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# Association between Early Mobilization in the ICU and Psychiatric Symptoms after Surviving a Critical Illness: A Multi-Center Prospective Cohort Study

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**Abstract:** This is a prospective multicenter cohort study aiming to investigate the association between early mobilization (EM), defined as a rehabilitation level of sitting at the edge of the bed or higher within 72 h of ICU admission, and psychiatric outcome. Consecutive patients, admitted to the ICU for more than 48 h, were enrolled. The primary outcome was the incidence of psychiatric symptoms at 3 months after hospital discharge defined as the presence of any of three symptoms: depression, anxiety, or post-traumatic stress disorder (PTSD). Risk ratio (RR) and multiple logistic regression analysis were used. As a sensitivity analysis, two methods for inverse probability of treatment weighting statistics were performed. Of the 192 discharged patients, 99 (52%) were assessed. The patients who achieved EM had a lower incidence of psychiatric symptoms compared to those who did not (25% vs. 51%, *p*-value 0.008, odds ratio (OR) 0.27, adjusted *p* = 0.032). The RR for psychiatric symptoms in the EM group was 0.49 [95% Confidence Interval, 0.29–0.83]. Sensitivity analysis accounting for the influence of death, loss to follow-up (OR 0.28, adjusted *p* = 0.008), or potential confounders (OR 0.49, adjusted *p* = 0.046) consistently showed a lower incidence of psychiatric symptoms in the EM group. EM was consistently associated with fewer psychiatric symptoms.

## 1. Introduction

Critical illness may result in severe psychiatric disorders, such as depression, anxiety, and post-traumatic stress disorder (PTSD) [1,2], which adversely affect the quality of life and prevent intensive care unit (ICU) survivors from returning to their original lives [3]. Psychiatric symptoms occur in 10–70% of ICU survivors [1,2,4,5] and could last for several months or years after hospital discharge [6,7]. Although research interest is growing as shown by the increasing body of literature, there is no strategy with definitive effects to prevent the development of these symptoms.

Immobility induced by physical restriction is associated with the development of psychiatric disorders [8,9], while the potential benefits of regular physical exercise in non-ICU settings to decrease psychiatric symptoms have been described [10,11]. Active physical rehabilitation during the ICU stay, especially when initiated within the first 72 h of ICU stay, is recommended to prevent physical disabilities and improve clinical outcomes of ICU patients [12]. However, the effects of physical rehabilitation early in the ICU stay on psychiatric symptoms are unknown in the existing literature [13].

Therefore, we conducted a multicenter prospective cohort study to investigate the incidence rate of psychiatric symptoms at 3 months after hospital discharge and the association between active physical rehabilitation within 72 h of ICU admission and psychiatric symptoms. We focused on 3 months since a similar trend and incidence rate of psychiatric symptoms at 3 months and 1 year after hospital discharge have been observed [14,15].

## 2. Materials and Methods

### 2.1. Study Design and Patient Selection

This multicenter prospective cohort study was approved by the Ethics Committee of Nagoya Medical Center (2018093) and eight other participating hospitals (Hitachi General Hospital, Nagasaki University Hospital, Fukuyama City Hospital, Naha City Hospital, Yuuai Medical Center, Tokushukai General Hospital, Showa University Hospital, Tokyo Women's Medical University Hospital) and registered in UMIN (ID: 000036503). We followed the STROBE guidelines [16], and all methods in this study were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all patients.

Consecutive patients, up to 25 patients in each participating hospital, who stayed in the ICU for more than 48 h between June and December in 2019, were eligible for enrollment. Patients less than 18 years of age, unable to walk independently before admission, with neurological complications, lacking communication skills due to pre-existing mental diseases, or in a terminal state were excluded (Table S1). Our study excludes patients with a history of psychiatric disorders (depression, anxiety, PTSD). Patients who died or did not complete the assessment at 3 months follow-up after hospital discharge, were also excluded. In the present study, mobilization was defined as physical rehabilitation at the level of sitting on the edge of the bed or higher [17], and patients were divided into two groups. The patients were allocated into the early mobilization (EM) group when they achieved rehabilitation at the level of mobilization within 72 h of ICU admission [17–19]. Patients were allocated into the non-EM group when they did not receive mobilization during the ICU stay or achieved mobilization more than 72 h after ICU admission. All patients equally aimed to receive mobilization daily under a protocol tailored to the circumstances of participating hospitals, though mobilization could not be achieved when the patient did not meet the criteria (Table S2). Patients were not randomized in this study, and whether patients could undergo mobilization depended on the EM protocol used in each participating hospital.

*2.2. EM Protocol*

The early goal-directed protocol for rehabilitation [19–21] was developed more than 6 months before this study was initiated, and the details of the contents were arranged based on the situation of participating hospital. This protocol is used in multiple centers in routine practice and safety validation has already been reported [22]. The EM protocol details are shown in Table S2.

The protocol provides patients with five rehabilitation levels (level 1, passive range of motion and respiration physical therapy; level 2, active range of motion; level 3, sitting exercise; level 4, standing exercise; and level 5, walking exercise) based on their medical condition. At each participating site, ICU physicians or physiotherapists made the final decision of the rehabilitation level based on the patient's condition while referring to the protocol. All patients were supposed to receive at least one rehabilitation session per day for 20 min on weekdays.

Regarding other ICU care, all participating hospitals followed the 2018 Clinical Practice Guidelines [23] and the clinical practice guideline for the management of ARDS [24].

After transfer out of the ICU, all patients underwent rehabilitation, such as muscle strengthening, balancing, walking, and stair exercises, for more than 20 min on weekdays by physical or occupational therapists according to the rehabilitation policy in the general ward of each hospital without any specific protocol.

*2.3. Follow-Up Protocol*

Table S3 shows the details of the follow-up protocol. At 3 months after hospital discharge, a doctor, a nurse, or physiotherapist at each participating hospital made a phone call to the patient to confirm their survival. Once survival was confirmed, evaluation of the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) [25] was verbally performed during the same phone call. Then, questionnaires and response sheets for Hospital Anxiety and Depression Scale (HADS) and Impact of Events Scale-Revised (IES-R) were mailed to the patient' home. The questionnaires were sent back to each participating hospital with the patient's responses. Despite several phone calls, if the patient did not respond, they were excluded from analysis as lost to follow-up.

*2.4. Data Collection*

Baseline characteristics were collected at the time of ICU admission and during the ICU stay by co-investigators at each hospital, including age, gender, body mass index, Charlson comorbidity index [26], Barthel Index before hospitalization [27], ICU admission diagnosis, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, and use of mechanical ventilation, continuous vasopressors, continuous analgesia, continuous sedation, steroids, neuromuscular blocking agents, dialysis, time to first out of bed mobilization from the time of ICU admission, highest ICU Mobility Scale (IMS) during ICU stay, and the number of daily rehabilitation sessions on the ward. Barthel index before hospitalization was scored at the time of ICU admission based on the information from the family or the patients if they were conscious. The average sedation level, described according to the Richmond Agitation-Sedation Scale (RASS), from days 1 to 3 was calculated based on data in the electronic medical record. The IMS provides a sensitive 11-point ordinal scale, ranging from nothing (lying/passive exercises in bed, score of 0) to independent ambulation (score of 10) [28].

