INTRODUCTION

Patients who undergo mechanical ventilation or sedation in the intensive care unit (ICU) may require long-term rehabilitation because they develop post-intensive care syndrome (PICS).1 PICS is a collection of symptoms that persist even after successful discharge from the ICU. Patients with PICS may have new or worsening cognitive, emotional, and physical symptoms.1,2

Patients receiving mechanical ventilation in the ICU may require long-term rehabilitation if they develop severe physical impairments such as abnormal gait even after they have recovered from their acute illness and are discharged from the ICU.1,2 Gait disability after discharge from the ICU occurs in 40%–70% of ICU survivors1–4 and may last for several months or years after hospital discharge.5

Early mobilization (EM) is recommended to address these issues and improve functional prognosis.6 Previous studies have indicated that initiating EM soon after ICU admission could reduce the incidences of ICU-acquired weakness (ICU-
Although many reports have indicated that EM improves functional outcomes among ICU patients, there is no clear information regarding the optimal timing and targets for EM. Furthermore, the definition of “early” in the literature varies from 2 to 7 days after admission. Moreover, consensus and clarification from Japanese experts are lacking, making inter-study comparisons difficult.13,14) Morris et al.15) reported that mobilization within 5 days of admission was associated with shorter ICU and hospital stays, although this study did not adequately evaluate physical function such as gait independence. Schweickert et al. applied EM and determined the time to achieve mobilization within 72 h of ICU admission and reported higher independent functionality at hospital discharge.5) In contrast, initiating mobilization later, such as after 1 week of ICU admission, exhibited no beneficial effect.14) The Extra Physiotherapy in Critical Care (EPICC) trial conducted on ICU patients reported that EM in the ICU showed no difference in physical outcomes after 6 months relative to standard care.16) In contrast, some of the studies conducted in recent years have not reported positive outcomes in relation to EM.17,18) This is because the subjects, content of the intervention, duration of mobilization, and initiation criteria are different in each study. Whereas previous studies have recommended out-of-bed mobilization as soon as possible, there are few reports with a clear start time.19) Similarly, few reports have described the intensity of rehabilitation that should be achieved in the ICU. The purpose of early rehabilitation in ICU patients is to promote physical activity and improve muscle strength and walking ability as soon as possible. As such, a unified early rehabilitation program should be established to allow the efficacy of mobilization to be determined.20) To optimize the outcomes of ICU patients, there is significant need for a defined rehabilitation start time and intensity that could be used as indicators of the efficacy of EM in the ICU, thereby allowing the collection of a body of evidence for the Japanese population.

In this study, it was hypothesized that EM in the ICU would improve outcomes. Here, the term “mobilization” indicates restoring strength (rehabilitation) by sitting on the edge of the bed, and “EM” indicates that the time to achieve mobilization is within 5 days of ICU admission. The Intensive Care Rehabilitation Expert Consensus in Japan recommends that mobilization be started within 5 days of ICU admission.12) These definitions are based on previous studies13,14,20–23) and medical costs.10,11) Although many reports have indicated that EM improves functional outcomes among ICU patients, there is no clear information regarding the optimal timing and targets for EM. Furthermore, the definition of “early” in the literature varies from 2 to 7 days after admission. Moreover, consensus and clarification from Japanese experts are lacking,12) making inter-study comparisons difficult.13,14) Morris et al.15) reported that mobilization within 5 days of admission was associated with shorter ICU and hospital stays, although this study did not adequately evaluate physical function such as gait independence. Schweickert et al. applied EM and determined the time to achieve mobilization within 72 h of ICU admission and reported higher independent functionality at hospital discharge.5) In contrast, initiating mobilization later, such as after 1 week of ICU admission, exhibited no beneficial effect.14) The Extra Physiotherapy in Critical Care (EPICC) trial conducted on ICU patients reported that EM in the ICU showed no difference in physical outcomes after 6 months relative to standard care.16) In contrast, some of the studies conducted in recent years have not reported positive outcomes in relation to EM.17,18) This is because the subjects, content of the intervention, duration of mobilization, and initiation criteria are different in each study. Whereas previous studies have recommended out-of-bed mobilization as soon as possible, there are few reports with a clear start time.19) Similarly, few reports have described the intensity of rehabilitation that should be achieved in the ICU. The purpose of early rehabilitation in ICU patients is to promote physical activity and improve muscle strength and walking ability as soon as possible. As such, a unified early rehabilitation program should be established to allow the efficacy of mobilization to be determined.20) To optimize the outcomes of ICU patients, there is significant need for a defined rehabilitation start time and intensity that could be used as indicators of the efficacy of EM in the ICU, thereby allowing the collection of a body of evidence for the Japanese population.

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20 min/day on weekdays.

Data Collection
Patients’ electronic medical records were searched to collect relevant data. Baseline characteristics recorded on ICU admission included age; sex; body mass index; Charlson Comorbidity Index;24) admission source; diagnosis at ICU admission; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; Sequential Organ Failure Assessment (SOFA) score; and the use of mechanical ventilation, vasopressors, continuous sedation, continuous analgesia, corticosteroids, neuromuscular blocking agents, and/or dialysis. The average Richmond Agitation Sedation Scale (RASS) score was recorded by the nurse every 2 h during days 1–5 in the ICU. Data regarding medical costs and discharge destination were collected from the medical affairs department. Medical costs were calculated based on the diagnosis procedure combination/per-diem payment system and were converted from Japanese yen to US dollars at an exchange rate of 108 yen/dollar.25

Study Outcomes
The primary outcome was gait independence at hospital discharge. The secondary outcomes included medical costs, the survival rate at 90 days after ICU discharge, duration of mechanical ventilation, duration of ICU and hospital stays, discharge destination (home, rehabilitation center, another hospital, nursing home, or death), delirium during the ICU stay, nosocomial pneumonia during the hospital stay, and ICU-AW status at ICU discharge. Other outcomes included ICU rehabilitation parameters (time to first rehabilitation and mobilization, number of total and daily rehabilitation exercises, and highest mobility score in the ICU) and ward rehabilitation parameters (number of total and daily rehabili-

