ORIGINAL PAPER

Nagoya J. Med. Sci. **83**. 443–464, 2021
doi:10.18999/nagjms.83.3.443

Changes in barriers to implementing early mobilization in the intensive care unit: a single center retrospective cohort study

Shinichi Watanabe[1], Keibun Liu[2], Yasunari Morita[3], Takahiro Kanaya[1], Yuji Naito[1], Ritsuro Arakawa[3], Shuichi Suzuki[3], Hajime Katsukawa[4], Alan Kawarai Lefor[5], Yoshinori Hasegawa[6] and Toru Kotani[7]

[1]*Department of Rehabilitation Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan*
[2]*Critical Care Research Group, the Prince Charles Hospital, Brisbane, Australia*
[3]*Department of Critical Care Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan*
[4]*Japanese Society for Early Mobilization, Tokyo, Japan*
[5]*Department of Surgery, Jichi Medical University, Shimotsuke, Japan*
[6]*National Hospital Organization, Nagoya Medical Center, Nagoya, Japan*
[7]*Department of Intensive Care Medicine, Showa University School of Medicine, Tokyo, Japan*

ABSTRACT

This study was undertaken to investigate the rate of mobilization, defined as a rehabilitation level of sitting on the edge of a bed or higher, and its association with changes in barriers in the intensive care unit (ICU). Consecutive patients from January 2016 to March 2019 admitted to the ICU, 18 years old or older, who did not meet exclusion criteria, were eligible. The primary outcome was the rate of mobilization. Barriers, their changes on a daily basis, and clinical outcomes, such as walking independence at hospital discharge, were also investigated. The association between the barriers and mobilization, and walking independence were analyzed by multivariate logistic regression analysis. During the study period, 177 patients were enrolled. Mobilization was achieved by 116 patients (66%) by the 7th ICU day. The barrier to mobilization was circulatory status on days 1 and 2, consciousness level on days 3 to 5, and medical staff factors on days 6 and 7. Multivariate analysis showed that consciousness level (OR: 0.38, p=0.01), and medical staff factors (OR: 0.49, p=0.01) were significantly associated with mobilization. By hospital discharge 125 patients (71%) could walk independently. Consciousness level was associated (OR: 0.52, p=0.04) with walking independence. In this study, over half of patients could achieve mobilization within the first 7 days. Barriers to mobilization in the ICU change over time. Consciousness level is significantly associated with both mobilization and independent walking at discharge.

Keywords: mobilization, barrier, adverse event, survival rate, walking independence

Abbreviations:
ICU: intensive care unit
EM: early mobilization
RASS: Richmond Agitation Sedation Scale
APACHE II: Acute Physiology and Chronic Health Evaluation II

Received: July 29, 2020; accepted: November 20, 2020

Corresponding Author: Shinichi Watanabe, PT, PhD
Department of Rehabilitation Medicine, National Hospital Organization, Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan
Tel: +81-52-951-1111, Fax: +81-52-951-0663, E-mail: 00091846@hosp.go.jp

SOFA: Sequential Organ Failure Assessment
IMS: ICU Mobility Scale
IQR: interquartile range
OR: odds ratio
CI: confidence interval

INTRODUCTION

Outcomes of critically ill patients, such as mortality, have improved over time due to the development of improved critical care strategies,[1] while health-related quality of life and activities of daily living have not been sufficiently investigated and are the focus of recent studies.[2] Patients who have undergone mechanical ventilation in the intensive care unit (ICU) need long-term rehabilitation not only because of subsequent respiratory impairment, but also physical dysfunction, referred to as ICU acquired weakness.[3,4] In order to improve this functional disability, an early mobilization (EM) strategy in the ICU is recommended.[5-7] Prior studies showed that initiating EM after ICU admission may reduce the incidence of ICU acquired weakness and delirium,[8,9] the length of ICU and hospital stays,[10,11] the duration of mechanical ventilation,[9,12] medical costs,[11,13] and result in an improved quality of life.[14] Previous studies showed that achieving mobilization, such as sitting on the edge of the bed, standing, and ambulating early in the ICU stay may improve outcomes[9-12,15] and delaying mobilization, for example mobilization more than one week after ICU admission, could be harmful.[16] It is necessary to develop an efficient method to achieve EM in the ICU.

While early rehabilitation of severely ill patients and mobilization is expected to have many effects, daily changes in the implementation of mobilization, especially the acute phase of critical illness, were not fully evaluated. Although many barriers to its implementation in the ICU were reviewed in previous studies,[17-19] changes in barriers on a daily basis and the clinical importance of these barriers on mobilization and outcomes remain unknown. Investigating changes in the rate of mobilization and associated barriers at the same time could provide guidance for planning rehabilitation allowing patients to achieve EM and prevent delays in initiating EM. Information regarding daily changes in barriers to EM could contribute to appropriate staff planning and proper allocation of resources.

The aim of this study is to investigate the daily rate of mobilization. Daily changes in barriers to prevent mobilization and their association with the implementation of mobilization and clinical outcomes are also investigated.

METHODS

Study design and subject

This was a single center retrospective cohort study approved by the ethics committee of the Nagoya Medical Center which confirmed waiver of informed consent due to its retrospective nature. All patients from January 2016 to March 2019 were screened at the time of ICU admission. Patients discharged from the ICU within 48 hours, age under 18 years, inability to walk independently before hospitalization,[20] neurologically impaired, difficulty communicating in Japanese, presence of a condition limiting mobilization including unstable pelvic fractures, considered in terminal/ end of life status, or who died during ICU stay, were excluded.