*2.5. Study Outcomes*

The primary outcome was the incidence of psychiatric symptoms at 3 months after hospital discharge, which was defined as the presence of at least one of three symptoms: depression, anxiety, or PTSD. Depression and anxiety were assessed using the HADS that contains 14 items, seven for anxiety assessment and seven for depression, with a score of 0–3 for each item. Within a maximum score of 21 for each subset for depression or anxiety assessment, the presence of depression or anxiety was defined as a score of 8 or more [29].

PTSD was evaluated using the IES-R, a 22-item self-reported measure with scores ranging between 0 and 88 points (score 0–4 per item). The presence of PTSD was defined as a score of 25 or more [30].

Secondary outcomes were the scores on HADS subsets for depression or anxiety and the IES-R score for PTSD at 3 months after hospital discharge, as well as the change in each score between hospital discharge and at 3 months.

Other variables included the EQ-5D-5L which is a standardized assessment for HRQoL [25] at 3 months follow-up and at hospital discharge, walking independence at discharge [21], duration of mechanical ventilation, length of ICU and hospital stays, Barthel Index at hospital discharge, incidence of delirium during ICU stay, incidence of ICU-acquired weakness (ICU-AW) at ICU discharge. Patients who could walk 45 m or more with or without braces were regarded as walking independent [19]. For the assessment of delirium, either Confusion Assessment Method for the Intensive Care Unit [31] or Intensive Care Delirium Screening Checklist [32] was used as delirium screening tool. ICU Acquired Weakness is defined that Medical Research Council-sum score evaluating by physical therapists is less than 48 at the time of ICU discharge [33].

*2.6. Statistical Analysis*

A sample size of 240 patients is needed with 80% power and a two-sided significance level of 0.05, under the assumption of a follow-up achievement rate of 80%, 60% of non-EM patients will develop psychiatric symptoms and EM patients will have a 20% reduction based on previous studies [14,15,34].

Data are presented as a median with interquartile range or as a number with percentage. The Mann–Whitney U test was used to analyze continuous variables and the $\chi^2$ test or Fisher's exact test for nominal variables, as appropriate. Before using a non-parametric test, the distribution of each parameter was evaluated with the Shapiro–Wilk test.

In addition to the comparison of baseline characteristics between the two groups, given the influence of death and loss to follow-up, we also compared them between patients discharged from the ICU and those who completed follow-up at 3 months. The same analysis was conducted among patients discharged from ICUs and those who completed follow-up both in the EM and non-EM groups.

Multiple logistic regression analysis was performed to identify an association of the primary outcome with the following covariates: Age, male gender, Barthel index before hospitalization, ICU admission diagnosis, APACHE II score, and use of mechanical ventilation, continuous analgesia, continuous sedation, steroids, and neuromuscular blocking agents, and dialysis, which were considered as factors related to the primary outcome in previous reports (Table S4) [35–47]. To analyze secondary and other outcomes, multiple linear and logistic regression analyses were performed for log-transformed continuous and categorical variables, respectively, using the same covariates as used in analyzing the primary outcome. Each relative risk ratio (RR) for the incidence of depression, anxiety, or PTSD in the EM group against the non-EM group was described. Pearson's correlation coefficient was used to assess the correlation between the number of days from ICU admission to first mobilization and the HADS subset scores for depression or anxiety or the IES-R score for PTSD.

As a post hoc analysis, two methods for inverse probability of treatment weighting (IPTW) statistics were used. The first adjusted the influence of death and follow-up loss and the second adjusted as many confounding factors from baseline characteristics such as severity, baseline comorbidity, ICU admission diagnosis, consciousness level, which could affect the outcomes. The methodological details of the analysis are shown in Table S5 [48,49].

All analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Statistical tests were two-sided, and statistical significance was defined as *p*-values of <0.05.

## 3. Results

### 3.1. Baseline Characteristics

Of the 1014 patients screened, 203 were enrolled (Figure 1). Of these, 192 patients were discharged from the ICU and were eligible for follow-up assessment. Excluding patients who died or who missed the 3-month follow-up, a total of 99 patients, including 60 in the EM group and 39 in the non-EM group, completed the 3-month follow-up. There were differences among the measured baseline characteristics between the two groups, for the Acute Physiology and Chronic Health Evaluation II score (17 vs. 21, $p = 0.026$) and the use of mechanical ventilation (53% vs. 74%, $p = 0.034$), steroids, neuromuscular blockade (0% vs. 13%, $p = 0.008$), and dialysis (12% vs. 28%, $p = 0.037$) (Table 1). The average RASS score within the first 3 days of the ICU stay was not significantly lower in the EM group. Among the rehabilitation items, the EM group had a shorter time from ICU admission to first rehabilitation (1.7 days vs. 5.3 days, $p < 0.001$), and a higher IMS score during their ICU stay (8 vs. 4, $p < 0.001$).
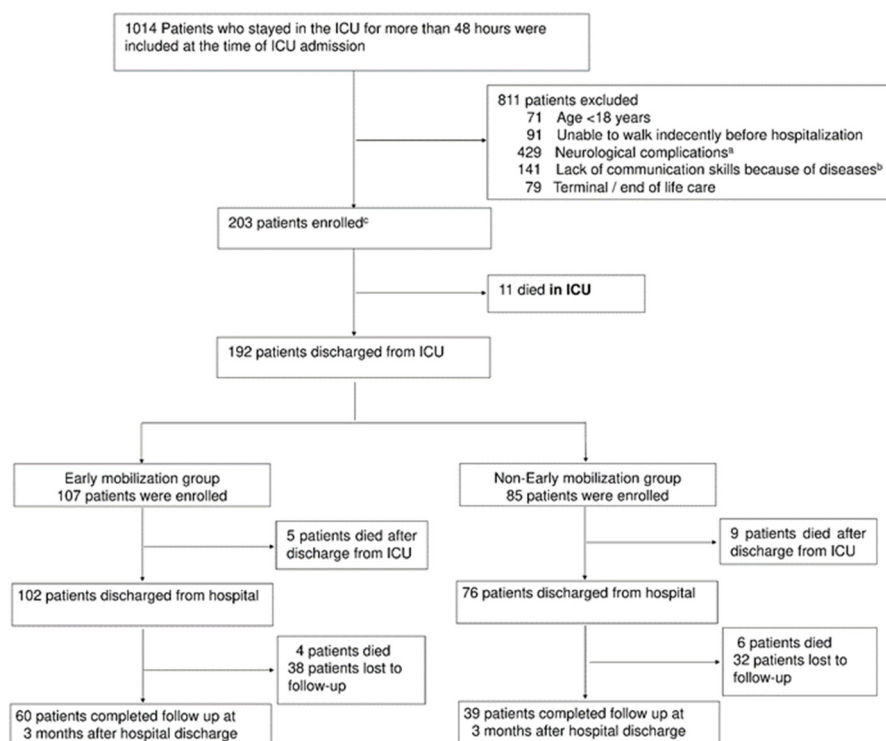