### Table 1. Early mobilization protocol of the Nagoya Medical Center

| Level 1 Respiratory | Level 2 HOB | Level 3 Sitting | Level 4 Standing | Level 5 Walking |
|---------------------|-------------|----------------|-----------------|----------------|
| RASS −5 to −3       | RASS ≥ −3   | RASS ≥ −1      | RASS ≥ 0        | RASS ≥ 0       |
| Physical therapy    | Physical therapy | Physical therapy | Physical therapy | Physical therapy |
| □Passive ROM exercise | □Positioning | □Passive ROM exercise | □Positioning | □Positioning |
| □Respiratory physical therapy | □Active ROM exercise | □Active ROM exercise | □Active ROM exercise | □Active ROM exercise |
| □Respiratory physical therapy | □Continuous lateral rotation therapy | □Continuous lateral rotation therapy | □Continuous lateral rotation therapy | □Continuous lateral rotation therapy |
| Positioning         | Positioning | Positioning | Positioning | Positioning |
| □Posture change | □Posture change | □Posture change | □Posture change | □Posture change |
| □HOB ≤45°           | □HOB ≥60°   | □HOB ≥60°      | □HOB ≥60°      | □HOB ≥60°      |

**Step up criteria to level 3 or higher are defined as**
- RASS: −2 to +1
- BPS ≤3 or NRS ≤5
- SpO2 ≥90%
- FIO2 <0.6
- PEEP <10 cm H2O
- Respiratory rate: <35 times/min
- Mean blood pressure ≥65 mmHg
- Heart rate: 50 to 120 beats/min
- There were no new arrhythmias
- No additional administration of vasopressors
- No bleeding, no wound with the possibility of separation
- No unstable fracture.

ROM, range of motion; HOB, head of bed; BPS, behavioral pain scale; NRS, numeric rating scale; PEEP, positive end expiratory pressure.

The EM protocol includes 5 levels: Level 1: head of bed elevation ≤45° and passive ROM; Level 2: head of bed elevation ≥60°, active ROM, and continuous lateral rotation therapy; Level 3: sitting on the side 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. From Watanabe et al.21)
The ICU mobility scale (IMS) is a sensitive 11-point ordinal scale with scores ranging from 0 (no mobilization) to 10 (independent ambulation). At the time of ICU discharge, physiotherapists assessed the patient’s muscle strength by using the Medical Research Council sum score to determine whether ICU-AW was present (full strength: 60/60 points, ICU-AW: <48/60 points).

Statistical Analysis

The EM and LM groups were compared to identify differences in baseline characteristics, clinical and economic outcomes, and mobilization outcomes. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the $\chi^2$ test. Propensity score matching was applied to reduce the influence of potential confounding factors that were expected to influence the outcomes, as per the current literature (Table 3). Logistic regression analysis was used to calculate the propensity scores, and 1:1 pair-matching (nearest-neighbor matching) was performed using a greedy matching technique and a caliper width of 0.2. Standardized differences were used to measure covariate balances, and a meaningful imbalance was considered at values of $>10\%$. In sensitivity analysis, the inverse probability of treatment weighting (IPTW) method based on propensity scores was applied to the outcome factors that were associated with EM. By using the estimated propensity scores to construct data weights, we were able to adjust for confounding factors between the binary groups; this approach facilitated an evaluation of causal effects without reducing the sample size. Variables were modeled as continuous data when appropriate or were dichotomized using clinically relevant cutoff values. Univariate logistic regression analysis was performed based on the propensity score matching and IPTW odds ratios (ORs) and confidence intervals (CIs).

Furthermore, a sub-analysis was performed to investigate the effectiveness of EM in patients who stayed in the ICU for 5 days and more. Multiple logistic regression analysis was performed to determine the primary outcome with covariates, including admission source, APACHE II score, SOFA score, continuous vasopressor use, and RASS score from days 1 to 5, which were considered factors related to the primary and secondary outcome in previous reports. For the sub-analysis of secondary outcomes and other outcomes, multiple linear and logistic regression analyses were performed for log-transformed continuous and categorical variables, respectively; the covariates used for the secondary and other outcomes were the same as those used in analyzing the primary outcome. The sub-analysis was conducted to compare patients who fulfilled the EM initiation criteria but had delayed mobilization with those who achieved EM. To analyze only patients who satisfied the EM initiation criteria, multiple linear and logistic regression analyses, adjusted for the same covariates, were performed after excluding patients in the LM group who did not meet the criteria for mobilization by day 5 of admission to the ICU.

By changing the definition of “early mobilization” into mobilization within 3, 4, 6, or 7 days of ICU admission, we...
### Table 3. Comparison of items related to baseline data

