	0 (0)		3 (1.6)
Operating room (elective)	0 (0)	1 (1.6)		4 (2.1)
Operating room (emergency)	9 (25.7)	21 (34.4)		45 (23.4)
Primary diagnosis at the time of admission in ICU, N (%)			0.075	

Data are presented as median [interquartile range] or number (percentage).

Abbreviations: PICS: Post-intensive care syndrome, BMI: Body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, DNAR: Do not attempt resuscitation, ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome, ECMO: Extracorporeal membrane oxygenation, IABP: Intra-aortic balloon pumping

[a] one missing datum

[b] three missing data

* the education status or the employment status of the remaining persons were unknown

	non-PICS (N = 35)	PICS (N = 61)	P value	Overall (N = 192)
Cardiogenic	2 (5.7)	13 (21.3)		25 (13.0)
Acute respiratory failure	18 (51.4)	16 (26.2)		67 (34.9)
Infection	8 (22.9)	13 (21.3)		56 (29.2)
Trauma	3 (8.6)	8 (13.1)		16 (8.3)
Others	4 (11.4)	11 (18)		28 (14.6)
ARDS, N (%)	5 (14.3)	12 (19.7)	0.51	35 (18.2)
Sepsis, N (%)	11 (31.4)	20 (32.8)	0.89	79 (41.1)
Management in ICU, N (%)				
Inotrope/vasopressor	27 (77.1)	50 (82.0)	0.6	148 (77.1)
Paralytic agent	3 (8.6)	9 (14.8)	0.53	24 (12.5)
Renal replacement therapy in ICU	6 (17.1)	6 (9.8)	0.34	40 (20.8)
ECMO in ICU	0 (0)	4 (6.6)	0.29	7 (3.6)
IABP in ICU	0 (0)	3 (4.9)	0.3	6 (3.1)
Tracheostomy	4 (11.4)	9 (14.8)	0.76	29 (15.1)
Data are presented as median [interquartile range] or number (percentage).				
Abbreviations: PICS: Post-intensive care syndrome, BMI: Body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, DNAR: Do not attempt resuscitation, ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome, ECMO: Extracorporeal membrane oxygenation, IABP: Intra-aortic balloon pumping				
[a] one missing datum				
[b] three missing data				
* the education status or the employment status of the remaining persons were unknown				

Hospital Outcomes

Among the patients included in the study, ICU mortality, hospital mortality, and 6-month mortality were observed in 15 (7.8%), 33 (17.2%), and 48 (29.6%) patients, respectively. Table 2 shows the hospital outcomes and 6-month outcomes among the patients who were enrolled for assessment at 6 months after ICU admission. The median ICU length of stay, hospital length of stay, and duration of mechanical ventilation were 7 [5–14] days, 33.5 [19–61.8] days, and 6 [3–11] days, respectively. Among PICS patients, only 24 (39.3%) were discharged home from the hospital.

Table 2
Patients' hospital and 6-months outcome: overall and stratified by the PICS status

	non-PICS (N = 35)	PICS (N = 61)	P value	Overall (N = 192)
Mortality				
ICU mortality	NA	NA		15 (7.8)
Hospital mortality	NA	NA		33 (17.2)
6-month mortality	NA	NA		48 (29.6)[a]
ICU length of stay (days)	7 [5–-12]	7 [5–13]	0.78	7 [5–14]
Hospital length of stay (days)	28 [17–47]	39 [19–71.5]	0.10	33.5 [19–61.8]
Days of mechanical ventilation	5 [3–7]	5 [3–11]	0.96	6 [3–11]
Delirium, N (%)	11 (31.4)	20 (32.8)	0.89	61 (31.8)
Discharged from hospital among survivors, N (%)			0.026	N = 159
Home	22 (62.9)	24 (39.3)		71 (44.7)
Another facility	13 (37.1)	37 (60.1)		87 (54.7)
Nursing home	0	0		1 (0.7)
Data are presented as median [interquartile range] or number (percentage).				
Abbreviations: PICS: Post-intensive care syndrome, ICU: Intensive care unit				
[a] 31 missing data				

