Original Article

Activities of daily living status and psychiatric symptoms after discharge from an intensive care unit: a single-center 12-month longitudinal prospective study

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Aim: In post-intensive care syndrome (PICS), long-term survivors of critical illness present various physical and mental symptoms that can persist for years after discharge. Post-intensive care syndrome in Japan has not been well described, so this study aims to elucidate its epidemiology.

Methods: We undertook a single-center prospective longitudinal cohort study in a mixed intensive care unit (ICU) in a Japanese tertiary hospital. Adult patients emergently admitted to the ICU were eligible for inclusion in the study. To assess activity of daily living (ADL) status and psychiatric symptoms, we posted a questionnaire at 3 and 12 months after discharge from the ICU. We evaluated ADL status, anxiety, depression, and post-traumatic stress disorder symptoms using the Barthel index, Hospital Anxiety and Depression Scale, and Impact of Event Scale – Revised, respectively.

Results: Enrolled in this study were 204 patients. We received responses from 117/147 (80%) and 74/98 (76%) patients at 3 and 12 months, respectively. At 3 months, the prevalence of ADL disability, anxiety, depression, and post-traumatic stress disorder symptoms was 32%, 42%, 48%, and 20%, respectively. At 12 months, the prevalence was 22%, 33%, 39%, and 21%, respectively. The prevalence of any symptoms was 66% at 3 months and 55% at 12 months. Barthel index score at 12 months was improved significantly from that at 3 months. Hospital Anxiety and Depression Scale and Impact of Event Scale – Revised scores at 12 months showed no improvement.

Conclusions: At 3 and 12 months after ICU discharge, over half of our Japanese patients suffered ADL disability and/or psychiatric symptoms. The ADL disability improved at 1 year, but psychiatric symptoms did not.

Key words: Anxiety, Barthel index, depression, post-intensive care syndrome, post-traumatic stress disorder

INTRODUCTION

I NTENSIVE CARE MEDICINE is gradually evolving and in-hospital mortality of patients with critical illness has decreased considerably over time.^{1,2} Accordingly, longterm survivors of critical illness have also dramatically increased. In the USA, the annual number of new 3-year survivors after severe sepsis approximately doubled within a

Corresponding: Kyohei Miyamoto, MD PhD, Department of Emergency and Critical Care Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama City, Wakayama, Japan. E-mail: gomadofu@wakayama-med.ac.jp *Received 3 Jun, 2020; accepted 17 Jul, 2020* Funding Information No funding information provided. decade.³ These patients have been reported to often have various physical and mental symptoms that could persist for years after discharge from the intensive care unit (ICU).^{4,5} These symptoms not only worsen the quality of life of these patients, but also that of their families.⁶ Moreover, these patients could require substantial medical resources, regarded as an important economic problem by relevant stakeholders.^{7,8} Such symptoms have been recently called post-intensive care syndrome (PICS), which was advocated by the Society of Critical Care Medicine conference held in 2010.⁹

Post-intensive care syndrome symptoms include physical, cognitive, and mental health impairments. Nearly 60% of survivors of critical illness were reported to have suffered from at least one of these symptoms.¹⁰ Various interventions, such as psychological intervention and early

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rehabilitation, have been substantially investigated with the goal of overcoming these PICS symptoms.^{11,12}

Describing the epidemiology of PICS is the first step to investigate these interventions, but there are few Japanese reports that describe the long-term psychiatric symptoms or disabilities after critical illness. We therefore undertook this study to elucidate the epidemiology of PICS in Japan.

METHODS

Study design

THIS IS A single-center prospective longitudinal cohort study comprising patients who were emergently admitted to an ICU at a tertiary hospital in Japan. Patients were enrolled between September 2016 and August 2018, with follow-up until August 2019. This study was approved by the Wakayama Medical University Institutional Review Board (approval number 1864) and was registered at UMIN Clinical Trial Registry on 1 September, 2016 (registration no. UMIN000023743, https://upload.umin.ac.jp/cgi-openbin/ctr/ctr_view.cgi?recptno=R000027346). Written informed consent was obtained from patients or legally authorized guardians by attending physicians after explanation that there would be no difference in care or treatment regardless of whether or not they participate in this study.