| Baseline characteristics | Total population | Matched population |
|--------------------------|------------------|--------------------|
|                          | Early mobilization n=85 | Late mobilization n=92 | SD | P          | Early mobilization n=37 | Late mobilization n=37 | SD | P          |
| Age (years)              | 69 [60–78]       | 70 [63–79]       | 0.109 | 0.680 | 71 [64–80]       | 69 [64–79]       | 0.042 | 0.492 |
| Male, n (%)              | 57 (67)          | 64 (70)          | 0.054 | 0.720 | 25 (68)          | 26 (70)          | 0.058 | 0.802 |
| Body mass index (kg/m²)  | 21 [18–24]       | 21 [17–24]       | 0.070 | 0.458 | 21 [18–24]       | 20 [18–25]       | 0.006 | 0.721 |
| Charlson comorbidity index | 2 [1–4]        | 2 [1–4]          | 0.038 | 0.684 | 2 [1–3]          | 2 [1–3]          | 0.071 | 0.745 |
| Admission source, n (%)  |                 |                  |       |       |                 |                  |       |       |
| Emergency department     | 61 (72)          | 68 (74)          | 0.024 | 0.748 | 30 (81)          | 31 (84)          | 0.071 | 1.000 |
| Hospital ward            | 24 (28)          | 24 (26)          |       |       | 7 (19)           | 6 (16)           |       |       |
| ICU admission diagnosis, n (%) |            |                  |       |       |                 |                  |       |       |
| Respiratory, including pneumonia | 25 (29) | 20 (22) | 0.177 | 0.242 | 10 (27) | 10 (27) | 0.000 | 1.000 |
| Cardiovascular           | 18 (21)          | 19 (21)          | 0.013 | 0.932 | 9 (24)          | 12 (32)          | 0.181 | 0.439 |
| Gastrointestinal         | 20 (24)          | 14 (15)          | 0.211 | 0.161 | 5 (14)          | 4 (11)           | 0.083 | 1.000 |
| Trauma                   | 4 (5)            | 3 (3)            | 0.074 | 0.712 | 2 (5)           | 2 (5)            | 0.000 | 1.000 |
| Sepsis, non-pulmonary    | 7 (8)            | 19 (21)          | 0.359 | 0.020 | 6 (16)          | 5 (14)           | 0.076 | 1.000 |
| Others                   | 11 (13)          | 17 (18)          | 0.153 | 0.313 | 5 (14)          | 4 (11)           | 0.083 | 1.000 |
| APACHE II score          | 19 [15–26]       | 22 [17–30]       | 0.481 | 0.008 | 23 [18–26]       | 21 [15–27]       | 0.007 | 0.478 |
| SOFA score at ICU admission | 6 [4–8]     | 8 [6–10]         | 0.831 | <0.0001 | 7 [6–9] | 7 [5–10] | 0.027 | 0.952 |
| Patients receiving mechanical ventilation (%) | 55 (65) | 73 (79) | 0.331 | 0.030 | 26 (70) | 26 (70) | 0.000 | 1.000 |
| Patients receiving continuous vasopressor (%) | 46 (54) | 68 (74) | 0.421 | 0.006 | 24 (65) | 24 (65) | 0.000 | 1.000 |
| Patients receiving continuous sedation (%) | 63 (74) | 80 (87) | 0.329 | 0.030 | 28 (76) | 29 (78) | 0.064 | 0.782 |
| RASS score from day 1 to 5 | −1 [−2 to 0] | −3 [−4 to 1] | 0.122 | <0.0001 | −2 [−3 to 0] | −1 [−3 to 0] | 0.013 | 0.987 |
| Patients receiving continuous analgesia (fentanyl), n (%) | 57 (67) | 74 (80) | 0.307 | 0.043 | 28 (76) | 28 (76) | 0.000 | 1.000 |
| Patients receiving steroids, n (%) | 27 (32) | 32 (35) | 0.064 | 0.671 | 11 (30) | 9 (24) | 0.122 | 0.794 |
| Patients receiving neuromuscular blocking agent, n (%) | 10 (12) | 16 (17) | 0.160 | 0.291 | 3 (8) | 6 (16) | 0.250 | 0.479 |
| Patients receiving dialysis (%) | 15 (18) | 33 (36) | 0.421 | 0.006 | 7 (19) | 7 (19) | 0.067 | 1.000 |

Data are presented as median [interquartile range] or number (%). Analysis by independent-sample Mann–Whitney U-test or χ² test.
employed the same method (univariate logistic regression analysis after propensity score matching) as the primary analysis to investigate the impact on outcomes of the differences in the definition of “early mobilization”. All analyses were performed using JMP (version 13.0; SAS Institute, Cary, NC, USA) and IBM SPSS software (version 23.0; IBM, Armonk, NY, USA), and the differences were considered statistically significant at two-sided P-values of <0.05.

Ethics and Consent

The study was conducted after receiving approval from the Institutional Review Board (IRB) at Nagoya Medical Center Hospital (IRB approval number 2019–78). All data were de-identified to protect the confidentiality of the personal information. The study qualified for exempt status according to the IRB because the data were collected from existing patient records. Therefore, the need for patient consent was waived.

RESULTS

During the study period (January 2016 to March 2019), the ICU admitted 1429 patients, of which 177 patients were eligible for this study (Fig. 1). However, considering the exclusion criteria, 19 patients who died during the ICU stay were excluded. Before the propensity score matching, the LM group had significantly lower values for the ICU admission diagnosis (sepsis) (P=0.020), APACHE II score (P=0.008), SOFA score (P<0.001), mechanical ventilation use (P=0.030),
continuous vasopressor use (P=0.006), continuous sedation (P=0.030), analgesia use (P=0.043), and median RASS score during days 1–5 (P <0.001) (**Table 3**). The propensity scores were calculated using logistic regression analysis that was adjusted for 20 background factors; this produced 37 pairs of patients from the EM and LM groups (**Fig. 2**).

After the matching, the two groups had very similar propensity scores (EM: 0.515 ± 0.237; LM: 0.512 ± 0.237), and no significant difference was observed in the baseline characteristics (**Table 3**). Patient background factors generally had a standard deviation (SD) of <0.1; however, intraoperative admission diagnosis, cardiovascular complications, and continuous administration of steroids and neuromuscular blocking agents had an SD >0.1.

Gait independence at discharge was significantly different between the EM (89%) and LM (65%) groups (P=0.025). Medical costs in the EM group were approximately 30% lower than those in the LM group; however, no significant difference was observed [median: 25th–75th percentile; USD 16,773 (range: USD 10,769–27,852) vs. USD 23,895 (range: USD 15,100–29,277); P=0.054]. The EM group had significantly shorter times to first rehabilitation (P=0.009) and first out-of-bed mobilization (P <0.001), as well as the highest IMS score in the ICU (P<0.001). There was a significant intergroup difference in the number of daily rehabilitation exercises per person (P=0.005) (**Table 5**). In addition, the frequency of rehabilitation exercises of intensity levels 3 and 4 was significantly higher in the EM group than in the LM group (P=0.024).

Univariate logistic regression analysis based on propensity score matching revealed significant associations between EM and independent gait at discharge (OR: 4.47, 95% CI: 1.39–17.43, P=0.011), length of hospital stay (<28 days) (OR: 0.29, 95% CI: 0.11–0.75, P=0.010), and the presence of pneumonia (P=0.009) (**Table 6**). Sensitivity analysis performed using the IPTW method showed a similar trend, with significant association between EM and independent gait at discharge (OR: 4.26, 95% CI: 1.29–14.04, P=0.017). Similarly, multivariate logistic regression analysis of patients who stayed in the ICU for more than 5 days revealed significant association between independent gait at discharge and EM (adjusted P=0.014) (**Table 7**). Notably, multivariate logistic regression analysis, which excluded patients in the LM group (who did not meet the criteria for mobilization by day 5 after admission to the ICU) from propensity score matching showed a similar trend (**Table 7**).