Patient-reported Outcomes At 6 Months

SF-36 score

Figure 2 shows that SF-36 PCS score and MCS score changed significantly at 6 months compared with the baseline score among all enrolled patients. At 6 months, PCS score worsened and MCS score improved. PCS score at baseline and 6 months was 37.2 [18.2–49.2] and 30.4 [15.2–41.5], respectively (P = 0.045). MCS score at baseline and 6 months was 50.3 [42.5–56.7] and 54.3 [47.3–63.3], respectively (P = 0.0015). Physical and mental impairment, defined by worsening of PCS and MCS scores by more than 10 points, occurred in 32 (33.3%) and 14 (14.6%) patients, respectively.

SMQ score

Figure 2 also shows change in SMQ score from baseline to 6 months among all enrolled patients. SMQ score at 6 months worsened significantly. SMQ score at baseline and 6 months was 43 [36–45] and 40 [31–44], respectively (P = 0.0069). The cognitive impairment, defined by worsening of SMQ score and SMQ score at 6 months < 40, occurred in 36 (37.5%) patients.

PICS

In total, 96 patients completed all surveys about physical, mental, and cognitive status. The number of patients whose baseline PCS and MCS scores were < 50, and SMQ score was < 40 was 74 (77.1%), 46 (47.9%), and 30 (31.3%), respectively. PICS was observed in 61 (63.5%) patients. The proportion of patients with one, two, and three PICS impairments is shown in Fig. 3. Table 3 shows the multivariate analysis. After adjusting for confounding variables, education duration of nine years or less (OR: 3.8, 95% CI: 1.1–17.9, P = 0.036) was an independent predictor of the occurrence of PICS at 6 months of ICU admission.

Table 3
Multivariate logistic regression analysis for PICS

	OR (95% CI)	P value
Age	0.98 (0.95–1.0)	0.32
APACHE II score	0.96 (0.89–1.0)	0.24
Charlson comorbidity index	1.1 (0.83–1.5)	0.56
Education duration ≤ 9 years	3.8 (1.1–17.9)	0.036

Abbreviations: PICS: Post-intensive care syndrome, OR: Odds ratio, CI: Confidence interval, APACHE: Acute Physiology and Chronic Health Evaluation

Return to work

Among patients who completed the 6-month outcome survey, the data of four patients regarding job were missing. Among the remaining patients, 31 (33.7%) patients (20 in PICS group and 11 in non-PICS group) worked prior to ICU admission. The number of patients who returned to work was 26 (83.9%). All patients of non-PICS group returned to work, while 15 (75%) patients of PICS group returned to work.

Subjective significance of SF-36 score

Additional Table 1 shows the change in SF-36 PCS and MCS scores based on Global Assessment Rating change. A 10-point change in SF-36 PCS meant moderate negative change. A linear relationship was not observed between the Global Assessment Rating change and the value change in SF-36 MCS score.

Sensitivity Analysis

The sensitivity analysis was conducted based on different definitions of PICS, i.e., SF-36 PCS and MCS scores at 6 months < 50, and SMQ score < 40. Based on these criteria, PICS was identified in 93 (96.9%) patients. The proportion of patients with one, two, and three PICS impairments are shown in Additional Fig. 1.

Discussion

Summary of key findings

In total, 192 ICU patients who were expected to receive mechanical ventilation for more than 48 hours were registered in the J-PICS study. The 6-months mortality rate was 30%. The prevalence of PICS at 6 months after ICU admission was 64% among 96 adult ICU survivors. New or worsened physical, mental, and cognitive impairments occurred in 33.3%, 14.6%, and 37.5% patients, respectively. The percentage of patients who had two or more PICS impairments was 19.9%. A low education level was associated with the occurrence of PICS. A 10-point change in SF-36 PCS score was correlated with moderate negative changes in physical state, as analyzed by anchor-based subjective questions.