Participants and data collection

Patients who were emergently admitted to the ICU through the emergency department and aged 20 years or older were eligible. We excluded patients who were expected to die within 48 h according to the attending physicians' judgement. We made a follow-up questionnaire including questions from the Barthel index (BI),13 Hospital Anxiety and Depression Scale (HADS),¹⁴ and Impact of Event Scale – Revised (IES-R).¹⁵ We posted the questionnaire to participants at 3 and 12 months after their discharge from the ICU. To reduce patients lost to follow-up, before posting questionnaires, we telephoned participants to request return of the questionnaires. Data on patient characteristics and treatment during their ICU stay were collected from medical records. We assessed age, sex, Acute Physiology And Chronic Health Evaluation II score (calculated at 24 h after admission), BI score before admission, mental illness prior to ICU admission, admission route (i.e., admission from the emergency department, operating room, or general wards) and reason for ICU admission (i.e., sepsis, trauma, cardiovascular disease, central nervous system disease, or others), number of patients with a disease that could directly influence brain function (e.g., traumatic brain injury), number of patients that received corticosteroids during ICU stay, number of patients that received mechanical ventilation during ICU stay, ventilator-days in ICU, number of patients with delirium during ICU stay, length of ICU stay, and length of hospital stay. "Mental illness prior to ICU admission" was defined as diagnosis in a medical institution or drugs prescribed for it. "Receiving corticosteroids" was defined as receiving corticosteroids for over 48 h. "Delirium" was defined as at least one positive screening on the *Confusion Assessment Method for the Intensive Care Unit* during their ICU stay.

Outcome measurements

Primary outcomes were the activities of daily living (ADL) status and psychiatric symptoms at 3 and 12 months after discharge from ICU. The ADL status was evaluated using BI.¹³ The BI consists of 10 items that measure functional independence regarding ADL (e.g., feeding, dressing, and chair/bed transfer). The score ranges from 0 (total dependence when carrying out ADL) to 100 (fully independent in carrying out ADL). There is no standardized cut-off value, but we applied a strict definition of ADL disability as a BI score of 60 or less.¹⁶ A minimal clinically important difference of BI is 9.25 points.¹⁷ Psychiatric symptoms were evaluated using HADS and the Japanese-language version of IES-R. The HADS consists of two subscales concerning (HADS-Anxiety [HADS-A]) and depression anxiety (HADS-Depression [HADS-D]) symptoms. Each subscale consists of seven questions scored from 0 to 3, resulting in a score range between 0 and 21 in each subscale. A subscale score of 8 or more is defined as the presence of the respective state.¹⁸ The IES-R consists of 22 questions scored from 0 to 4, resulting in a score range between 0 and 88 with a higher score indicating worse post-traumatic stress disorder (PTSD) symptoms. A score of 25 or more was defined as the presence of clinically important PTSD symptoms.¹⁹ If half or more questions within each score (BI, HADS-A, HADS-D, and IES-R) were missing, we regarded that score as unavailable. If less than half of the questions within each score were missing, we calculated each score by regarding the missing questions as "no symptoms (no disability)", or "no change" (if baseline BI was available) for estimating the prevalence of PICS symptoms following the most optimistic scenario.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as number and percentage (%). Among patients who responded to

both questionnaires at 3 and 12 months, we compared the BI, HADS, and IES-R between each time point by Wilcoxon's signed rank sum test. As a sensitivity analysis, we also compared BI, HADS, and IES-R, excluding patients with a disease that could directly influence brain function. We showed the co-occurrence of ADL disability and psychiatric symptoms in a Venn diagram. We compared primary outcomes between surgery and non-surgery patients.