The results of univariate logistic regression analysis when using different definitions of EM—within 3, 4, 6, or 7 days—are shown in **Table 8**. No significant correlation was observed between 90-day survival and gait independence at discharge; however, shorter times to EM (5 days or less) showed stronger correlations of EM with total medical costs, duration of mechanical ventilation, and length of hospital stay (**Table 8**).

**DISCUSSION**

This study focused on associations between EM (within 5 days) and clinical outcomes, especially survival. The results revealed that EM within 5 days showed significant association with decreased length of hospital stay and independent gait at discharge. However, no significant difference in survival after 90 days or in medical costs were found. The results were no different even after adjusting for previously reported prognostic factors among ICU patients, which included the most common barriers to achieving mobilization, circulatory status on ICU days 1 and 2, and consciousness level on days 3–5.2) A similar trend was observed with the exclusion of patients who stayed in the ICU for more than 5 days or those
in the LM group who did not meet the mobilization criteria by day 5 of admission to the ICU. In addition, reducing the number of days to EM seemed to further shorten the length of hospital stay and the duration of mechanical ventilation and to reduce medical costs. A recent systematic review indicated that ambitious targets toward achieving EM did not affect the risk of mortality. The current study showed that there was no difference in survival even after adjusting for the prognostic factors that were reported as independent factors associated with survival in previous studies.

Furthermore, continuous vasopressor use and RASS scores were recorded from days 1–5 as covariates based on the authors’ previous studies on barriers to achieving mobilization. This study suggests that EM-based interventions alone might be insufficient to improve survival outcomes.

The post-matching IPTW analyses identified significant relationships between EM and independent gait at discharge. However, some recent randomized studies have failed to detect significant improvements in the EM group, which may have been related to the mobilization initiation being delayed for approximately 1 week after ICU admission. A 10% reduction in muscle mass has been observed between days 1 and 7 among ICU patients, with a 17.7% reduction observed on day 10. Therefore, delaying the start of measures designed to achieve EM may mitigate any improvements in functional outcomes. In the present study, the median time to mobilization was 4 days in the EM group and 7 days in the LM group, and the EM group had better clinical outcomes (stronger likelihood of independent gait at discharge and shorter hospital stays). Previous reports have also indicated that achieving EM within 1 week does not affect survival but is effective in improving functional outcomes and shortening hospital stays.

Table 4. Comparison of clinical and economic primary outcomes

| Table 4. Comparison of clinical and economic primary outcomes |
|-------------------------------------------------------------|
| **Baseline characteristics**                                 |
| **Total population**                                         |
| Early mobilization | Late mobilization | P   |
|---------------------|-------------------|-----|
| n=85                | n=92              |     |
| **Primary outcome**                                         |
| Gait independence at discharge, n (%)                        |
| 77 (91)             | 48 (52)           | <0.0001 |
| **Secondary outcome**                                       |
| 90-day survival, n (%)                                      |
| 80 (94)             | 70 (76)           | <0.0001 |
| Total medical costs (USD)                                   |
| [19,210–28,789]     | [10,769–27,852]   | 0.054 |
| Duration of mechanical ventilation, days                     |
| 2 [0–4]            | 6 [2–9]           | <0.0001 |
| ICU length of stay, days                                    |
| 4 [3–5]            | 7 [4–10]          | <0.0001 |
| Hospital length of stay, days                               |
| 23 [17–39]         | 38 [27–62]        | <0.0001 |
| Discharge destination, n (%)                                 |
| Home               | 69 (82)           | 44 (48) | <0.0001 |
| Rehabilitation center                                      |
| 4 (5)              | 9 (10)            |       |
| Another hospital                                            |
| 7 (8)              | 16 (17)           |       |
| Nursing home                                                |
| 3 (3)              | 3 (3)             |       |
| Death                                                        |
| 2 (2)              | 20 (22)           |       |
| Complications                                               |
| Delirium during ICU stay, n (%)                             |
| 21 (25)            | 45 (49)           | 0.001 |
| Nosocomial pneumonia, n (%)                                 |
| 7 (8)              | 32 (35)           | <0.0001 |
| ICU-AW at ICU discharge, n (%)                              |
| 23 (27)            | 44 (48)           | 0.004 |

Data are presented as median [interquartile range] or number (%). Analysis by independent-sample Mann–Whitney U-test or χ² test.
### Table 5. Comparison of clinical outcomes between study groups

| Baseline characteristics | Total population | | Matched population | | P | | P |
|--------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                          | Early mobilization | Late mobilization | P | Early mobilization | Late mobilization | P |
|                          | n=85 | n=92 | | n=37 | n=37 | |
| **ICU rehabilitation** | | | | | | |
| Time to first rehabilitation | 2 [2–4] | 5 [2–7] | <0.0001 | 2 [2–4] | 4 [2–6] | 0.009 |
| Time to first out-of-bed mobilization, days | 4 [3–5] | 9 [7–14] | <0.0001 | 4 [3–5] | 7 [6–8] | <0.001 |
| Number of total rehabilitations per person, days | 2 [0–3] | 4 [1–6] | <0.0001 | 3 [1–4] | 2 [0–5] | 0.791 |
| Number of total rehabilitations per person, times | 3 [0–7] | 6 [1–10] | 0.014 | 6 [1–10] | 3 [0–9] | 0.302 |
| Number of daily rehabilitations per person, times/day | 2 [2–3] | 2 [1–2] | <0.0001 | 2 [2–2] | 2 [1–2] | 0.005 |
| Highest IMS at ICU entry | 3 [3–5] | 1 [1–3] | <0.0001 | 5 [3–6] | 1 [1–3] | <0.001 |
| **EM protocol level, sessions** | | | | | | |
| Level 1 | 2 [1–2] | 4 [2–6] | <0.0001 | 2 [1–3] | 2 [1–5] | 0.174 |
| Level 2 | 1 [0–2] | 2 [1–3] | <0.0001 | 1 [0–2] | 2 [1–3] | 0.069 |
| Level 3 | 1 [0–1] | 0 [0–1] | <0.0001 | 1 [0–1] | 0 [0–0] | 0.001 |
| Level 4 | 0 [0–0] | 0 [0–0] | <0.0001 | 0 [0–0] | 0 [0–0] | 0.009 |
| Level 5 | 0 [0–0] | 0 [0–0] | <0.0001 | 0 [0–0] | 0 [0–0] | 0.004 |
| **Ward rehabilitation** | | | | | | |
| Number of total rehabilitations per person, days | 7 [1–16] | 16 [8–26] | <0.0001 | 7 [2–14] | 15 [8–21] | 0.024 |
| Number of total rehabilitations per person, times | 9 [1–16] | 18 [9–34] | <0.0001 | 11 [3–16] | 18 [10–30] | 0.014 |
| Number of daily rehabilitations per person, times/day | 1 [1–1] | 1 [1–1] | 0.008 | 1 [1–1] | 1 [1–2] | 0.112 |