Hospital

Nagoya Medical Center is a tertiary care hospital with 740 general beds and a 6-bed mixed ICU. ICU physicians provide formal consultations for all patients admitted to the ICU. Patients are admitted to the ICU directly from the emergency room or the ward beds. Supplemental Table 1 shows the ICU day shift staff during the study period.

Table 1 Baseline characteristics at the time of ICU admission

Variable	Total n = 177
Age (years)	70 [62–79]
Male gender (%)	121 (68)
Body mass index (kg/m^2)	21 [18–24]
Charlson comorbidity index	2 [1–4]
Admitted from (%)	
Emergency Department	129 (73)
Hospital ward	48 (27)
ICU admission diagnosis (%)	
Respiratory (including pneumonia)	47 (27)
Cardiovascular	39 (22)
Gastrointestinal	36 (20)
Trauma	7 (4)
Sepsis, non-pulmonary	20 (11)
Other	28 (16)
APACHE II score	22 [16–28]
SOFA score at ICU admission	7 [5–9]
Patients receiving mechanical ventilation (%)	124 (70)
Patients receiving continuous vasopressor (%)	114 (64)
Patients receiving continuous sedation (%)	143 (81)
Average RASS score from day 1 to day 7	–1 [0–2]
Patients receiving continuous analgesia (Fentanyl) (%)	131 (74)

Median [25th–75th percentile] or the number of patients (percentage).
APACHE II: Acute Physiology and Chronic Health Evaluation
SOFA: Sequential Organ Failure Assessment
RASS: Richmond Agitation Sedation Scale
ICU: intensive care unit

Early mobilization protocol

Problems in the ICU related to implementing an EM strategy, effective evaluation systems, protocols, discontinuous criteria, and potential adverse events were assessed based on existing literature.[9,10,13,21] The EM protocol was an early goal-directed protocol including 5 levels and was not revised during the study period. The details of the protocol are shown in Supplemental Table 2 and Supplemental Figure 1. The rehabilitation intensity higher than the level of sitting at the bedside (Level 3) was defined as “mobilization”.[22]

All patients were supposed to receive at least one rehabilitation session by a physical therapist for 20 minutes on each weekday based on the assessment by the physical therapists and ICU physicians. Mobilization at the level of sitting on the edge of the bed or higher (levels 3, 4, and 5) was performed by a team consisting of ICU physicians, nurses, and physical therapists. After ICU discharge, or on the general ward, all patients underwent rehabilitation by physical or occupational therapists without a specific protocol. Protocols for routine care in the ICU, including pain management, sedation, delirium, or weaning from mechanical ventilation, and the rehabilitation policy on the general ward, are shown in Supplemental Table 1.

Data collection

Patient data was retrieved retrospectively from the electrical medical records. Baseline characteristics of all enrolled patients were collected at the time of ICU admission, including age, gender, body mass index, Charlson comorbidity index, admission source,[23] ICU admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[24] Sequential Organ Failure Assessment (SOFA) score,[25] need for mechanical ventilation, vasopressor use, continuous sedation, continuous analgesia, and hemodialysis. The average Richmond agitation sedation scale (RASS; recorded every 2 hours)[26] score from days 1 to 7 in the ICU was also retrieved.

Data associated with rehabilitation sessions were recorded daily by a physical therapist soon after the session, including highest activity level as the ICU mobility scale (IMS),[27] incidence of adverse events, and thing that preventing achieving the mobilization at that session. We collected these data within the first 7 days of ICU stay.

Perceived barriers included predefined and non-defined barriers described in prior studies.[15,16,28] These included consciousness factors, subjective symptoms, respiratory factors, circulatory factors, device factors, and medical staff factors.[29] Details of these factors are shown in Supplemental Table 3. During each rehabilitation session, an ICU physician determined the primary barrier to preventing mobilization by the end of the session according to the algorithm shown in Supplemental Figure 2. Only one primary barrier category, not the individual components of categories, was recorded. Adverse events which occurred during rehabilitation were listed in the same way by a physical therapist if they were on a predefined list of adverse events, shown in Supplemental Table 4.[30,31]

Study Outcomes

The primary outcome was to investigate the rate of achieving mobilization during the first 7 days of ICU stay by assessing the highest level of activity at each rehabilitation session. The most relevant barriers within the same period preventing mobilization were also analyzed. Secondary outcomes included the contents and daily changes in adverse events during the first 7 days of ICU admission. Other outcomes, such as ICU rehabilitation, duration of mechanical ventilation, ICU and hospital lengths of stay, nosocomial pneumonia, ICU Acquired Weakness at ICU discharge, the ability to walk independently at discharge,[32] discharge destination, 90-days survival after ICU discharge were also reviewed. The association between barriers and other outcomes, such as 90-days survival and independent walking, were also investigated.