RESULTS

THE PATIENT flowchart is shown in Figure 1; 204 patients were enrolled. One patient met exclusion criteria for being under 20 years old. The 3- and 12-month questionnaires were answered by 117 (80% response rate) and 74 (76% response rate) patients, respectively. Characteristics of all participants and 3- and 12-month responders are detailed in Table 1. The median age of patients was 72 years, 59% were men, and 43% of participants had sepsis. The BI at baseline was 100 (IQR, 80–100).

The primary outcome is shown in Table 2. At 3 months, the data availability of BI, HADS-A, HADS-D, and IES-R was 100%, 75%, 78%, and 71%, respectively. At 12 months, the data availability was 93%, 82%, 82%, and 76%, respectively. Approximately 10–17% of scores in returned questionnaires were missing some answers (Table S1). At 3 months, the prevalence of ADL disability, anxiety, depression, and PTSD symptoms was 32%, 42%, 48%, and 20%, respectively. At 12 months, the prevalence of HDL disability, respectively. The mean difference of BI between baseline and at 3 months was -11.93 (95% confidence interval, -18.91 to -4.95), which reached minimal

clinically significant difference. In contrast, the mean difference of BI at 3 months and at 12 months was 5.70 (95% confidence interval, 1.82 to 9.58), which did not reach minimal clinically significant difference. The BI score did not differ significantly between 12 months and baseline. The HADS-A, HADS-D, and IES-R scores at 12 months were similar to those at 3 months (Fig. 2). After excluding patients with diseases that would directly influence brain function (e.g. traumatic brain injury), we found similar results. There were no significant differences between subgroups of surgery and non-surgery patients (Tables S2 and S3).

At 3 months, among 88 patients with scores in both ADL disability and psychiatric symptoms, 54 (61%) patients had one or more psychiatric symptoms. Similarly, at 12 months, among 56 patients, 29 (52%) had one or more psychiatric symptoms (Fig. 3). Among patients with psychiatric symptoms, 30% (16/54) and 28% (8/29) had ADL disability at 3 and 12 months, respectively. Among patients with ADL disability, 80% (16/20 and 8/10 at 3 and 12 months, respectively) had psychiatric symptoms.

DISCUSSION

IN THIS SINGLE -center longitudinal prospective study, after critical illness approximately 30–50% of participants had anxiety or depression symptoms, and approximately 20% of them had PTSD symptoms. These symptoms persisted at 12 months. In contrast, ADL was worsened at 3 months after ICU discharge, but it recovered to the previous level by 12 months. This result suggests that the course of psychiatric symptoms and ADL disability have different trajectories to recovery.



Fig. 1. Flowchart of patient selection for this study. ICU, intensive care unit.

Table 1. Characteristics of childany in Japanese patients entergently admitted to an interisive care unit (iCO)			
Characteristic	All patients $(n = 204)$	Responders to 3- month questionnaire (n = 117)	Responders to 12-month questionnaire (n = 74)
Age, years	72 (61–81)	71 (60–78)	69 (56–76)
Male sex	121 (59)	67 (57)	45 (61)
APACHE II score at ICU admission	21 (17–26)	19 (16–23)	20 (16–24)
Barthel index before acute illness [†]	100 (80–100)	100 (79–100)	100 (84–100)
Mental illness prior to ICU admission ‡	25 (12)	14 (12)	7 (9)
Admission route			
Emergency department	126 (62)	76 (65)	46 (62)
Operating room	68 (33)	37 (32)	24 (32)
General wards	10 (5)	4 (3)	4 (5)
Reason of ICU admission			
Sepsis	87 (43)	47 (40)	34 (46)
Trauma	40 (20)	21 (18)	14 (19)
Cardiovascular	5 (2)	3 (3)	O (O)
Central nervous system	9 (4)	5 (4)	2 (3)
Others	63 (31)	41 (35)	24 (32)
Patients with disease that could directly influence brain function ${}^{\$}$	32 (16)	17 (15)	10 (14)
Patients who received corticosteroid during ICU stay [¶]	46 (23)	26 (22)	18 (24)
Patients who received mechanical ventilation during ICU stay	186 (91)	103 (88)	67 (91)
Ventilator-days in ICU, days	4 (2–8)	4 (2–7)	5 (2–9)
Patients experienced delirium in ICU ^{††}	61 (30)	36 (31)	24 (32)
Length of ICU stay, days	5 (3–9)	5 (3–9)	6 (3–9)
Length of hospital stay, days	28 (15–42)	30 (18–48)	32 (19–51)

Table 1. Characteristics of critically ill Japanese patients emergently admitted to an intensive care unit (ICU)

Data are shown as median (interquartile range) or *n* (%).