Data are presented as median [interquartile range] or number (%).
Analysis by independent-sample Mann–Whitney U-test or $\chi^2$ test.
to independent gait at discharge, and shorter hospital stays.\(^{(4)}\)

Similarly, these results indicated that a higher rate of gait independence at discharge and shortened length of hospital stay could have contributed to the lower medical costs in the EM group. Consequently, achieving EM in the ICU, as shown in this study, might help prevent disuse syndrome, achieve independent gait, and potentially decrease medical costs.

For this study, EM was defined as initiating rehabilitation by achieving a seated position on the edge of the bed within 5 days of ICU admission. The literature includes various mobilization timings\(^{(13,14)}\), however, recent studies have indicated that the initiation of mobilization within 48–72 h might be optimal.\(^{(22)}\) In a previous study, EM also included passive range-of-motion exercises on the bed.\(^{(42,43)}\) Previous studies have described improvements, not only in physical function but also in respiratory function and the level of consciousness,\(^{(44)}\) as an effect of sitting on the edge of the bed. The results of the current study suggest that it is adequate to achieve mobilization of sitting on the edge of a bed or higher within 5 days of ICU admission. However, comparing the number of times the EM protocol was performed in the ICU and the protocol intensities, the frequency of rehabilitation exercises of intensity level 3 or higher was significantly higher in the EM group than in the LM group. In this study, we focused on the timing of EM initiation; future studies should also investigate the relationships between outcomes and the maximum intensities of mobilization in the ICU.

The present study’s major limitations are a lack of complete data, a small sample size, and a single-center design. In addition, a comparison of patients after propensity score matching showed that intraoperative inpatient diagnosis, cardiovascular complications, and continuous administration of steroids and neuromuscular blockers did not have an SD of <0.1 because of the small sample size. Furthermore, only relatively short-term survival and functional outcomes were evaluated. However, the prevention of physical dysfunction has become a new challenge in the field of emergency and intensive care, with greater emphasis being placed on the long-term post-discharge quality of life and functional outcomes.\(^{(2,45)}\) Furthermore, in this study, unmeasured confounders influenced the relationships observed between EM and independent gait at discharge, length of hospital stay, and medical costs. For example, data regarding medications, sedation dose, pain, infection, ventilator settings, and weaning were not collected despite having the potential to influence the findings.\(^{(12,46–48)}\) Therefore, further prospective studies are needed to investigate whether these factors influ-

### Table 6. Propensity score matched and weighted odds ratios for achievement of early mobilization within 5 days

| Baseline characteristics | After PS matching OR (95% CI) P | IPTW OR (95% CI) P |
|--------------------------|---------------------------------|-------------------|
| Physical function        |                                 |                   |
| Gait independence at discharge | 4.47 (1.39–17.43) 0.011 | 4.26 (1.29–14.04) 0.017 |
| Survival                 |                                 |                   |
| <90 days                 | 2.64 (0.67–13.12) 0.169         | 5.53 (0.78–17.20) 0.103 |
| Total hospital costs     |                                 |                   |
| <2500 USD                | 0.51 (0.19–1.29) 0.154         | 0.57 (0.21–1.55) 0.268 |
| Outcome                  |                                 |                   |
| Home                     | 1.61 (0.62–4.30) 0.329         | 0.96 (0.34–2.69) 0.937 |
| Duration of mechanical ventilation |                     |                   |
| >2 days                  | 0.89 (0.35–2.26) 0.814         | 0.80 (0.33–1.97) 0.626 |
| ICU length of stay       |                                 |                   |
| >7 days                  | 0.51 (0.18–1.43) 0.201         | 0.79 (0.24–2.54) 0.688 |
| Length of hospital stay  |                                 |                   |
| >28 days                 | 0.29 (0.11–0.75) 0.010         | 0.47 (0.18–1.25) 0.129 |
| Complications            |                                 |                   |
| Delirium                 | 0.70 (0.27–1.82) 0.468         | 0.54 (0.21–1.41) 0.209 |
| Pneumonia                | 0.15 (0.02–0.65) 0.009         | 0.66 (0.15–2.82) 0.571 |
| ICU-AW                   | 0.59 (0.21–1.61) 0.308         | 0.89 (0.35–2.27) 0.799 |

PS, propensity score.
Table 7. Comparison of EM and LM groups in patients who stayed in the ICU for 5 days or more or excluding patients in the LM group who did not meet the mobilization criteria by day 5 of admission to the ICU