ICU Acquired Weakness was evaluated by the physical therapists and defined as a Medical Research Council-sum score less than 48 at the time of ICU discharge.[33,34] Patients who could ambulate 45 m or more with or without braces, equal to a score of 15 on the mobility in the Barthel Index,[35] were defined as walking independently.[36,37]

Statistical analysis

Continuous variables and categorical data were described using the median with interquartile range (IQR) and numbers with percentages respectively. Multiple logistic regression analysis was performed to examine the association between barriers and achieving mobilization or other outcomes shown as the odds ratio (OR), confidence interval (CI). In multivariate analyses, explanatory variables included the presence of three factors associated with barriers, such as circulatory factors from days 1 to 2, consciousness factors from days 3 to 5, and medical staff factors from days 6 to 7. Statistical analyses were performed using JMP, version13.0. All statistical tests were two-sided, and a value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline patient characteristics

During the study period from January 2016 to March 2019, a total of 1429 patients were screened, and 177 patients enrolled in this study (Figure 1). Baseline characteristics are shown in Table 1. There were 121 males (68%), with a median age of 70y [IQR 62–79]. The median APACHE II and SOFA scores at ICU admission were 22 [IQR 16–28] and 7 [IQR 5–9], respectively. Of the 177 patients enrolled, 124 (70%) underwent mechanical ventilation. Supplemental Tables 5 and 6 show the SOFA score at the time of ICU admission and the daily changes in RASS score from ICU days 1 to day 7.

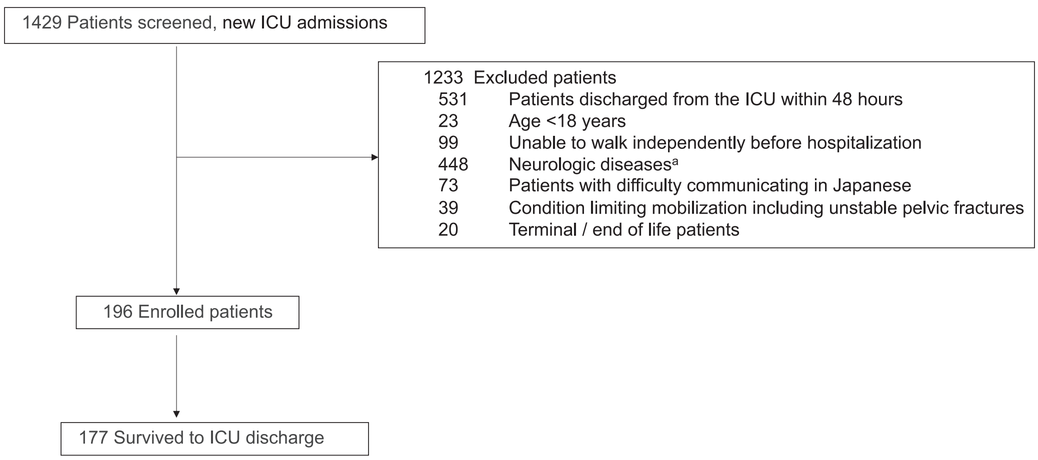


Fig. 1 Flow chart of the patient selection process

ICU: intensive care unit

Neurological diseases include cerebral infraction, cerebral hemorrhage, acute subdual hematoma, acute epidural hematoma, traumatic subarachnoid hemorrhage, and encephalitis.

The rate of achieving mobilization (Figure 2)

A total of 116 patients (66%) achieved mobilization within the first 7 days of the ICU stay. On ICU day 1, 159/177 patient (90%) underwent rehabilitation at the level of IMS 0, 16 patients (9%) at IMS 1–2, and 1 patient (1%) at IMS 4–6. The rate of patients who underwent rehabilitation at a level of IMS 0 decreased from 90% to 42% on day 3, and to 11% on day 7. The rate of IMS 1 to 10 did not change within 7 days of ICU admission. The rate of IMS 3 or more is low on ICU days 1 (1%) and 2 (7%), increasing from days 3 (21%) to 5 (27%), and maintained the same level on ICU days 6 (27%) and 7 (24%). There were trends for the rate of mobilization according to ICU admission diagnosis (Supplemental Figure 3). All rehabilitation sessions were performed for 20 minutes regardless of the intensity.

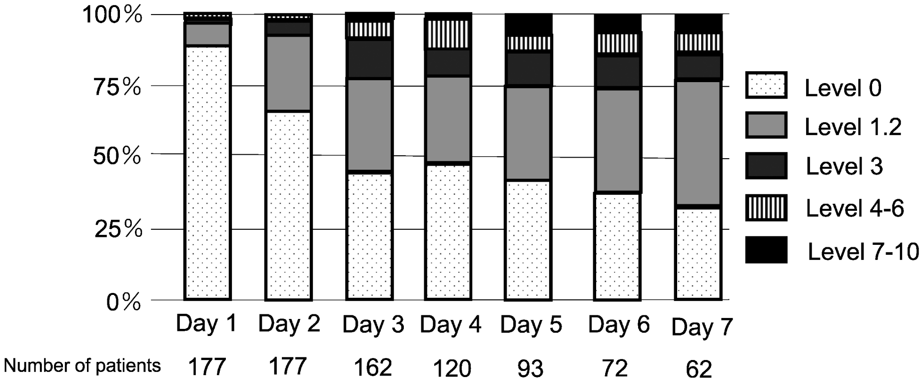


Fig. 2 Maximum level of activity from days 1 to 7
Measured by Intensive care unit Mobility Scale, 0=no activity, 1=exercises in bed, 2=passively moved to the chair, 3=sitting on the edge of the bed, 4=standing, 5=transferring from bed to chair through standing, 6=marching on the spot, 7=walking with assistance of two people, 8=walking with assistance of one person, 9=walking independence with assistive device and 10=walking independently.