Comparison To Other Studies

This study investigated the co-occurrence of PICS symptoms at 6 months after ICU admission. To the best of our knowledge, only two studies have investigated the co-occurrence of PICS symptoms. One was a small cohort study, wherein, the study population comprised patients with ICU length of stay of at least 2 days [6]. This study reported the occurrence of PICS among the patients and at least one PICS impairment was high in 84% of the patients. The prevalence of two or more PICS impairments was 56%. Another study [7], which comprised the patients with respiratory failure or shock, reported that the prevalence of PICS was 64% at 3 months and 56% at 12 months after hospital discharge. Two or more PICS impairments occurred in 25% patients at 3 months and 21% patients at 12 months. The results of the latter study were similar to those of our cohort. In contrast, the results of the former study showed a higher prevalence of PICS than the results of our cohort. This difference may be due to the difference in baseline data. In our cohort, baseline SF-36 PCS and MCS scores were lower than NBS. The sensitivity analysis, which was not done at baseline, showed a high prevalence of PICS, similar to the former study. The former study did not evaluate baseline status; and the latter study excluded patients with preexisting physical, mental, and cognitive impairments. Additionally, the former study reported that PICS occurred in 54% of the survivors and these patients reported worse symptoms after critical illness. The aforementioned observations suggest that the evaluation of baseline status is an important factor for interpreting the prevalence of PICS. The exclusion of patients with preexisting physical, mental, and cognitive impairments was also effective in interpreting the prevalence of PICS. However, that leads to the exclusion of many patients from the study. Therefore, we should evaluate the baseline status of the patients in PICS study.

In our study, low education level was an independent predictor for the occurrence of PICS. This observation is consistent with that of the previous studies [7, 48]. This may be because low education level is associated with lower income, smaller social network to use resources for recovery, and less accurate recall [7, 49].

We also evaluated the subjective significance of SF-36 score among ICU patients. A previous study showed that the mental status of PICS patients was significantly associated with self-reported unacceptable outcomes [50], and the underlying reason was considered to be the small sample size of the study. As indicated by the improvement in SF-36 MCS score at 6 months among all patients, there were only 18 patients with mental impairment. We could not assess the subjective significance of MCS changes correctly. Further, resilience and post-traumatic growth have been reported to affect the patient's reported mental outcomes [6]. Clinically significant differences, rather than statistically significant differences, are important to assess HRQOL. The smallest meaningful change in a score is indicated by the minimal clinically important difference (MCID). In the present study, we used a 10-point change in PCS or MCS score as the criterion of PICS. However, some studies have used a 5-point change as the criterion of PICS [51]. MCID can be determined by two approaches: anchor-based method and distribution method. MCID values should be determined by systematic review and evaluation processes such as the modified Delphi method [52]. Our study had a small sample size and the evaluation was done only by an anchor-based method. Future study with a larger population is required to clarify the MCID of SF-36 among ICU patients to standardize the definition of PICS globally.

Strength And Limitations

The present study has several strengths. First, we investigated not only the PICS symptoms but also the co-occurrence of PICS symptoms. Second, we assessed the baseline status of the patients. Third, we evaluated the clinically significant difference in SF-36 score change. Fourth, the J-PICS study was the first multicenter observational study of PICS in Japan. To date, a few studies have investigated the occurrence of PICS in Asian populations.

The present study also has some limitations. First, the long-term outcomes were assessed at only one time point. The change in the data was unknown. Second, our data may have some bias, for example, recall bias because the outcome measures were self-reported by the patients or proxies. Third, we could not include a large number of patients in our study, which is also the limitation of majority of the similar studies. This may have affected the mortality rate and prevalence of PICS.

Conclusions

Our data suggest that 64% of ICU survivors had PICS impairments. Approximately 20% of survivors had a co-occurrence of PICS impairments. A low education level was associated with the occurrence of PICS. A 10-point change in PCS score was considered a moderately important change for the patients. Future studies are needed to elucidate the modifiable risk factors of PICS to prevent the occurrence of PICS. We

attempted to clarify the MCID of SF-36 among the ICU population. The subjective significance of MCS was unknown due to the small sample size. More research is required for the assessment of MCID of SF-36 among the ICU population. Additionally, generalizability of the definition of PICS is needed.