| Baseline characteristics                  | Patients who stayed in ICU for 5 days or more | Patients excluding LM group members who did not meet mobilization criteria by day 5 of admission to ICU |
|-------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|
|                                           | Early mobilization n=29 | Late mobilization n=64 | Adjusted P<sup>a</sup> | Early mobilization n=85 | Late mobilization n=46 | Adjusted P<sup>a</sup> |
| Primary outcome                           |                                |                                |                        |                                |                                |                        |
| Gait independence at discharge, n (%)     | 25 (86)                        | 32 (50)                        | 0.014                  | 77 (91)                        | 27 (59)                        | 0.002                  |
| 90-day survival, n (%)                    | 27 (93)                        | 48 (75)                        | 0.110                  | 80 (94)                        | 39 (85)                        | 0.162                  |
| Total medical costs (USD)                 | 23,193                         | 34,783                         | 0.744                  | 19,210                         | 27,885                         | 0.073                  |
| Duration of mechanical ventilation, days  | 5 [3–6]                        | 8 [6–11]                       | 0.623                  | 2 [0–4]                        | 4 [2–7]                        | 0.334                  |
| ICU length of stay, days                  | 5 [5–7]                        | 9 [7–12]                       | 0.134                  | 4 [3–5]                        | 6 [4–9]                        | 0.950                  |
| Hospital length of stay, days             | 31 [22–49]                     | 42 [30–68]                     | 0.567                  | 23 [17–39]                     | 43 [29–66]                     | 0.014                  |
| Discharge destination, n (%)              | 19 (66)                        | 27 (42)                        | 0.371                  | 69 (82)                        | 27 (59)                        | 0.464                  |
| Complications                             |                                |                                |                        |                                |                                |                        |
| Delirium during ICU stay, n (%)           | 12 (41)                        | 34 (53)                        | 0.217                  | 21 (25)                        | 22 (48)                        | 0.168                  |
| Nosocomial pneumonia, n (%)               | 4 (14)                         | 26 (41)                        | 0.049                  | 7 (8)                          | 16 (35)                        | 0.015                  |
| ICU-AW at ICU discharge, n (%)            | 12 (41)                        | 35 (55)                        | 0.919                  | 23 (27)                        | 18 (39)                        | 0.751                  |

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

<sup>a</sup> The covariates were selected from patient characteristics reported as significant independent factors associated with the primary outcome, i.e., admission source, APACHE II score, SOFA score, continuous vasopressor use, RASS score from day 1 to day 5.
enced our findings. Furthermore, a multicenter, prospective, randomized controlled trial that includes all ICU patients is needed to validate and correlate the unanswered questions of this study.

**CONCLUSION**

The present study revealed that EM was not significantly associated with 90-day survival or medical costs but was associated with a higher likelihood of independent gait at discharge and shorter hospital stays. EM, which refers to achieving the strength to sit on the edge of the bed within the first 5 days of the ICU stay, might be an adequate target to improve clinical outcomes. Further validations of the results are necessary.

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**CONFLICTS OF INTEREST**

The authors report no conflicts of interest.

## REFERENCES

1. Brahmbhatt N, Murugan R, Milbrandt EB: Early mobilization improves functional outcomes in critically ill patients. Crit Care 2010;14:321. DOI:10.1186/cc9262, PMID:20880413
2. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Rendell J, Votto J, Harvey MA: Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders’ conference. Crit Care Med 2012;40:502–509. DOI:10.1097/CCM.0b013e318232da75, PMID:21946660
3. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, Larson EB: Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA 2010;303:763–770. DOI:10.1001/jama.2010.167, PMID:20179286

### Table 8. Propensity score matched for different definition of early mobilization

| Variable                  | Definition of early mobilization in ICU days | Within 3 days | Within 4 days | Within 5 days | Within 6 days | Within 7 days |
|---------------------------|--------------------------------------------|---------------|---------------|---------------|---------------|---------------|
| Physical function         |                                            |               |               |               |               |               |
| Gait independence at discharge |                                            | 2.22 (0.53–15.22) | 3.46 (0.85–23.45) | 4.47 (1.39–17.43) | 8.62 (2.67–30.67) | 7.56 (2.16–28.47) |
| Survival                  |                                            | 3.80 (0.65–72.53) | 2.64 (0.63–11.15) | 3.00 (0.75–12.14) | 3.60 (0.80–15.10) |
| Total hospital costs      |                                            | 0.30 (0.06–1.05) | 0.27 (0.07–0.85) | 0.51 (0.19–1.29) | 0.51 (0.18–1.41) | 0.43 (0.13–1.41) |
| Outcome                   |                                            | 2.56 (0.72–12.10) | 2.75 (0.87–10.59) | 1.61 (0.62–4.30) | 2.79 (0.98–8.08) | 2.16 (0.65–7.18) |
| Duration of mechanical ventilation |                                            | 0.12 (0.02–0.42) | 0.27 (0.09–0.77) | 0.89 (0.35–2.26) | 1.06 (0.37–2.93) | 1.50 (0.46–4.92) |
| ICU length of stay        |                                            | 0.32 (0.04–1.33) | 0.35 (0.08–1.23) | 0.51 (0.18–1.41) | 0.39 (0.13–1.16) | 0.30 (0.09–1.03) |
| Length of hospital stay   |                                            | 0.29 (0.07–0.94) | 0.23 (0.07–0.69) | 0.29 (0.11–0.75) | 0.09 (0.02–0.32) | 0.12 (0.02–0.49) |
| Complications             |                                            | 0.57 (0.14–1.89) | 0.34 (0.08–1.06) | 0.70 (0.27–1.82) | 0.69 (0.24–1.96) | 0.72 (0.22–2.44) |
| Delirium                  |                                            | 0.31 (0.02–1.82) | 0.21 (0.01–1.18) | 0.15 (0.02–0.65) | 0.21 (0.05–0.75) | 0.15 (0.04–0.57) |
| Pneumonia                 |                                            | 0.83 (0.21–2.80) | 0.73 (0.21–2.23) | 0.59 (0.21–1.61) | 0.58 (0.20–1.74) | 0.23 (0.06–0.76) |