Barriers to mobilization (Table 2)

Circulatory instability (e.g. systolic blood pressure: ≤90; mean blood pressure: ≤65 mmHg; heart rate: ≤50; additional administration of vasopressors) was most frequently described as the barrier to mobilization on days 1 (60%) and 2 (38%). Level of consciousness was the factor most frequently considered a barrier (e.g. unable to perform a requested action, unable to exercise spontaneously; consciousness disorder, RASS: ≤ –3 or ≥+2) on days 3 (27%), 4 (35%), and 5 (29%). On days 6 and 7, the most frequently described barriers were related to medical staff factors (e.g. lack of staff, holidays, many examinations, lack of time) (28 % and 34 % respectively). Among patients undergoing mechanical ventilation, the same factors were cited as barriers at the same time points.

Among the three major barriers detected within the first week in the ICU stay, consciousness factors from days 3 to 5 (OR 0.38; CI 0.18–0.78, p=0.01), and medical staff factors from days 6 to 7 (OR 0.49; CI 0.18–0.92, p=0.01) were significantly associated with achieving mobilization during the first week (Table 3).

Table 2 Primary barriers preventing a higher level of mobilization

	Achievement of mobilization	Consciousness factors	Subjective symptoms	Respiratory factors	Circulatory factors	Device factors	Medical staff factors	Other
Day 1 Total patients (n=177)	2 (1)	12 (7)	4 (2)	33 (18)	104 (60)	4 (2)	2 (1)	16 (9)
Ventilated patients (n=124)	1 (1)	11 (9)	1 (1)	28 (22)	70 (56)	2 (2)	2 (2)	9 (7)
Day 2 Total patients (n=177)	12 (7)	41 (23)	9 (5)	21 (12)	68 (38)	8 (5)	15 (7)	3 (2)
Ventilated patients (n=124)	5 (4)	35 (28)	2 (2)	20 (16)	47 (38)	4 (3)	10 (8)	1 (1)
Day 3 Total patients (n=162)	35 (21)	44 (27)	7 (4)	16 (9)	26 (16)	7 (4)	26 (16)	1 (1)
Ventilated patients (n=123)	20 (16)	39 (32)	6 (5)	16 (13)	18 (15)	4 (3)	19 (15)	1 (1)
Day 4 Total patients (n=120)	24 (20)	41 (35)	5 (4)	10 (8)	9 (7)	9 (5)	25 (21)	1 (1)
Ventilated patients (n=105)	18 (17)	40 (38)	5 (5)	10 (10)	7 (6)	5 (5)	20 (19)	0 (0)
Day 5 Total patients (n=93)	25 (27)	27 (29)	7 (7)	9 (9)	3 (3)	5 (5)	17 (18)	0 (0)
Ventilated patients (n=87)	24 (28)	26 (30)	6 (7)	9 (10)	3 (3)	4 (5)	15 (17)	0 (0)
Day 6 Total patients (n=72)	19 (27)	16 (22)	6 (8)	5 (7)	3 (4)	3 (4)	20 (28)	0 (0)
Ventilated patients (n=69)	18 (27)	16 (23)	5 (7)	5 (7)	3 (4)	2 (3)	20 (29)	0 (0)
Day 7 Total patients (n=62)	15 (24)	15 (24)	3 (5)	4 (6)	3 (5)	2 (2)	20 (34)	0 (0)
Ventilated patients (n=61)	15 (24)	15 (24)	3 (5)	4 (6)	3 (5)	1 (2)	20 (34)	0 (0)

Number of patients (percent).

Table 3 Association between barriers and achieving mobilization

	OR (95% CI) Achieving mobilization within 1 week
Circulatory factors from days 1 to 2	0.59 (0.29–1.17, p=0.14)
Consciousness factors from days 3 to 5	0.38 (0.18–0.78, p=0.01)
Medical staff factors from days 6 to 7	0.49 (0.18–0.92, p=0.01)

OR: odds ratio
CI: confidence interval

Adverse events during rehabilitation (Table 4 and 5)

A total of 994 rehabilitation sessions were conducted over 7 days for 177 patients. There were a total of 25 adverse events (2.5%), including 5 episodes of desaturation, 6 tachypnea or bradypnea, 5 tachycardia or bradycardia, and 9 hypertension or hypotension, occurring in 17 patients. The incidence of adverse events increased from day 1 (0.5%) to day 5 (5.3%) and then decreased to 4.0% on day 7.

Table 4 Adverse events

Variable	Number (%)	Event rate per 1000 rehabilitation sessions
Adverse event		
Total number of adverse events	25 (2.5)	25
Cardiopulmonary arrest, time	0 (0)	0
Fall to knees or ground, time	0 (0)	0
Inadvertent removal of medical devices, time	0 (0)	0
Desaturation, time	5 (0.5)	5
Tachypnea or bradypnea, time	6 (0.6)	6
Tachycardia or bradycardia, time	5 (0.5)	5
Hypertension or hypotension, time	9 (0.9)	9
New arrhythmia, time	0 (0)	0

Number of adverse events (percentage).
There were 994 rehabilitation sessions in the first 7 days of intensive care unit stay.

Table 5 Incidence of adverse events

Variable	Rehabilitation session	Patients (N)	Adverse events
Day 1	195	177	1 (0.5)
Day 2	196	177	3 (1.5)
Day 3	189	162	5 (2.6)
Day 4	142	119	4 (2.8)
Day 5	114	93	6 (5.3)
Day 6	84	72	3 (4.0)
Day 7	74	62	3 (4.0)

Number of patients (percentage).