**Figure 1.** Study flow chart. ICU = intensive care unit. [a] Neurological complications include cerebral infarction, cerebral hemorrhage, acute subdual hematoma, acute epidural hematoma, traumatic subarachnoid hemorrhage, and encephalitis. [b] Diseases include depression, anxiety, schizophrenia, dementia, cerebral infarction, cerebral hemorrhage, and alcoholism. [c] Four out of nine hospitals could not enroll 25 patients and enrolled 14, 21, 22, and 21 patients.

Considering the bias due to death and loss to follow-up, no differences were observed in all baseline characteristics comparing patients discharged from the ICU and who completed the 3-month follow-up in each comparison (Table S6).

### 3.2. Primary and Secondary Outcomes

The incidence of psychiatric symptoms at the 3-month follow-up point was significantly lower in the EM group than in the non-EM group [odds ratio (OR): 0.27, adjusted $p = 0.032$] even after adjustment for the baseline characteristics of the two groups, whereas the incidence at the time of hospital discharge was not different (OR: 1.03, adjusted $p = 0.965$) (Table 2).

**Table 1.** Baseline characteristics.

| Variables | Early Mobilization Group (*n* = 60) | Non-Early Mobilization Group (*n* = 39) | *p* Value |
|---|---|---|---|
| Age (years), median (IQR) | 70 (61–75) | 73 (57–79) | 0.416 |
| Gender (male), *n* (%) | 39 (65) | 23 (59) | 0.545 |
| BMI (kg/m$^2$), median (IQR) | 23 (21–25) | 24 (21–27) | 0.439 |
| Charlson Comorbidity Index, median (IQR) | 2 (1–2) | 1 (0–2) | 0.591 |
| Barthel index before hospitalization, median (IQR) [a] | 100 (100–100) | 100 (100–100) | 0.638 |
| ICU admission diagnosis, *n* (%) | | | 0.652 |
| Acute respiratory failure (including pneumonia) | 6 (10) | 6 (15) | |
| Cardiovascular disease | 30 (50) | 18 (46) | |
| Gastric or colonic surgery | 10 (17) | 4 (10) | |
| Sepsis, non-pulmonary | 9 (15) | 5 (13) | |
| Other diagnoses | 5 (8) | 6 (15) | |
| APACHE II score, median (IQR) | 17 (12–22) | 21 (16–26) | 0.026 |
| SOFA at ICU admission, median (IQR) | 7 (3–8) | 7 (4–11) | 0.121 |
| The use of mechanical ventilation during ICU stay, *n* (%) | 32 (53) | 29 (74) | 0.034 |
| The use of continuous vasopressor during ICU stay, *n* (%) | 34 (57) | 25 (64) | 0.461 |
| The use of continuous analgesia during ICU stay, *n* (%) | 37 (62) | 26 (67) | 0.613 |
| The use of continuous sedation during ICU stay, *n* (%) | 45 (75) | 28 (71) | 0.723 |
| The use of steroid during ICU stay, *n* (%) | 7 (12) | 14 (35) | 0.006 |
| The use of neuromuscular blocking agent during ICU stay, *n* (%) | 0 (0) | 5 (13) | 0.008 |
| The use of dialysis during ICU stay, *n* (%) | 7 (12) | 11 (28) | 0.037 |
| Average RASS score during the day shift from ICU day 1 to ICU day 3, median (IQR) [b] | 0 (0–0) | 0 (−2–0) | 0.070 |
| Time to first out of bed mobilization after ICU admission (days) | 1.7 (0.9–2.0) | 5.3 (4.0–8.0) | <0.001 |
| Highest ICU mobility scale score during ICU stay | 8 (6–10) | 4 (3–7) | <0.001 |
| Number of daily rehabilitations per person on the ward (minute/time) | 31 (22–43) | 34 (27–40) | 0.331 |

Data are presented as median (interquartile range) or number (%). IQR = interquartile range; BMI = Body mass index; ICU = Intensive Care Unit; APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; RASS = Richmond agitation sedation scale. [a] Barthel index before hospitalization was scored at the time of ICU admission based on the information from the family or the patients if they were conscious. [b] In all participating hospitals, RASS score, as a sedation scale, was monitored every 2 h during the day shift by nurses and recorded in the medical record. The best RASS score, which means the recorded number closest to zero during the day, of each day from days 1 to 3 was used to calculate the average value of RASS.

At 3 months follow-up, the EM group showed a significantly lower incidence of PTSD (OR: 0.06, adjusted *p* = 0.026) and had a significantly lower HADS subset score for anxiety (adjusted *p* = 0.004) and IES-R (adjusted *p* = 0.009) compared with the non-EM group. The EM group demonstrated no significant differences in the incidence of depression, anxiety, and PTSD, the HADS subset scores for depression and anxiety, and the IES-R score at the time of hospital discharge. When comparing the assessment scores at hospital discharge and at 3 months follow-up, only changes in the HADS subset scores for anxiety in the EM group were significantly higher (adjusted *p* = 0.032).

The risk for developing psychiatric symptoms [RR: 0.49, confidence interval (CI): 0.29–0.83, *p* = 0.010], depression (RR: 0.52, CI: 0.27–0.99, *p* = 0.006), anxiety (RR: 0.27, CI: 0.10–0.71, *p* < 0.001), and PTSD (RR: 0.07, CI: 0.01–0.54, *p* < 0.001) at 3 months follow-up were lower in the EM group, while no significant difference in the risk ratios was observed at the time of hospital discharge (Table 3).

The time from ICU admission to first mobilization correlated weak linearly with the HADS subset scores for depression (r = 0.244, *p* = 0.011) and anxiety (r = 0.350, *p* < 0.001), and the IES-R score (r = 0.289, *p* = 0.003) at 3 months follow-up (Figure S1). Multiple linear regression analysis also demonstrated that EM was significantly associated with the HADS subset score for anxiety [β coefficient: 0.311, adjusted *p* = 0.004] and the IES-R score (β coefficient: 0.278, adjusted *p* = 0.009) at 3 months follow-up. Changes in the HADS subset scores for anxiety were significantly associated with achieving EM (β coefficient: −0.242, adjusted *p* = 0.032) (Table S7).