APACHE II, Acute Physiology And Chronic Health Evaluation II.

[†]Missing for 30 patients.

[‡]If diagnosed by a medical institution or drugs had been prescribed.

[§]Including cardiopulmonary arrest, traumatic brain injury, stroke, and acute poisoning.

[¶]If the duration of receiving corticosteroid was 48 h or longer.

⁺⁺Defined as at least one positive Confusion Assessment Method for the Intensive Care Unit through their ICU stay.

Previous studies have shown ADL disability is common among ICU survivors. The prevalence of any ADL disability (i.e., Katz ADL score ≥ 1 and BI < 100) was reportedly 32–51% at 3 months and 27–33% at 12 months.^{20–23} The prevalence of ADL disability in our study was marginally lower than in previous studies, probably because more severe dependence (i.e., BI ≤ 60) was defined as ADL disability in this study. Similarly, psychiatric symptoms have been reported to be common among ICU survivors. A recent meta-analysis reported that the prevalence of anxiety and depression symptoms at 3 and 12 months was 30–40%, and PTSD symptoms approximately 20%, which is consistent with the results of the current study.^{24–26}

Some studies have reported gradual recovery of physical function after discharge.^{22,27–30} A prospective observational study reported that BI at 12 months after discharge from ICU was significantly higher than that at 3 months, from 97

(IQR, 53.7–100) at 3 months to 100 (IQR, 90–100) at 12 months. Similarly, the prevalence of ADL disability also decreased over time, from 51.4% at 3 months to 32.8% at 12 months.²² In the current study, we found that the BI score was improved at 12 months compared with at 3 months. In contrast, IES-R, HADS-A, and HADS-D scores did not improve, which was concordant with the abovementioned studies. However, the mean difference between BI scores at 3 months and at 12 months did not reach minimal clinically significant difference. The improvement of BI from 3 months to 12 months might not be clinically important.

In this study, over half of patients suffered ADL disability and/or psychiatric symptoms at 3 and 12 months. While 80% of those with ADL disability had psychiatric symptoms, only approximately 30% of those with psychiatric symptoms had ADL disability. The co-occurrence of ADL

Table 2.Primaryemergently admitted	outcomes in to an intensive ca	Japanese patients re unit
	Responders to 3-month questionnaire (n = 117)	Responders to 12-month questionnaire (n = 74)
Barthel index		
Data available	117 (100)	69 (93)
Score	95 (48–100)	100 (83–100)
Score ≤ 60	37 (32)	15 (22)
HADS-Anxiety		
Data available	88 (75)	61 (82)
Score	6 (2–9)	5 (3–8)
Score ≥ 8	37 (42)	20 (33)
HADS-Depression		
Data available	91 (78)	61 (82)
Score	7 (4–10)	6 (3–10)
Score ≥ 8	44 (48)	24 (39)
IES-R		
Data available	83 (71)	56 (76)
Score	10 (3–23)	13 (2–23)
Score ≥ 25	17 (20)	12 (21)

Data shown as median (interguartile range) or n (%).

HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale – Revised. disability and psychiatric symptoms was 18% and 14% at 3 and 12 months, respectively. Marra *et al.* reported that cooccurrence of disability (score \geq 1 on the Katz ADL) and depression (score \geq 13 on the Beck Depression Inventory, 2nd Edition) was seen in 10% and 8% of their patients.¹⁰ In that study, less than half of patients with disability had depression. The exact cause of this discrepancy is unknown, but it might be attributable to the differing definitions of disability and depression. In the current study, a substantial number of patients suffered from co-occurrence of ADL disability and psychiatric symptoms. The results of our study imply that ADL disability could worsen the psychiatric symptoms, but we could not conclude this hypothesis because our study did not evaluate the association between ADL disability and psychiatric symptoms.