Abbreviations

APACHE II Acute Physiology and Chronic Health Evaluation II

ARDS Acute respiratory distress syndrome

BMI Body mass index

CI Confidence interval

CCI Charlson comorbidity index

DNAR Do not attempt resuscitation

ECMO Extracorporeal membrane oxygenation

HRQOL Health-related quality of life

IABP Intra-aortic balloon pumping

ICU Intensive care unit

IQR Interquartile range

KCGH Kobe City Medical Center General Hospital

MCID Minimal clinically important difference

MCS Mental component scale

NBS Norm-based scoring

OR Odds ratio

PCS Physical component scale

PICS Post-intensive care syndrome

RRT Renal replacement therapy

SF-36 36-item Short Form

SMQ Short-Memory Questionnaire

SOFA Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

The study protocol was approved by the KCGH ethics committee and the ethics committees of all participating hospitals (KCGH approval number: Zn181008).

Consent for publication

Written informed consent was obtained from all patients or authorized surrogates.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design: DK, SF, and TM

Acquisition of data: All declared authors

Analysis and interpretation of data: DK, SF, and TM

Drafting of the manuscript: DK

Critical revision of the manuscript for important intellectual content: All declared authors.

DK has full access to all the data in the study and takes responsibility for the integrity of the data. All authors have read and approved the final manuscript.