**Table 2.** Outcomes: psychiatric disorders in ICU survivors.

| Outcomes | Early Mobilization Group (*n* = 60) | Non-Early Mobilization Group (*n* = 39) | *p* Value | Adjusted [b] *p* Value |
|---|---|---|---|---|
| **Primary Outcome** | | | | |
| Follow-up at 3 months after discharge | | | | |
| Patients with psychiatric symptoms, *n* (%) [a] | 15 (25) | 20 (51) | 0.008 | 0.032 |
| At the time of hospital discharge | | | | |
| Patients with psychiatric symptoms, *n* (%) [a] | 20 (33) | 17 (46) | 0.214 | 0.965 |
| **Secondary Outcomes** | | | | |
| Follow-up at 3 months after discharge | | | | |
| Patients who scored HADS subset for depression ≥8, *n* (%) | 12 (20) | 15 (39) | 0.044 | 0.107 |
| HADS subset score for depression, median (IQR) | 4 (2–7) | 6 (2–9) | 0.142 | 0.223 |
| Patients who scored HADS subset for anxiety ≥8, *n* (%) | 5 (8) | 12 (30) | 0.004 | 0.104 |
| HADS subset score for anxiety, median (IQR) | 3 (1–5) | 6 (4–8) | <0.001 | 0.004 |
| Patients who scored IES-R ≥25, *n* (%) | 1 (2) | 9 (23) | <0.001 | 0.026 |
| IES-R score, median (IQR) | 4 (1–9) | 9 (4–20) | <0.001 | 0.009 |
| At the time of hospital discharge | | | | |
| Patients who scored HADS subset for depression ≥8, *n* (%) | 16 (27) | 15 (40) | 0.155 | 0.917 |
| HADS subset score for depression, median (IQR) | 4 (2–8) | 6 (4–9) | 0.086 | 0.471 |
| Patients who scored HADS subset for anxiety ≥8, *n* (%) | 11 (18) | 7 (19) | 0.943 | 0.772 |
| HADS subset score for anxiety, median (IQR) | 3 (1–6) | 4 (2–7) | 0.392 | 0.448 |
| Patients who scored IES-R ≥25, *n* (%) | 2 (3) | 5 (14) | 0.102 | 0.266 |
| IES-R score, median (IQR) | 6 (2–12) | 10 (4–17) | 0.052 | 0.163 |
| Changes between follow-up at 3 months and hospital discharge | | | | |
| HADS subset score for depression, median (IQR) | 1 (−2–3) | 1 (−1–3) | 0.928 | 0.418 |
| HADS subset score for anxiety, median (IQR) | 1 (−2–4) | −1 (−4–1) | 0.006 | 0.032 |
| IES-R score, median (IQR) | 1 (−2–7) | −1 (−7–5) | 0.053 | 0.131 |

Data are presented as number (%) or median (interquartile range). ICU = Intensive Care Unit, HADS = Hospital anxiety and depression scale, IQR = interquartile range, IES-R = Impact of event scale-revised, EQ-5D-5L = EuroQol-5 Dimensions-5 Levels. [a] Psychiatric symptoms were defined as the presence of at least one of three symptoms; depression, anxiety, and PTSD. [b] Multiple linear for continuous variable or multiple logistic regression analysis for nominal variables were performed to identify an association of the primary outcome with the following covariates. The covariates in the multi-variates analysis included age, male gender, Barthel index before hospitalization, ICU admission diagnosis (acute respiratory failure, cardiovascular disease, gastric or colonic surgery, sepsis, other), acute physiology and chronic health evaluation II score, use of mechanical ventilation, use of continuous analgesia, use of continuous sedation, use of steroids, use of neuromuscular blocking agents, and use of dialysis.

**Table 3.** Association between early mobilization and the presence of psychiatric symptoms.

| Variables | Risk Ratio (95% CI) | Unadjusted Odds Ratio (95% CI) | Adjusted [b] Odds Ratio (95% CI) |
|---|---|---|---|
| **Follow-up at 3 months after discharge** | | | |
| Presence of psychiatric Symptoms [a] | 0.49 (0.29–0.83) * | 0.32 (0.13–0.74) ** | 0.27 (0.08–0.89) * |
| HADS depression score ≥8 | 0.52 (0.27–0.99) ** | 0.40 (0.16–0.98) * | 0.37 (0.11–1.24) |
| HADS anxiety score ≥8 | 0.27 (0.10–0.71) *** | 0.20 (0.06–0.61) ** | 0.23 (0.06–1.31) |
| IES-R score ≥25 | 0.07 (0.01–0.54) *** | 0.06 (0.01–0.32) *** | 0.06 (0.01–0.70) * |
| **At hospital discharge** | | | |
| Presence of psychiatric Symptoms [a] | 0.73 (0.44–1.20) | 0.59 (0.25–1.36) | 1.03 (0.33–3.14) |
| HADS depression score ≥8 | 0.66 (0.37–1.16) | 0.53 (0.22–1.27) | 1.07 (0.29–3.91) |
| HADS anxiety score ≥8 | 0.97 (0.41–2.27) | 0.96 (0.34–2.87) | 1.23 (0.30–5.05) |
| IES-R score ≥25 | 0.25 (0.05–1.20) | 0.22 (0.03–1.09) | 0.01 (0.01–52.4) |

The data are presented as risk ratio or odds ratio with 95% confidence interval. * <0.05, ** <0.01, *** <0.001. HADS = Hospital anxiety and depression scale, IES-R = Impact of event scale-revised, CI = Confidence interval. [a] Psychiatric symptoms are defined as the presence of at least one of three symptoms; depression, anxiety, and PTSD. [b] Multiple logistic regression analysis was performed to identify an association of the primary outcome with the following covariates. The covariates in the multi-variates analysis included age, male gender, Barthel index before hospitalization, ICU admission diagnosis (acute respiratory failure, cardiovascular disease, gastric or colonic surgery, sepsis, other), acute physiology and chronic health evaluation II score, use of mechanical ventilation, use of continuous analgesia, use of continuous sedation, use of steroids, use of neuromuscular blocking agents, and use of dialysis.

### 3.3. Other Variables

There was no difference between the two groups in the EQ-5D-5L at 3 months follow-up and at hospital discharge. The EM group had a shorter length of ICU and hospital stays, a higher Barthel Index at hospital discharge, and a lower incidence of delirium and ICU-AW. (Table 4).