Other outcomes (Table 6)

The median interval from ICU admission to first time out of bed, or mobilization level, was 5 (3–8) days. Overall, 71% of patients could walk independently at the time of hospital discharge, and the 90-day survival after hospital discharge was 85% (Table 6).

Table 6 Other outcomes

Variable	Total Population n = 177
Time to first rehabilitation	2 [1-3]
Time to first out of bed mobilization, day	5 [3-8]
Highest IMS during ICU stay	3 [1-5]
Duration of mechanical ventilation, day	3 [0-6]
ICU length of stay, day	4 [2-7]
Hospital length of stay, day	33 [20–52]
Nosocomial pneumonia during the hospital stay, n (%)	39 (22)
ICU-AW at ICU discharge, n (%)	67 (38)
Walking independence at hospital discharge, n (%)	125 (71)
Discharge destination, n (%)	
Home	113 (64)
Rehabilitation center	13 (7)
Another hospital	23 (13)
Nursing home	6 (3)
Death	22 (13)
90-days survival after ICU discharge, n (%)	150 (85)

Median (25th–75th percentile) or the number of patients.
IMS: ICU mobility scale
ICU-AW: ICU acquired weakness
ICU: intensive care unit

The relationship between mobilization barriers and outcomes (Table 7)

Circulatory factors from days 1 to 2 (OR 0.95; CI 0.40–2.25, p=0.92), consciousness factors from days 3 to 5 (OR 0.47; CI 0.19–1.15, p=0.10), and medical staff factors from days 6 to 7 (OR 0.58; CI 0.15–2.27, p=0.44) were not significantly associated with 90-day survival. Consciousness factors from days 3 to 5 (OR 0.52; CI 0.25–0.96, p=0.04) were significantly associated with the ability to walk independently at hospital discharge.

Table 7 Association between barriers and outcomes

	OR (95% CI) 90-day survival	OR (95% CI) Achievement of walking independence
Circulatory factors from days 1 to 2	0.95 (0.40–2.25, p=0.92)	0.82 (0.41–1.62, p=0.58)
Consciousness factors from days 3 to 5	0.47 (0.19–1.15, p=0.10)	0.52 (0.25–0.96, p=0.04)
Medical staff factors from days 6 to 7	0.58 (0.15–2.27, p=0.44)	0.64 (0.24–1.70, p=0.36)

OR: odds ratio
CI: confidence interval

DISCUSSION

We focused on the rate of achieving mobilization in the ICU, where a standardized program of early mobilization was conducted, within the first 7 days of ICU stay. This study also reviewed barriers which prevent mobilization and their daily changes. This is the first study to investigate the relationship between daily changes in barriers to mobilization and the rate of mobilization, the incidence of adverse events, and outcomes such as 90-day survival and the ability to walk independently. This study shows that there is a change in barriers during the ICU stay, while the barriers identified are similar to those reported in previous studies.[15-17]

In this study, a total of 116 patients (66%) achieved mobilization within the first 7 days of ICU stay. This study also showed daily changes in the rate of achieving mobilization, which was very low on ICU days 1 (1%) and 2 (7%), increased from days 3 (21%) to 5 (27%), and maintained the same rate on ICU days 6 (27%) and 7 (24%). Observed trends were not associated with a specific reason for admission to the ICU. Although the overall rate of achieving mobilization (66%) is comparable to a prior study,[18] the rate of achieving mobilization on each day was not so high.

Table 2 shows daily changes in barriers which prevent mobilization and this is a unique result of the present study. Circulatory factors were identified in more than half of patients as the main barriers to achieving mobilization on days 1 and 2 in the ICU. Since the SOFA cardiovascular system score was 3 at the time of ICU admission (Supplemental Table 5), most patients were probably hemodynamically unstable requiring vasopressor support. Consistent with an expert consensus which stated that it is difficult to get out of bed, or achieve mobilization when a patient is receiving catecholamines, most patients in this study might not tolerate mobilization.[29] In the presence of circulatory instability, the rate of mobilization is usually low,[38] and passive exercise, cycle ergometer[31] and neuromuscular electrical stimulation[39] is likely to be used. However, the PADIS guidelines state that receiving continuous vasopressors should not prevent the initiation of mobilization if the hemodynamics are stable with the use of vasopressors.[7] Other investigators also concluded that appropriate vasopressor administration could help patients be mobilized.[38] Vasopressor titration protocols combined with optimal selection of the rehabilitation level, especially when catecholamines are needed to stabilize the hemodynamics of the patient, should be a focus of future studies.

Consciousness factors emerged as major barriers from days 3 to 5. The RASS score from day 1 to 2 was very low at "-3" (Supplemental Table 6), but since circulatory status was the more apparent issue, consciousness was thought not to be the major factor on days 1 and 2. Similar to a previous study which showed that deep sedation, with a RASS of -2, was a barrier to mobilization,[40] consciousness factors, with a RASS of -2, could have impeded mobilization in this study. On days 6 and 7, when the RASS was -1 and 0, the major barriers identified changed from consciousness to medical staff factors. In previous studies, most patients that achieved mobilization had a RASS of -1 or higher.[40] As noted in Table 1, as many as 80% of patients were sedated in this study, and deep sedation, which keeps a patient at a low RASS level (e.g. <-2), was a major common barrier to achieving mobilization.[41] The PAD guidelines recommend routine use of a sedation protocol that targets light sedation.[7] However, no study has examined whether an appropriate sedation protocol promotes EM, and its effect remains unknown.[28] The impact of initiating routine use of a sedation protocol in the ICU on mobilization should be studied in the future.