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Figures

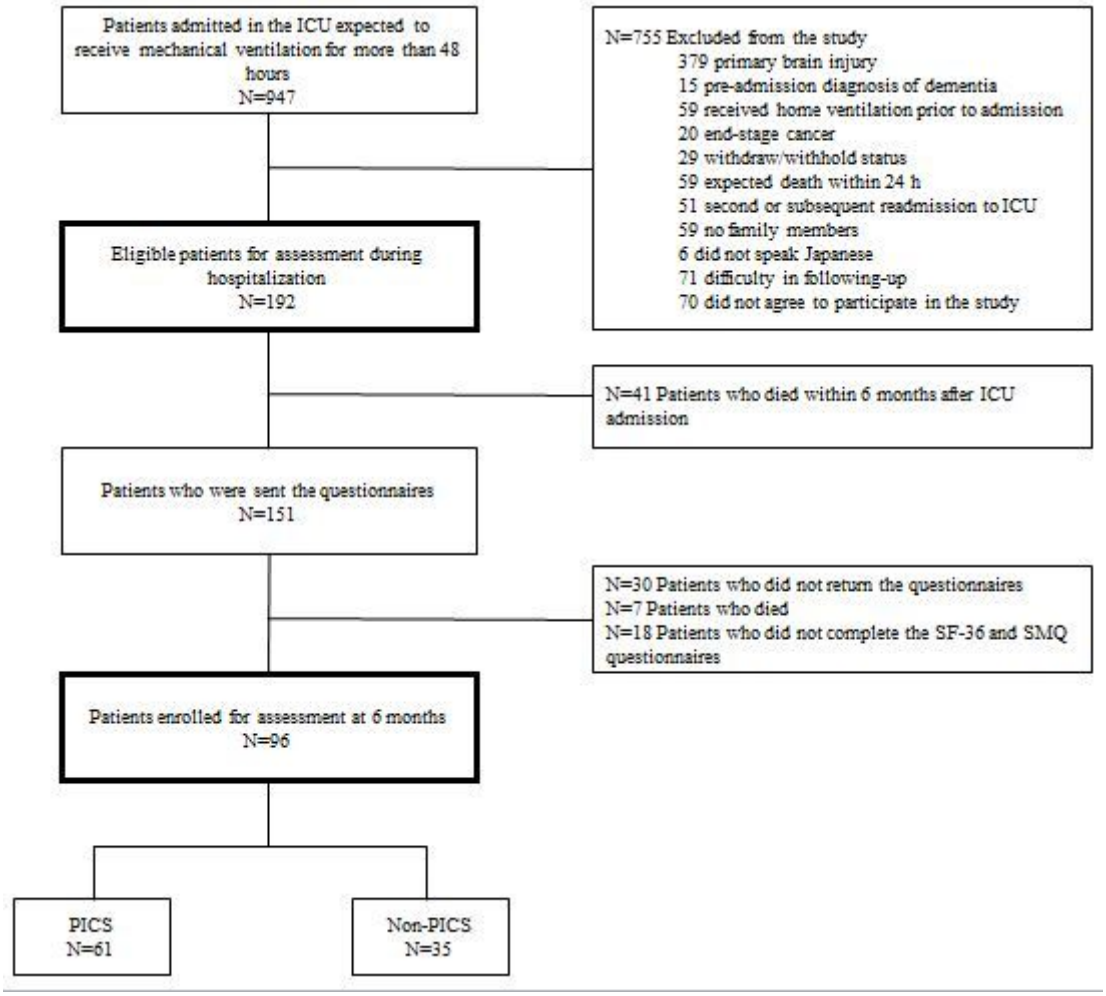

Figure 1

Flowchart depicting the enrolment of subjects in the study Abbreviations: ICU: Intensive care unit, SF-36: 36-item Short Form health survey questionnaire, SMQ: Short-Memory Questionnaire, PICS: Post-intensive care syndrome

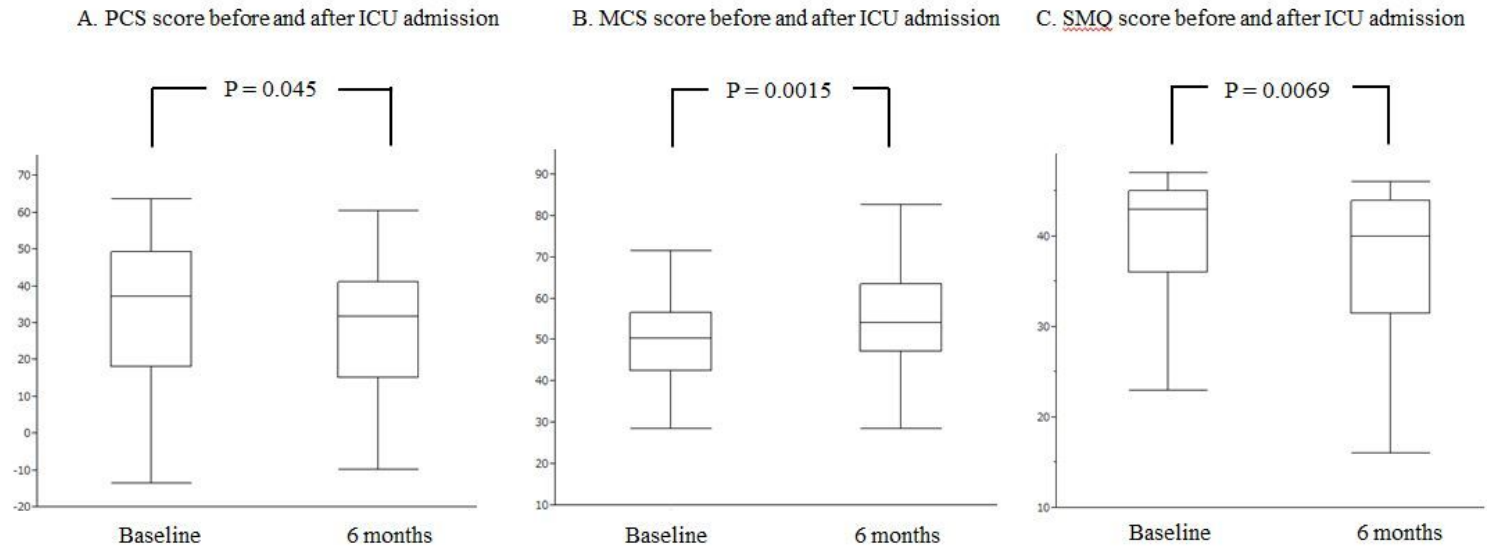

Figure 2

Changes in SF-36 PCS, MCS, and SMQ scores before and after ICU admission Abbreviations: SF-36: 36-item Short Form health survey questionnaire, PCS: Physical component scale, MCS: Mental component scale, SMQ: Short-Memory Questionnaire, ICU: Intensive care unit