**Table 4.** Comparison of clinical outcomes between early mobilization group and non-early mobilization group.

| Outcomes | Early Mobilization Group (*n* = 60) | Non-Early Mobilization Group (*n* = 39) | *p* Value | Adjusted [a] *p* Value [a] |
|---|---|---|---|---|
| Health-related quality of life | | | | |
| The EQ-5D-5L index at the time of 3 month after hospital discharge | 0.89 (0.70–0.94) | 0.82 (0.70–0.94) | 0.235 | 0.952 |
| The EQ-5D-5L index at the time of hospital discharge | 0.81 (0.71–0.89) | 0.70 (0.44–0.94) | 0.384 | 0.926 |
| Clinical outcomes and physical assessment | | | | |
| The number of patients who can walk independently at the time of hospital discharge | 58 (97) | 33 (85) | 0.032 | 0.136 |
| Duration of mechanical ventilation (days) | 1.4 (1–2) | 4.4 (2–8.7) | <0.001 | 0.326 |
| ICU length of stay (days) | 4 (3–5) | 7 (5–13) | <0.001 | <0.001 |
| Hospital length of stay (days) | 22 (19–29) | 32 (22–51) | 0.004 | 0.009 |
| Barthel index at hospital discharge | 100 (90–100) | 90 (70–100) | 0.022 | 0.020 |
| The number of patients who diagnosed as delirium during ICU stay | 11 (18) | 16 (41) | 0.013 | 0.001 |
| The number of patients who diagnosed as ICU acquired weakness at the time of ICU discharge | 2 (3) | 8 (21) | 0.006 | 0.004 |

Data are presented as median (interquartile range) or number (%). IQR = interquartile range; ICU = Intensive Care Unit; IMS = ICU mobility scale. [a] Multiple linear for continuous variable or multiple logistic regression analysis for nominal variable were performed to identify an association of the primary outcome with the following covariates. The covariates in the multi-variates analysis included age, male gender, Barthel index before hospitalization, ICU admission diagnosis (acute respiratory failure, cardiovascular disease, gastric or colonic surgery, sepsis, other), acute physiology and chronic health evaluation II score, use of mechanical ventilation, use of continuous analgesia, use of continuous sedation, use of steroids, use of neuromuscular blocking agents and use of dialysis.

### 3.4. Post Hoc Sensitivity Analysis

The model created by IPTW considering the influence of death and follow-up loss showed that EM correlated significantly with a lower incidence of psychiatric symptoms (OR: 0.28, CI: 0.11–0.73, adjusted *p* = 0.008), lower incidence of anxiety and PTSD, and a lower HADS subset score for anxiety and IES-R score at 3 months follow-up (Table S8). In the IPTW analysis using the propensity score with adjustment of 19 baseline variables, EM correlated significantly with a lower incidence of psychiatric symptoms at 3 months (OR: 0.49, CI: 0.14–0.93, adjusted *p* = 0.046) and a lower incidence of PTSD and a lower HADS subset score for anxiety and IES-R score (Table S9).

### 4. Discussion

The incidence of psychiatric symptoms was significantly lower in the EM group and EM in the ICU was significantly associated with a lower incidence of psychiatric symptoms at 3 months follow-up after hospital discharge even after adjustment for significant differences in the baseline characteristics including severity and treatments received. The results were consistent even if the influence of patient death, loss to follow-up or potential confounding factors were included in the analysis. Furthermore, the interval from ICU admission to first mobilization correlated significantly with the score of HADS subsets for Depression and Anxiety and the score of IES-R for PTSD.

Mobilization, rehabilitation at the level of sitting on the edge of the bed or higher was significantly associated with improved psychiatric symptoms. A previous systematic review using mobilization in the ICU as an intervention did not show a significant improvement in psychiatric symptoms after ICU discharge [50]. Of note, most studies in that systematic review did not define the time point for mobilization, despite the potential benefit of mobilization within 72 h of ICU admission (Early Mobilization) which is described

in current literature [13,51]. For instance, providing EM improves independent physical function at the time of discharge, shortens delirium duration, and increases ventilator-free days [52], whereas mobilization initiated more than 72 h after ICU admission has no beneficial effect [13,53].

The present study supports the idea that the effect of EM on outcomes related to psychiatric symptoms after ICU discharge as well as other clinical outcomes might be maximized if mobilization is initiated within 72 h of ICU admission. The significant correlation between time from ICU admission to achieve EM and scores for diagnosing psychiatric symptoms support this idea. The interval until initiation of mobilization might be an essential aspect of physical rehabilitation in the ICU to maximize the effect on patient outcomes.

The EM group had a lower incidence of psychiatric symptoms at 3 months follow-up, but there was no significant difference between the groups at discharge. It has been reported that there is a time lag for the onset of anxiety and depression [54,55]. Therefore, the time of onset of each psychiatric symptom, such as depression, anxiety, and PTSD, could be different [56]. The time for the effect of EM on outcomes after hospital discharge to appear could vary among the psychiatric symptoms. Comparing the difference at 3 months and at hospital discharge, anxiety was the most improved among the psychiatric symptoms assessed. As previous studies have shown, an exercise period of at least 8 weeks is required to reduce depression, whereas anxiety disorders are improved with exercise in a relatively short period [13,57]. Considering these, the follow-up period might be adjusted depending on outcomes and interventions of the study related to psychiatric symptoms after ICU admission.

Several studies suggest an interaction between physical and psychiatric factors and these outcomes could be linked [58,59]. Physical impairment could result in poor psychiatric function and vice versa. For example, ICU-AW could lead to the development of delirium which is a potential risk factor for the development of psychiatric disorders [60]. There is evidence to support the idea that EM could reduce not only physical impairment, such as ICU-AW, but also delirium similar to the results of the present study [61] and might result in a synergistic and beneficial effect on psychiatric function. It has been suggested that exercise or mobilization improves mental health [62] and self-efficacy [63], increase endorphin and monoamine levels [63], decrease cortisol levels [64], and increase brain-derived neurotrophic factor [65], resulting in better psychiatric outcomes as a potential mechanism for mobilization improving psychiatric symptoms. In addition, there were several differences in outcomes at the time of hospital discharge, such as physical function, that could be not only intervening factors but also mediators of psychiatric symptoms after a critical illness. Further studies are warranted to validate the relationship between physical and psychiatric function, and the background mechanisms to capture the interaction between interventions such as mobilization, physical impairment at hospital discharge, and psychiatric symptoms at follow-up.

The comparability between the two groups is a primary limitation of this study. The calculated sample size could not be achieved, there was a relatively large influence of death and loss to follow-up and the study was not randomized. These factors may limit generalizability to other ICUs. Second, there are confounding factors which could not be adjusted for, such as educational history and clinical frailty. However, multivariate analysis with important clinical factors, IPTW, and propensity score matching adjusted by potential confounders showed consistent results even though there are several differences in important baseline characteristics of the two groups, for example the use of mechanical ventilation, steroids, neuromuscular blocking agents and dialysis. Third, outcomes were limited to short-term follow-up. Fourth, whether the patient could receive rehabilitation at the level of sitting on the edge of the bed or higher depended on the rehabilitation policy used in each participating hospital. Therefore, whether EM could not be provided due to poor general condition or other factors was not identified. Fifth, the psychiatric symptoms of the primary outcome of this study are diagnosed by scoring and are not based on criteria

by psychiatrists or psychiatric liaison teams. Finally, patients who died in the ICU were excluded from the analysis in this study because we targeted ICU survivors. This could result in selection bias and these findings should be interpreted with caution. To further validate these results and investigate causality, a multicenter randomized controlled trial with more patients is needed.