We found that many patients who discharged from ICU in Japan suffered from psychiatric symptoms and/or ADL disability. Notably, psychiatric symptoms persisted even at 1 year after ICU discharge, whereas ADL disability tended to alleviate between 3 and 12 months. The burden of psychiatric symptoms might relatively increase during long-term recovery from critical illness, compared with the burden of ADL disability. Our study implies that a system to facilitate recovery from both psychiatric symptoms (e.g., ICU diary



Fig. 2. Changes in Barthel index (A), Hospital Anxiety and Depression Scale (HADS)-Anxiety (B), HADS-Depression (C), and Impact of Event Scale – Revised (IES-R) (D) during follow-up of critically ill Japanese patients emergently admitted to an intensive care unit. Patients with missing values in any score are excluded from this figure. We compared the Barthel index, HADS, and IES-R between each time point by Wilcoxon's signed rank sum test. In box plots, we expressed median values as bold lines.



At 12 months (n = 56)

Fig. 3. Co-occurrence of activity of daily living (ADL) disability and psychiatric symptoms at 3 months (A) and 12 months (B) after discharge from the intensive care unit. Psychiatric symptoms are considered to be present if any of the three scales (Hospital Anxiety and Depression Scale [HADS]-Anxiety, HADS-Depression, and Impact of Event Scale – Revised) are indicative of these symptoms.

or psychological supporting program) and ADL disability (e.g., early mobilization program) is warranted.

This study has several limitations. First, the results of our study might underestimate the prevalence of PICS symptoms because we applied stricter cut-offs about ADL disability and we input some missing questions within each score as either "no symptoms" or "no change". As a first step in Japan, we aimed to estimate the most optimistic scenario in PICS epidemiology. The real-world clinical significance seems to be higher than that estimated in our study, which should increase the importance of our study. A second limitation is that there is a potential selection bias because a substantial number of patients were lost to follow-up in this study due to the long follow-up period. The response rate to the questionnaire was approximately 80%, however, which was better than reported in previous studies.^{31,32} Even if it does exist, selection bias seems to be relatively small because patient characteristics do not differ substantially between overall enrolled participants and questionnaire responders. Similarly, the possibility of information bias cannot be excluded because of the self-questionnaire-based outcome evaluation. We can estimate the presence or absence of psychiatric symptoms, but we cannot conclude that patients with higher scores of HADS or IES-R would always have a diagnosis of psychiatric illness. To overcome this, follow-up by an assessment system in collaboration with psychiatrists is needed. Moreover, this study is a single-center study, so the results might not be generalizable to other circumstances. Future multicenter studies in Japan are needed to confirm our results; however, the results of our study are almost concordant with those of previous studies, which could represent the robustness of our results.

CONCLUSIONS

O VER HALF OF our Japanese patients suffered ADL disability and/or psychiatric symptoms at 3 and 12 months after discharge from ICU. Although IES-R, HADS-A, and HADS-D scores did not improve, the BI score improved at 12 months compared with that at 3 months. Future multicenter studies in Japan are needed to confirm our results, and a system to facilitate recovery from psychiatric symptoms as well as ADL disability is warranted.

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DISCLOSURE

Approval of the research protocol: The protocol for this research project was approved by a suitably constituted institutional ethics committee (Wakayama Medical University, approval number 1864). It conforms to the provisions of the Declaration of Helsinki.

Informed consent: Written informed consent was obtained from all participants or legally authorized guardians before study enrollment.

Registry and registration no. of the trial: UMIN-CTR, UMIN000023743 (registered 1 September, 2016; https:// upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno= R000027346).

Animal studies: N/A.

Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Number of missing questions within each score. **Table S2.** Primary outcomes in the subgroups of surgical or non-surgical patients at 3 months.

 Table S3. Primary outcomes in the subgroups of surgical or non-surgical patients at 12 months.