Medical staff factors as barriers to mobilization became evident on days 6 and 7. These results show that even after recovery from hemodynamic instability and consciousness disturbances there are still major barriers. Medical staff barriers, such as lack of cooperation with relevant rehabilitation staff, lack of team leaders, and lack of knowledge, were reported as the main barriers to achieving EM in previous studies.[42-44] Therefore, to achieve mobilization, it is necessary to concentrate not only on patient factors but also on improving the staff structure in the ICU.[45] Previous studies suggested that consultation with other experts such as a psychiatrist and a neurologist improved the team's approach, but the EM system in our hospital currently lacks such a system.[46] In the future, a suitable ICU environment and system associated with EM should be discussed to improve the rates of mobilization. The rate of subjective factors, respiratory factors, device factors, and other problems remained unchanged within the first 7 days of ICU stay in this study.

Previous studies reported that the rate of mobilization can be increased by overcoming barriers to mobilization.[45] It has also been reported that an improved rate of mobilization may lead to improved physical function and shortening of the overall ICU length of stay.[46] This study suggests that improved management of two factors, consciousness and medical staff factors, both of which were significantly associated with achieving mobilization (Table 3), will improve the mobilization rate. Whether overcoming these two barriers leads to an increased rate of mobilization with improved outcomes should be investigated in future studies.

The incidence of adverse events during rehabilitation sessions was low on day 1 (0.5%), gradually increasing to day 5 (5.3%) as the maximum and decreasing on day 7 (4.0%). Passive rehabilitation was mainly performed on days 1 and 2 when circulatory instability resulted in a lower incidence of adverse events as previous studies demonstrated.[21] Even at the same level of RASS from days 3 to 5, achieving mobilization increased gradually, and an aggressive mobilization approach to patients with consciousness disorders might result in an increased rate of adverse events. Additionally, most adverse events detected from days 3 to 7 were associated with hemodynamic instability. Therefore, it is important to note that hemodynamic adverse events occur most frequently even when circulatory factors are not the major barrier to achieving mobilization, suggesting the need for careful monitoring.[30,47]

In this study, there was no relationship between 90-day survival and the three identified barriers to mobilization (circulatory, consciousness, and medical staff factors), while consciousness factors were significantly associated with the walking independence at the time of discharge from the hospital. Several studies reported that achieving early mobilization within one week does not affect survival but is helpful in improving functional prognosis.[19,48] Therefore, it is reasonable that consciousness factors, which are associated with achieving mobilization in the ICU, are associated with walking independence but not 90-day survival. The ability to walk independently is considered one of the most important factors related to returning home for ICU patients.[31,35] The impact of dealing with the consciousness factors on physical function and a causal relationship should be investigated in the future studies.

This study has several limitations. First, strict selection criteria enrolling only 14% of ICU patients could result in significant selection bias and limit the generalizability of this study to other patients and ICUs. Second, there may be unmeasured confounding factors affecting the results. Data regarding medications, use of sedatives and sedation level, assessment of pain, infection, ventilator settings and weaning, and incidence of delirium on a daily basis, should be investigated in a future study.[7,29,39,44]

Third, in this study, we investigated only the primary category of the barrier preventing mobilization. Other barriers which may exist during the rehabilitation session at the same time were not examined. The individual components of each barrier were not assessed. These should be investigated in a future study to efficiently facilitate mobilization in the ICU. Fourth, the outcomes of this study are limited to short-term outcomes. The post intensive care syndrome has become a new challenge in the field of intensive care. This study could not evaluate long-term outcomes after hospital discharge, such as quality of life and functional prognosis.[1,2,4] Finally, this is a single-center, retrospective study without comparison groups, which may limit the ability to generalize these results to other hospitals. A multicenter prospective randomized controlled study, with a greater overall percentage of the ICU patients, is necessary to validate these results and show causality.

CONCLUSIONS

In this study, a total of 116/177 patients (66%) achieved mobilization within the first 7 days of ICU stay, while the rate of achieving mobilization on each day was generally low. This study shows that barriers which limit mobilization during the ICU stay change over time. The major barriers to mobilization are circulatory factors on the first two days of ICU stay, consciousness factors from days 3 to 5, and medical staff factors from days 6 and 7. Multivariate analysis shows that consciousness and medical staff factors are significantly associated with achieving mobilization, and consciousness factors are also associated with the ability to walk independently at hospital discharge.

AUTHOR CONTRIBUTIONS

Authors' contributions WS and KL conducted the study design. WS, KL, MY, KT, NY, AR and SS participate in creating the protocol and introducing the protocol in our ICU. KL helped in the data collection and the statistical analysis. WS, KL, HK, AL, and TK helped in the development of this manuscript and AL also checked the English grammar. KL advised the statistical methods. All authors read and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIALS

The dataset generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was approved by the ethics committee of each participating hospitals and the ethics committee of the Nagoya Medical Center Hospital (Institutional Review Board approval number 96).

ACKNOWLEDGMENTS

The authors would like to thank the study coordinators, Akiko Kada. We would also like to thank the entire ICU staff at Nagoya Medical Center Hospital.

CONFLICTS OF INTEREST

The authors and all co-authors declare no conflict of interest.