## 5. Conclusions

EM in the ICU is significantly associated with lower rates of psychiatric symptoms, including depression, anxiety, and PTSD, at 3 months follow-up after hospital discharge. The interval from ICU admission to mobilization might be an important parameter to maximize the beneficial effects on patient outcomes.

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**Table S1**. Exclusion criteria.

| Exclusion Criteria | Details |
|---|---|
| Age < 18 years | |
| Unable to walk independently before ICU admission | Patients who require a wheelchair other than a cane or other walking assistance prior to admission or help from others to walk were considered unable to walk independently. |
| Neurological complications | Neurological complications include cerebral infarction, cerebral hemorrhage, acute subdual hematoma, acute epidural hematoma, traumatic subarachnoid hemorrhage, and encephalitis. |
| Lack of communication skill because of pre-existing mental diseases | Mental diseases include depression, anxiety, schizophrenia, dementia, cerebral infarction, cerebral hemorrhage, and alcoholism. |
| In terminal state or end of life | |

**Table S2**. Early Mobilization Protocol [a].

| Level 1 Respiratory RASS−5〜−3 | Level 2 HOB RASS ≥ −3 | Level 3 Sitting RASS ≥ −1 | Level 4 Standing RASS ≥ 0 | Level 5 Walking RASS ≥ 0 |
|---|---|---|---|---|
| **Physical therapy** Passive ROM exercise Respiratory physical therapy | **Physical therapy** Positioning Passive ROM exercise Active ROM exercise Respiratory physical therapy continuous lateral rotation therapy | **Physical therapy** Positioning Passive ROM exercise Active ROM exercise Sitting on the edge of bed Rising from the supine position | **Physical therapy** Positioning Passive ROM exercise Active ROM exercise Standing at side of bed Stand and pivot to a chair | **Physical therapy** Positioning Passive ROM exercise Active ROM exercise Walk with assistance Walk independently |
| **Positioning** Posture change HOB ≤ 45 degrees | **Positioning** Posture change HOB ≥ 60 | **Positioning** Posture change HOB ≥ 60 | **Positioning** Posture change HOB ≥ 60 | **Positioning** Posture change HOB ≥ 60 |
| **Step up criterion** Oxygenation/ hemodynamic stability Can withstand posture change Can withstand HOB ≤45 degrees | **Step up criterion** Can withstand supplementary motion of physical therapy Can withstand HOB ≤60 degrees Anti-gravity movement possible | **Step up criterion** Can endure the active movement of physical therapy Can withstand HOB ≤60 degrees Can withstand sitting on the edge bed | **Step up criterion** All exercise can be carried out Can withstand partial weight standing | **Step up criterion** Increase walking distance gradually |

**Step up criterion to level 3 or higher are defined as**

RASS: −2 to +1, BPS ≤ 3 or NRS ≤ 5, $SpO_2$ ≥ 90%, $FIO_2$ < 0.6, PEEP < 10cm$H_2O$, respiratory rate: <35 times/min, mean blood pressure ≥ 65 mmHg, heart rate: 50 to 120 times/min, there were no new arrhythmias, no additional administration of vasopressors, no bleeding, no wound with the possibility of separation, no unstable fracture.

RASS = Richmond agitation sedation scale; ROM = range of motion; HOB = head of bed; BPS = behavioral pain scale; NRS = numeric rating scale; $FIO_2$ = fraction of inspiratory oxygen; PEEP = positive end expiratory pressure; EM = early mobilization. [a] This table is cited from reference [1,2]. The EM protocol includes 5 levels: Level 1: head of bed elevation ≤45 degrees and passive range of motion (ROM); Level 2: head of bed elevation ≥60 degrees, active ROM, and continuous lateral rotation therapy; Level 3: sitting on the edge of the bed and rising from the supine position; Level 4: standing at the side of the bed, and standing and pivoting to a chair; and Level 5: walking with assistance and walking independently. Levels 0 and 1 were performed by physical therapists. Level 2 was performed by nurses and physical therapists. Levels 3, 4, and 5 were performed by a team of ICU physicians, nurses and physical therapists.

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**Table S3**. Details of follow-up.

| List | Details |
|---|---|
| Follow-up period | Between "*two and a half months after discharge*" and "*three and a half months after discharge*" All follow-up assessments were conducted during this one-month period. |
| Follow-up methods | A person in charge of follow-up at each hospital called the patients and confirmed their survival. Once their survivals were confirmed, the EQ-5D-5L (Japanese version for Japan) was evaluated over the same phone-call.<br><br>Questionnaires and response sheets for HADS and IES-R were then mailed to the patient's home. They answered the questionnaires by themselves or with help of relatives and sent it back to each participating hospital.<br><br>Despite several phone-calls, if it did not reach the patients, the patients were regarded as lost to follow-up and excluded from analysis. |
| Follow-up person | Follow-up was consistently conducted by the same person at each participating hospital. The person in charge of follow-up could be a doctor, a nurse, or a physiotherapist, depending on the situation of each participating hospital. |

EQ-5D-5L = EuroQol-5 Dimensions-5 Levels, HADS = Hospital anxiety and depression scale, IES-R = Impact of event scale-revised.

**Table S4**. The rationale for collected data.

| Long term outcomes | Factors associated with outcomes and collected in this study (references) |
|---|---|
| Psychiatric symptoms | Age [1], male [1], continuous analgesia [1]<br>mechanical ventilation [2], continuous sedation [2], activities of daily living before hospitalization [3] |
| Depression | Male [4,5], continuous sedation [4], age [6]. mechanical ventilation [6], admission diagnosis [7], steroids [8], dialysis [9], neuromuscular blocking agents [10] |
| Anxiety | Mobilization [11] |
| Post-traumatic stress disorder | Male [4], continuous analgesia [12,13]<br>mechanical ventilation [12,13], continuous sedation [12,13], severity [14] |
| Long term outcomes | Factors associated with outcomes and collected in this study (references) |
| Psychiatric symptoms | Age [1], male [1], continuous analgesia [1]<br>mechanical ventilation [2], continuous sedation [2], activities of daily living before hospitalization [3] |
| Depression | Male [4,5], continuous sedation [4], age [6], mechanical ventilation [6], admission diagnosis [7], steroids [8], dialysis [9], neuromuscular blocking agents [10] |
| Anxiety | Mobilization [11] |
| Post-traumatic stress disorder | Male [4], continuous analgesia [12,13]<br>mechanical ventilation [12,13], continuous sedation [12,13], severity [14] |

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## **Table S5**. Details of the post-hoc sensitivity analysis.