Data presented as odds ratio (95% confidence interval).
4. Lee M, Kang J, Jeong YJ: Risk factors for post-intensive care syndrome: a systematic review and meta-analysis. Aust Crit Care 2020;33:287–294. DOI:10.1016/j.aucc.2019.10.004, PMID:31839375
5. Marra A, Pandharipande PP, Girard TD, Patel MB, Hughes CG, Jackson JC, Thompson JL, Chandrasekhar R, Ely EW, Brummel NE: Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. Crit Care Med 2018;46:1393–1401. DOI:10.1097/CCM.0000000000003218, PMID:29787415
6. Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, Imaizumi H, Inoue S, Kakihama Y, Kotani K, Kushimoto S, Matsuda A, Matsumoto S, Nagae M, Onodera M, Ohnuma T, Oshima K, Saito N, Sakamoto S, Sakuraya M, Sasano M, Sato N, Sawamura A, Shimizu K, Shirai K, Takei T, Takeuchi M, Takimoto K, Taniguchi T, Matsuda H, Shime N, Yatabe T, Kondo Y, Sumi Y, Yasuda H, Aoyama K, Azuhata T, Doi K, Doi M, Fuke R, Fukuda T, Goto K, Hasegawa R, Hashimoto S, Hatakeyama J, Hayakawa M, Hifumi T, Higashibeppu N, Hirai K, Hirose T, Ide K, Kanzuka Y, Kan’o T, Kawasaki T, Kuroda H, Matsuda A, Matsumoto A, Nagae M, Onodera M, Ohnuma T, Oshima K, Saito N, Sakamoto S, Sakuraya M, Sasano M, Sato N, Sawamura A, Shimizu K, Shirai K, Takei T, Takeuchi M, Takimoto K, Taniguchi T, Tsutsumi H, Tsuruta R, Yama N, Yamakawa K, Yamashita C, Yamashita K, Yoshida T, Tanaka H, Oda S: The Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). Acute Med Surg 2018;5:3–89. DOI:10.1002/ams2.322, PMID:29445505
7. Watanabe S, Iida Y, Ito T, Mizutani M, Morita Y, Suzuki S, Nishida O: Effect of early rehabilitation for mechanically ventilated intensive care unit patients and oral ingestion. Prog Rehabil Med 2018;3:20180003. DOI:10.2490/prm.20180009, PMID:32789234
8. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franchzyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874–1882. DOI:10.1016/S0140-6736(09)60658-9, PMID:19446324
9. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L, Howard A, Dixon L, Leach S, Small R, Hite RD, Haponik E: Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008;36:2238–2243. DOI:10.1097/CCM.0b013e318180b90e, PMID:18596631
10. Watanabe S, Morita Y, Suzuki S, Someya F: Association between early rehabilitation for mechanically ventilated intensive care unit patients and oral ingestion. Prog Rehabil Med 2018;3:20180003. DOI:10.2490/prm.20180009, PMID:32789234
11. Liu K, Ogura T, Takahashi K, Nakamura M, Ohtake H, Fujiduka K, Abe E, Oosaki H, Miyazaki D, Suzuki H, Nishikimi M, Komatsu M, Lefor AK, Mato T: A progressive early mobilization program is significantly associated with clinical and economic improvement: a single-center quality comparison study. Crit Care Med 2019;47:e744–e752. DOI:10.1097/CCM.0000000000003850, PMID:3162197
12. Ad Hoc Committee for Early Rehabilitation, The Japanese Society of Intensive Care Medicine: Evidence based expert consensus for early rehabilitation in the intensive care unit [in Japanese]. Jpn J Int Care Med 2017;24:255–303.
13. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R: Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 2009;37:2499–2505. DOI:10.1097/CCM.0b013e3181a38937, PMID:19623052
14. Hodgson CL, Berney S, Harrild M, Saxena M, Bel lomo R: Clinical review: early patient mobilization in the ICU. Jpn J Int Care Med 2013;17:207.
15. Fuest K, Schaller SF: Recent evidence on early mobilization in critical-ill patients. Curr Opin Anaesthesiol 2018;31:144–150. DOI:10.1097/ACO.0000000000000568, PMID:29351145
16. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneal J, Henderson A, Hugill K, Howard P, Roy A, Bonner S, Baudouin S: Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax 2018;73:213–221. DOI:10.1136/thoraxjnl-2016-209858, PMID:28780504
17. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, Gough K, Hoorn S, Morris ME, Berney S: Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care 2013;17:R156. DOI:10.1186/cc12835, PMID:23883525

18. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M: A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med 2016;193:1101–1110. DOI:10.1164/rccm.201505-1039OC, PMID:26651376

19. Denehy L, Lanphere J, Needham DM: Ten reasons why ICU patients should be mobilized early. Intensive Care Med 2017;43:86–90. DOI:10.1007/s00134-016-4513-2, PMID:27562244

20. Watanabe S, Kotani T, Taito S, Ota K, Ishii K, Ono M, Katsukawa H, Kozu R, Morita Y, Arakawa R, Suzuki S: Determinants of gait independence after mechanical ventilation in the intensive care unit: a Japanese multicenter retrospective exploratory cohort study. J Intensive Care 2019;7:53. DOI:10.1186/s40560-019-0404-2, PMID:31798888

21. Watanabe S, Keibun L, Morita Y, Kanaya T, Naito Y, Arakawa R, Suzuki S, Katsukawa H, Lefor AK, Kotani T: Changes in barriers to implementing early mobilization in the intensive care unit: a single center retrospective cohort study. J Nagoya Med Sci 2021;83:443–464. DOI:10.1186/s40560-019-0404-2, PMID:31798888

22. Kuhn KF, Schaller SJ: Comment on Early versus delayed mobilization for in-hospital mortality and health-related quality of life among critically ill patients: a systematic review and meta-analysis (Okada et al., Journal of Intensive Care 2019). J Intensive Care 2020;8:21. DOI:10.1186/s40560-020-0436-7, PMID:32190331

23. Harrold ME, Salisbury LG, Webb SA, Allison GT, Australia and Scotland ICU Physiotherapy Collaboration: Early mobilisation in intensive care units in Australia and Scotland: a prospective, observational cohort study examining mobilisation practises and barriers. Crit Care 2015;19:336. DOI:10.1186/s13054-015-1033-3, PMID:26370550

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383. DOI:10.1016/0021-9681(87)90171-8, PMID:3558716

25. Nakagawa Y, Takemura T, Yoshihara H, Nakagawa Y: A new accounting system for financial balance based on personnel cost after the introduction of a DPC/DRG system. J Med Syst 2011;35:251–264. DOI:10.1007/s10916-009-9361-y, PMID:20703565

26. Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, Young P, Zanni J, Buhr H, Higgins A, Presneill J, Berney S: Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart Lung 2014;43:19–24. DOI:10.1016/j.hrtlng.2013.11.003, PMID:24733338