REFERENCES

1 Winters BD, Eberlein M, Leung J, et al. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276–1283. doi:10.1097/CCM.0b013e3181d8cc1d
2 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502–509. doi:10.1097/CCM.0b013e318232da75
3 Brahmbhatt N, Murugan R, Milbrandt EB. Early mobilization improves functional outcomes in critically ill patients. *Crit Care*. 2010;14(5):321. doi:10.1186/cc9262
4 Dowdy DW, Eid MP, Dennison CR, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med*. 2006;32(8):1115–1124. doi:10.1007/s00134-006-0217-3
5 Nishida O, Ogura H, Egi M, et al. The Japanese Clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). *Acute Med Surg*. 2018;5(1):3–89. doi:10.1002/ams2.322
6 Barr J, Fraser GL, Puntillo K, et al. American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263–306. doi:10.1097/CCM.0b013e3182783b72
7 Devlin JW, Skrobik Y, Gélinas C, et al. 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(9):e825–e873. doi:10.1097/CCM.0000000000003299
8 Hermans G, De Jonghe B, Bruyninckx F, et al. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev*. 2014;30(1):CD006832. doi:10.1002/14651858
9 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874–1882. doi:10.1016/S0140-6736(09)60658-9
10 Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med*. 2008;36(8):2238–2243. doi:10.1097/CCM.0b013e318180b90e
11 Watanabe S, Morita Y, Suzuki S, et al. Association between early rehabilitation for mechanically ventilated intensive care unit patients and oral ingestion. *Prog Rehabil Med*. 2018;3:1–9. doi:10.2490/prm.20180009
12 Kayambu G, Boots R, Paratz J. Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. *Crit Care Med*. 2013;41(6):1543–1554. doi:10.1097/CCM.0b013e31827ca637
13 Liu K, Ogura T, Takahashi K, et al. A progressive early mobilization program is significantly associated with clinical and economic improvement: a single-center quality comparison study. *Crit Care Med*. 2019;47(9):e744–e752. doi:10.1097/CCM.0000000000003850
14 Alison JA, Kenny P, King MT, et al. Repeatability of the six-minute walk test and relation to physical function in survivors of a critical illness. *Phys Ther*. 2012;92(12):1556–1563. doi:10.2522/ptj.20110410
15 Berney S, Harrold M, Webb S, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. *Crit Care Resusc*. 2013;15(4):260–265.
16 Nydahl P, Ruhl AP, Bartoszek G, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. *Crit Care Med*. 2014;42(5):1178–1186. doi:10.1097/CCM.0000000000000149
17 Crozier TM, Pilcher DV, Bailey MJ, et al. Long-stay patients in Australian and New Zealand intensive care units: demographics and outcomes. *Crit Care Resusc*. 2007;9(4):327–333.
18 Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. *Cardiopulm Phys Ther J*. 2012;23(1):5–13.
19 Okada Y, Unoki T, Matsuishi Y, et al. Early versus delayed mobilization for in-hospital 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

20 Katz PP. Measures of adult general functional status: the Barthel Index, Katz Index of Activities of Daily Living, Health Assessment Questionnaire (HAQ), MACTAR Patient Preference Disability Questionnaire, and Modified Health Assessment Questionnaire (MHAQ). *Arthritis Care Res*. 2003;49 Suppl 5:S15–S27. doi:10.1002/art.11415

21 Liu K, Ogura T, Takahashi K, et al. The safety of a novel early mobilization protocol conducted by ICU physicians: a prospective observational study. *J Intensive Care*. 2018;6:10. doi:10.1186/s40560-018-0281-0

22 Harrold ME, Salisbury LG, Webb SA, 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(1):336. doi:10.1186/s13054-015-1033-3

23 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8

24 Knaus WA, Draper EA, Wagner DP, et al. APACHEII: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–829.

25 Vincent JL, de Mendonga A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793–1800. doi:10.1097/00003246-199811000-00016

26 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond AgitationSedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338–1344. doi:10.1164/rccm.2107138

27 Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. *Heart Lung*. 2014;43(1):19–24. doi:10.1016/j.hrtlng.2013.11.003

28 Taito S, Shime N, Yasuda H, et al. Out-of-bed mobilization of patients undergoing mechanical ventilation with orotracheal tubes: a survey study. *J Crit Care*. 2018;47:173–177. doi:10.1016/j.jcrc.2018.06.022

29 Ad Hoc Committee for Early Rehabilitation, Japanese Society of Intensive Care Medicine. Evidence based expert consensus for early rehabilitation in the intensive care unit [in Japanese]. *J Int Care Med*. 2017;24(2):255–303. doi:10.3918/jsicm.24_255

30 Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med*. 2007;35(1):139–145. doi:10.1097/01.CCM.0000251130.69568.87

31 Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med*. 2009;37(9):2499–2505. doi:10.1097/CCM.0b013e3181a38937

32 Watanabe S, Kotani T, Taito S, et al. Determinants of gait independence after mechanical ventilation in the intensive care unit: Japanese multicenter retrospective exploratory cohort study. *J Intensive Care*. 2019;27:53. doi:10.1186/s40560-019-0404-2

33 Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. *J Neurol Neurosurg Psychiatry*. 2008;79(7):838–841. doi:10.1136/jnnp.2007.142430

34 Patel BK, Pohlman AS, Hall JB, Kress JP. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. *Chest*. 2014;146(3):583–589. doi:10.1378/chest.13-2046

35 Ranhoff AH, Laake K. The Barthel ADL Index: scoring by physician from patient interview is not reliable. *Age Aging*. 1993; 22(3): 171–174. doi:10.3109/09638288809164103