A.     The inverse probability of treatment weighting statistics, considering the bias related to follow-up loss and death

The inverse probability of treatment weighting (IPTW) method based on propensity scores was applied to outcome factors associated with early mobilization (EM) [1]. This allowed us to adjust for confounding factors between the binary groups, which facilitates an evaluation of causal effects without reducing the sample size by using the estimated propensity scores to construct data weights. Using data from 192 patients discharged from the intensive care unit (ICU), we select the confounders that were potentially associated with the outcome (able to follow up, lost to follow up, death) and calculated propensity scores using logistic regression analysis. Using these weights, the IPTW method based on the propensity score for the 99 patients analyzed in this study was applied to outcome factors associated with early mobilization, in addition to the same covariates used in the multiple analysis of the primary outcome: psychiatric symptoms, including age, male gender, use of mechanical ventilation, use of continuous analgesia, use of continuous sedation. Logistic regression analysis was performed on the basis of the IPTW odds ratios (OR) and confidence intervals (CI).

B.     The inverse probability of treatment weighting statistics considering 19 important cofounders potentially affecting the results

We used propensity score to reduce the effects of potential confounding [2] based on 19 variables; age, gender, body mass index, Charlson comorbidity index, Barthel index before hospitalization, ICU admission diagnosis including acute respiratory failure, cardiovascular disease, gastric or colonic surgery, and sepsis non-pulmonary, acute physiology and chronic health evaluation II score, sequential organ failure assessment score at ICU admission, use of mechanical ventilation, use of continuous vasopressor, use of continuous analgesia, use of continuous sedation, use of steroids, use of neuromuscular blocking agents, use of dialysis, average Richmond agitation sedation scale score

during day shift from day 1 to day 3, that were potentially associated with the outcome on the basis of our clinical experience and knowledge. Logistic regression analysis was used to calculate the propensity scores. The IPTW method based on propensity scores was applied to the outcome factors that were associated with EM [3]. This allowed us to adjust for confounding factors between the binary groups, which facilitates an evaluation of causal effects without reducing the sample size by using the estimated propensity scores to construct data weights. Logistic regression analysis was performed on the basis of the IPTW OR and CI.

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**Table S6**. Comparison of baseline characteristics of patients considering bias related to loss to follow-up and death.

| Baseline characteristics | All patients discharged from ICU n= 192 | All patients who completed follow up on 3 months n= 99 | Early Mobilization group who discharged from ICU n= 107 | Early Mobilization group who completed follow up on 3 months n= 60 | Non-Early Mobilization group who discharged from ICU n= 85 | Non-Early Mobilization group who completed follow up on 3 months n= 39 |
|---|---|---|---|---|---|---|
| Age (years), median (IQR) | 71 (60–79) | 70 (60–78) | 70 (61–78) | 70 (61–75) | 75 (60–81) | 73 (57–79) |
| Gender (male), n (%) | 124 (65) | 62 (62) | 72 (67) | 39 (65) | 52 (61) | 23 (59) |
| BMI (kg/m$^2$), median (IQR) | 23 (20–26) | 23 (21–26) | 23 (21–25) | 23 (21–25) | 23 (20–26) | 24 (20–27) |
| Charlson Comorbidity Index (IQR) | 2 (1–3) | 2 (0–2) | 2 (0–3) | 1 (0–2) | 2 (0–3) | 1 (0–2) |
| Barthel index before hospitalization, median (IQR) [a] | 100 (100–100) | 100 (100–100) | 100 (100–100) | 100 (100–100) | 100 (100–100) | 100 (100–100) |
| ICU admission diagnosis, n (%) | | | | | | |
| Acute respiratory failure (including pneumonia) | 36 (19) | 12 (12) | 17 (16) | 6 (10) | 19 (22) | 6 (15) |
| Cardiovascular disease | 75 (39) | 48 (48) | 44 (41) | 30 (50) | 31 (36) | 18 (46) |
| Gastric or colonic surgery | 29 (15) | 14 (14) | 19 (18) | 10 (17) | 10 (12) | 4 (11) |
| Sepsis, non-pulmonary | 32 (17) | 14 (14) | 18 (17) | 9 (15) | 14 (17) | 5 (13) |
| Other diagnoses | 20 (10) | 11 (11) | 9 (8) | 5 (8) | 11 (13) | 6 (15) |
| APACHE II score, median (IQR) | 20 (14–25) | 18 (14–26) | 18 (13–24) | 17 (12–22) | 20 (16–26) | 21 (16–26) |
| SOFA at ICU admission, median (IQR) | 7 (4–10) | 7 (3–10) | 6 (3–8) | 7 (3–8) | 8 (5–11) | 7 (4–11) |
| The use of mechanical ventilation during ICU stays, n (%) | 120 (63) | 61 (61) | 60 (56) | 32 (53) | 60 (71) | 29 (74) |
| The use of continuous vasopressor during ICU stays, n (%) | 109 (57) | 59 (59) | 53 (50) | 34 (57) | 56 (66) | 25 (64) |

| | | | | | | |
|---|---|---|---|---|---|---|
| The use of continuous analgesia during ICU stays, n (%) | 123 (64) | 63 (63) | 69 (65) | 37 (62) | 54 (64) | 26 (67) |
| The use of continuous sedation during ICU stay, n (%) | 136 (71) | 73 (73) | 73 (68) | 45 (75) | 63 (74) | 28 (71) |
| The use of steroids during ICU stays, n (%) | 38 (20) | 21 (21) | 10 (9) | 7 (12) | 28 (33) | 14 (35) |
| The use of neuromuscular blocking agents during ICU stays, n (%) | 10 (5) | 5 (5) | 1 (1) | 0 (0) | 9 (11) | 5 (13) |
| The use of dialysis during ICU stay, n (%) | 40 (21) | 18 (18) | 17 (16) | 7 (12) | 23 (27) | 11 (28) |
| Average RASS score during day shift from day 1 to day 3, median (IQR) [b] | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0 (-2–0) |

Data are presented as median (interquartile range) or number (%); IQR = interquartile range; BMI = Body mass index; ICU = Intensive Care Unit; APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; RASS = Richmond agitation sedation scale. There was no significant difference in all baseline characteristics between patients discharged from the ICU and patients who completed follow up at 3 months, early mobilization group discharged from the ICU and early mobilization group who completed follow up at 3 months, or non-early mobilization group discharged from the ICU and non-early mobilization group who completed follow up at 3 months. [a] Barthel index before hospitalization was scored at the time of ICU admission based on the information from the family or the patients if they were conscious.
[b] In all centers, RASS score, as a sedation scale, was monitored every two hours during the day shift by nurses and recorded in medical record. The best number of RASS, which means the recorded number closest to Zero during the day, of each day from day 1 to 3 was used to calculate the average number of RASS.