27. Conlon N, O’Brien B, Heribson GP, Marsh B: Long-term functional outcome and performance status after intensive care unit re-admission: a prospective survey. Br J Anaesth 2008;100:219–223. DOI:10.1093/bja/aem372, PMID:18156652

28. de Grooth HJ, Geenelen IL, Girbes AR, Vincent JL, Parienti JJ, Oudemans-van Straaten HM: SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis. Crit Care 2017;21:38. DOI:10.1186/s13054-017-1609-1, PMID:28231816

29. Fukunaga S, Nagami Y, Shiba M, Ominami M, Tanigawa T, Yamagami H, Tanaka H, Muguruma K, Watanabe T, Tominaga K, Fujiwara Y, Ohira M, Hirakawa K, Arakawa T: Long-term prognosis of expanded-indication differentiated-type early gastric cancer treated with propensity score analysis. Gastrointest Endosc 2017;85:143–152. DOI:10.1016/j.gie.2016.06.049, PMID:27365265

30. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, Byrum D, Carson SS, Devlin JW, Engel HJ, Esbrook CL, Hargett KD, Harmon L, Hielsberg C, Jackson JC, Kelly TL, Kumar V, Millner L, Morse A, Perme CS, Posa PJ, Puntillo KA, Schweickert WD, Stollings JL, Tan A, D’Agostino McGowan L, Ely EW: Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med 2019;47:3–14. DOI:10.1097/CCM.0000000000003482, PMID:30339549
31. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J, ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group: Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797–808. DOI:10.1056/NEJMoa1705835, PMID:29347874

32. Azoulay E, Adrie C, De Lassence A, Pochard F, Moreau D, Thiery G, Cheval C, Moine P, Garroute-Orgeas M, Alberti C, Cohen Y, Timsit JF: Determinants of post-intensive care unit mortality: a prospective multicenter study. Crit Care Med 2003;31:428–432. DOI:10.1097/01.CCM.0000048622.01013.88, PMID:12576947

33. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL: The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 2017;43:171–183. DOI:10.1007/s00134-016-4612-0, PMID:27864615

34. Wilcox MG, Howard TJ, Plaskon LA, Unthank JL, Madura JA: Current theories of pathogenesis and treatment of nonocclusive mesenteric ischemia. Dig Dis Sci 1995;40:709–716. DOI:10.1007/BF02064966, PMID:7720458

35. Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, Chiche JD, Cariou A, Mira JP, Pène F: Timing and causes of death in septic shock. Ann Intensive Care 2015;5:16. DOI:10.1186/s13613-015-0058-8, PMID:26092499

36. Leone M, Bechis C, Baumstarck K, Ouatara A, Collange O, Augustin P, Anname D, Arbelot C, Asehnoune K, Baldési O, Bourcier S, Delapierre L, Demory D, Hengy B, Ichai C, Kipnis E, Brasdefer E, Lasocki S, Legrand M, Mimoz O, Rimmelé T, Aliane J, Bertrand PM, Bruder N, Kipnis E, Briouc Q, Lévy B, Martinez O, Peytel E, Piton A, Richter E, Toufik K, Vogler MC, Wallet F, Boufi M, Allaouchiche B, Constantin JM, Martin C, Jaber S, Lefranc JY: Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. Intensive Care Med 2015;41:667–676. DOI:10.1007/s00134-015-3690-8, PMID:25731634

37. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelmann C, Hite RD, Nicklas B, Chatterjee A, Young MP: Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. JAMA 2016;315:2694–2702. DOI:10.1001/jama.2016.7201, PMID:27367766

38. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Padhke R, Dew T, Siddhu PS, Veloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE: Acute skeletal muscle wasting in critical illness. JAMA 2013;310:1591–1600. DOI:10.1001/jama.2013.278481, PMID:24108501

39. Ding N, Zhang Z, Zhang C, Yao L, Yang L, Jiang B, Wu Y, Jiang L, Tian J: What is the optimum time for initiation of early mobilization in mechanically ventilated patients? A network meta-analysis. PLoS One 2019;14:e0223151. DOI:10.1371/journal.pone.0223151, PMID:31589642

40. Okada Y, Unoki T, Matsuishi Y, Egawa Y, Hayashida K, Inoue S: Early versus delayed mobilization for inhospital mortality and health-related quality of life among critically ill patients: a systematic review and meta-analysis. J Intensive Care 2019;7:57. DOI:10.1186/s40560-019-0413-1, PMID:31867111

41. Corcoran JR, Herbsman JM, Bushnik T, Van Lew, Stolfi A, Parkin K, McKenzie A, Hall GW, Joseph W, Whiteson J, Flanagan SR: Early rehabilitation in the medical and surgical intensive care units for patients with and without mechanical ventilation: an interprofessional performance improvement project. PM R 2017;9:113–119. DOI:10.1016/j.pmrj.2016.06.015, PMID:27346093

42. Bakhru RN, McWilliams DJ, Wiebe DJ, Spuhler VJ, Schweickert WD: Intensive care unit structure variation and implications for early mobilization practices. an international survey. Ann Am Thorac Soc 2016;13:1527–1537. DOI:10.1513/AnnalsATS.201601-078OC, PMID:27268952

43. Fontela PC, Forgariini LA Jr, Friedman G: Clinical attitudes and perceived barriers to early mobilization of critically ill patients in adult intensive care units. Rev Bras Ter Intensiva 2018;30:187–194. PMID:29995084
44. Okubo N: Effectiveness of the sitting position without back support. Australas J Neurosci 2015;25:31–39. DOI:10.21307/ajon-2017-111

45. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE: Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med 2010;38:1276–1283. DOI:10.1097/CCM.0b013e3181d8cc1d, PMID:20308885

46. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Droout X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BR, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–e873. DOI:10.1097/CCM.0000000000003299, PMID:30113379

47. Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki ES, Markaki V, Zervakis D, Nanas S: Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. Crit Care 2010;14:R74. DOI:10.1186/cc8987, PMID:20426834

48. Leditschke AI, Green M, Irvine J, Bissett B, Mitchell IA: What are the barriers to mobilizing intensive care patients? Cardiopulm Phys Ther J 2012;23:26–29. DOI:10.1097/01823246-20123010-00005, PMID:22807652