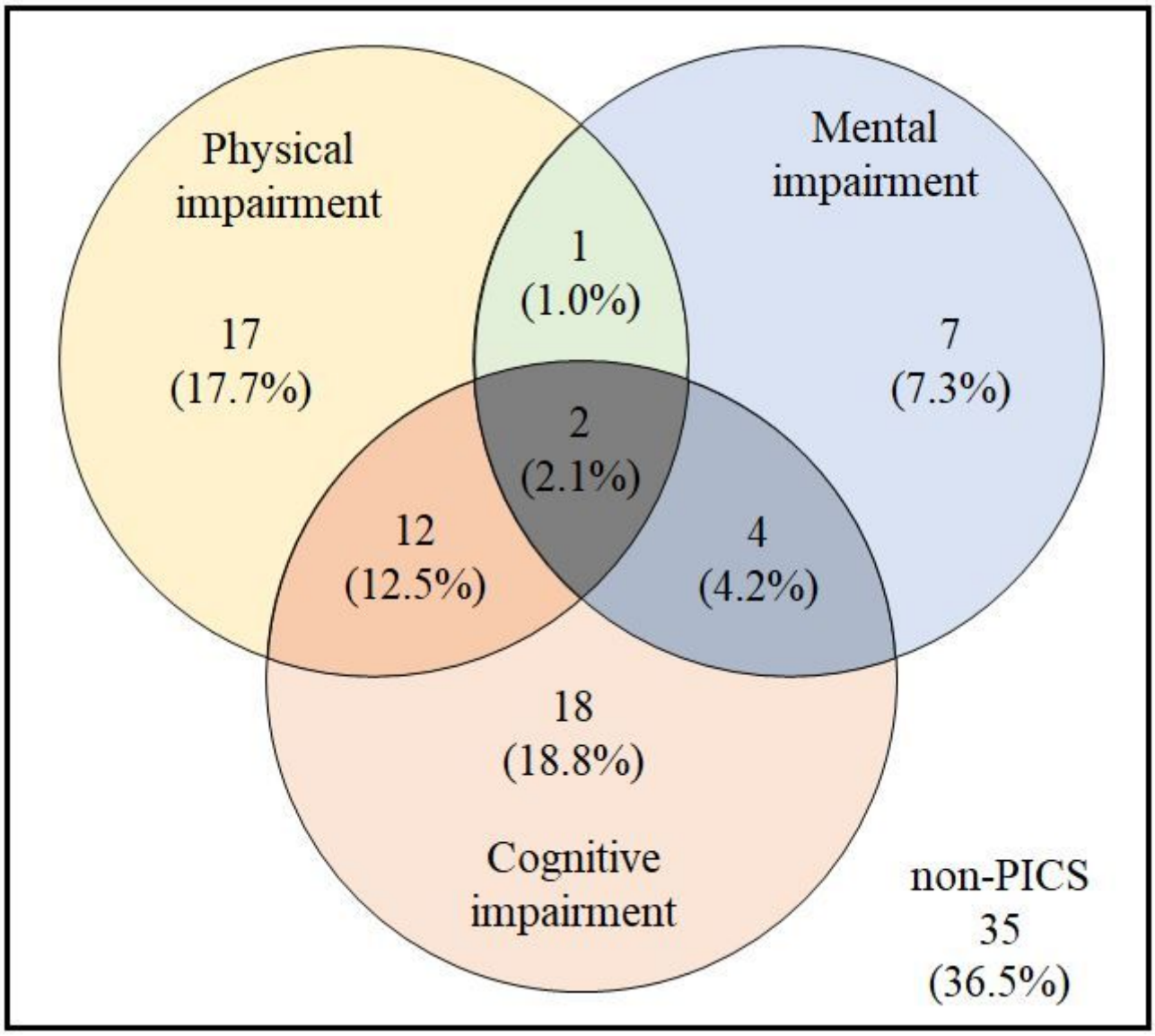

Figure 3

Occurrence of PICS problems among patients at 6 months after ICU admission Abbreviations: PICS: Post-intensive care syndrome

Supplementary Files

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