Table S7. Association between early mobilization and psychiatric disorder assessment score

| Outcomes | **Unadjusted** standardized partial regression coefficient (95%CI) | β coefficient | **Adjusted**[a] standardized partial regression coefficient (95%CI) | β coefficient |
|---|---|---|---|---|
| At follow up 3 months after hospital discharge | | | | |
| HADS depression score | 0.74 (−0.04–1.53) | 0.188 | 0.44 (−0.34–1.42) | 0.137 |
| HADS anxiety score | 1.39 (0.73–2.05) | 0.391 | 0.37 (0.36–1.85) | 0.311 |
| IES-R score | 4.57 (2.49–6.66) | 0.404 | 1.18 (0.79–5.50) | 0.278 |
| At hospital discharge | | | | |
| HADS depression score | 0.63 (−0.15–1.41) | 0.163 | 0.61 (−1.21–0.56) | 0.083 |
| HADS anxiety score | 0.32 (−0.42–1.28) | 0.102 | 0.51 (−1.41–0.63) | 0.092 |
| IES-R score | 2.53 (0.47–4.59) | 0.243 | 1.21 (−4.11–0.70) | 0.164 |
| Changes between follow-up at 3 months and hospital discharge | | | | |
| HADS depression score | −0.23 (−1.17–0.71) | −0.049 | −0.42 (−0.66–1.58) | −0.098 |
| HADS anxiety score | −1.09 (−1.87– -0.31) | −0.271 | 0.44 (0.08–1.86) | −0.242 |
| IES-R score | 2.57 (−0.15–5.28) | −0.217 | 1.28 (-0.59–4.49) | −0.177 |

Data are presented as coefficient with 95% confidence interval. *HADS* = Hospital anxiety and depression scale, *IES-R* = Impact of event scale-revised, *CI* = Confidence interval. [a] Multiple linear regression analysis was performed to determine the primary outcome with the covariates. The covariates in the multi-variates analysis included age, male gender, Barthel index before hospitalization, ICU admission diagnosis (acute respiratory failure, cardiovascular disease, gastric or colonic surgery, sepsis, other), acute physiology and chronic health evaluation II score, use of mechanical ventilation, use of continuous analgesia, use of continuous sedation, use of steroids, use of neuromuscular blocking agents, and use of dialysis.

Table S8. Sensitivity analysis using inverse probability of treatment weighted statistics considering bias from death and loss to follow-up.

| Outcomes | Adjusted odds ratio (95%CI) | P value |
|---|---|---|
| The Primary Outcome | | |
| At the time of follow up on 3 months after hospital discharge | | |
| Patients with psychiatric symptoms[a] | 0.28 (0.11–0.73) | 0.008 |
| At the time of hospital discharge | | |
| Patients with psychiatric symptoms[a] | 0.65 (0.28–1.52) | 0.320 |
| Secondary Outcomes | | |
| At follow up at 3 months after hospital discharge | | |
| Patients who scored HADS subset for depression ≥8 | 0.47 (0.15–1.48) | 0.123 |
| HADS subset score for depression | 0.21 (0.04–1.11) | 0.068 |
| Patients who scored HADS subset for anxiety ≥8 | 0.22 (0.06–0.85) | 0.031 |
| HADS subset score for anxiety | 0.08 (0.02–0.31) | 0.009 |
| Patients who scored IES-R ≥25 | 0.53 (0.01–0.66) | 0.019 |
| IES-R score | 0.01 (0.01–0.03) | 0.006 |
| At hospital discharge | | |
| Patients who scored HADS subset for depression ≥8 | 0.63 (0.27–1.51) | 0.296 |
| HADS subset score for depression | 0.33 (0.08–1.34) | 0.132 |
| Patients who scored HADS subset for anxiety ≥8 | 1.04 (0.37–2.90) | 0.952 |
| HADS subset score for anxiety | 0.40 (0.07–2.21) | 0.288 |
| Patients who scored IES-R ≥25 | 0.17 (0.03–0.86) | 0.029 |
| IES-R score | 0.01 (0.01–0.52) | 0.033 |

Data are presented as coefficient or odds ratio with 95% confidence interval. HADS = Hospital anxiety and depression scale, IES-R = Impact of event scale-revised, EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; CI = Confidence interval. The detail of the analysis is shown in Supplemental Table S2 A. [a] Psychiatric symptoms were defined as the presence of at least one of three symptoms; depression, anxiety, and PTSD.

Table S9. Sensitivity analysis using a propensity score with 19 confounding factors

| Outcomes | Odds ratio (95%CI) | P value |
|---|---|---|
| **Primary Outcome** | | |
| At follow up at 3 months after hospital discharge | | |
| Patients who demonstrated psychiatric symptoms[a] | 0.49 (0.14–0.93) | 0.046 |
| At hospital discharge | | |
| Patients who demonstrated psychiatric symptoms[a] | 0.93 (0.32–2.67) | 0.893 |
| **Secondary Outcomes** | | |
| At follow up at 3 months after hospital discharge | | |
| Patients who scored HADS subset for depression ≥8 | 0.41 (0.14–1.23) | 0.108 |
| HADS subset score for depression | 0.28 (0.03–2.41) | 0.252 |
| Patients who scored HADS subset for anxiety ≥8 | 0.35 (0.10–1.25) | 0.113 |
| HADS subset score for anxiety | 0.10 (0.03–0.39) | < 0.001 |
| Patients who scored IES-R ≥25 | 0.07 (0.01–0.63) | 0.011 |
| IES-R score | 0.01 (0.01–0.46) | 0.016 |
| At hospital discharge | | |
| Patients who scored HADS subset for depression ≥8 | 0.78 (0.26–2.35) | 0.647 |
| HADS subset score for depression | 0.61 (0.09–4.32) | 0.622 |
| Patients who scored HADS subset for anxiety ≥8 | 1.42 (0.44–4.57) | 0.545 |
| HADS subset score for anxiety | 0.77 (0.13–4.58) | 0.783 |
| Patients who scored IES-R ≥25 | 0.23 (0.04–1.36) | 0.101 |
| IES-R score | 0.03 (0.01–3.30) | 0.137 |

Data are presented as coefficient or odds ratio with 95% confidence interval. HADS = Hospital anxiety and depression scale, IES-R = Impact of event scale-revised, EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; RR=Risk ratio; CI=Confidence interval. The detail of the analysis is shown in Supplemental Table S2 B.
[a] Psychiatric symptoms were defined as the presence of at least one of three symptoms; depression, anxiety, and PTSD.