36 Collin C, Wade DT, Davies S, Home V. The Barthel ADL Index : a reliability study. *Int Disabil Stud*. 1988;10(2):61–63. doi:10.1093/ageing/22.3.171

37 Watanabe S, Iida Y, Ito T, et al. Effect of early rehabilitation activity time on critically ill patients with intensive care unit-acquired weakness: a Japanese retrospective multicenter study. *Prog Rehabil Med*. 2018;3:20180003. doi:10.2490/prm.20180003

38 Iida Y, Sakuma K. Skeletal muscle dysfunction in critical illness. In:Tan U. ed. Physical Disabilities - Therapeutic *Implications*. Intech;2017:142–168. doi:10.5772/intechopen.69051

39 Routsi C, Gerovasili V, Vasileiadis I, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Crit Care*. 2010;14(2):R74. doi:10.1186/cc8987

40 TEAM Study Investigators, Hodgson C, Bellomo R, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. *Crit Care*. 2015;19(1):81. doi:10.1186/s13054-015-0765-4

41 Clemmer TP. Why the reluctance to meaningfully mobilize ventilated patients? 'The answer my friend is blowin' in the wind.' *Crit Care Med*. 2014;42(5):1308–1309. doi:10.1097/CCM.0000000000000184

42 Hopkins RO, Spuhler VJ, Thomsen GE. Transforming ICU culture to facilitate early mobility. *Crit Care Clin*. 2007;23(1):81–96. doi:10.1016/j.ccc.2006.11.004
43 Zanni JM, Korupolu R, Fan E, et al. Rehabilitation therapy and outcome in acute respiratory failure: an observation pilot project. *J Crit Care*. 2010;25(2):254–262. doi:10.1016/j.jcrc.2009.10.010
44 Leditschke IA, Green M, Irvine J, Bissett B, Mitchell IA. What are the barriers to mobilizing intensive care patients? *Cardiopulm Phys Ther J*. 2012;23(1):26–29. doi:10.1016/j.ccc.2006.11.00
45 Dubb R, Nydahl P, Hermes C,et al. Barriers and strategies for early mobilization of patients in intensive care units. *Ann Am Thorac Soc*. 2016;13(5):724–730. doi:10.1513/AnnalsATS.201509-586CME
46 Needham DM, Korupolu R, Zanni J, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil*. 2010;91(4):536–542. doi:10.1016/j.apmr.2010.01.002
47 Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med*. 2010;38(11):2089–2094. doi:10.1097/CCM.0b013e3181f270c3
48 Ding N, Zhang Z, Zhang C, et al. What is the optimum time for initiation of early mobilization in mechanically ventilated patients? A network meta-analysis. *PLoS One*. 2019;14(10):e0223151. doi:10.1371/journal.pone.0223151

Supplemental Table 1 Daily care in the Nagoya Medical Center intensive care unit

ICU staff	
Nurses	Nurse-to-patient ratio is 1:2
Doctors	Doctor-to-patient ratio is 1:2 (1–3)
Rehabilitation therapists	One full-time physiotherapist and one half-time speech therapist
Analgesia	ICU doctors use NRS and BPS to assess pain and adjust the dose of analgesics.
Sedation	ICU doctors assess RASS and prescribe sedatives and analgesics based on the assessment.
Agitation and delirium	ICU doctors prescribe or adjust sedatives or antipsychotics based on the assessment of delirium
Mechanical ventilation	No specific ventilation protocols are in place. The ICU physicians adjust the mode or settings based on the patient's condition
General ward rehabilitation	Rehabilitation on the general ward included muscle strength exercises, balance exercises, walking, and stair training only on weekdays for 20 minutes.

ICU: intensive care unit
NRS: numerical rating scale
BPS: behavioral pain scale
RASS: Richmond Agitation Sedation Scale
ICDSC: intensive care delirium screening checklist
ICU day shift staff throughout the study period included ICU physicians (3 intensivists and 1 junior resident), nurses, (including at least one certified in critical care), a physical therapist, a speech therapist, a pharmacist, and a dietitian.

Supplemental Table 2 Nagoya Medical Center- Early Mobilization Protocol

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	**Physical therapy**	**Physical therapy**	**Physical therapy**	**Physical therapy**
Passive ROM exercise Respiratory physical therapy	Positioning Passive ROM exercise Active ROM exercise Respiratory physical therapy continuous lateral rotation therapy	Positioning Passive ROM exercise Active ROM exercise Sitting at side of bed Rising from the supine position	Positioning Passive ROM exercise Active ROM exercise Standing at side of bed Stand and pivot to a chair	Positioning Passive ROM exercise Active ROM exercise Walk with assistance Walk independently
Positioning	**Positioning**	**Positioning**	**Positioning**	**Positioning**
Posture change HOB ≤45 degrees	Posture change HOB ≥60	Posture change HOB ≥60	Posture change HOB ≥60	Posture change HOB ≥60

Step up criterion	Step up criterion	Step up criterion	Step up criterion	Step up criterion
Oxygenation/ hemodynamic stability Can withstand posture change Can withstand HOB ≤45 degrees	Can withstand supplementary motion of physical therapy Can withstand HOB ≤60 degrees Anti-gravity movement possible	Can endure the active movement of physical therapy Can withstand HOB ≤60 degrees Can withstand sitting at side of bed	All exercise can be carried out Can withstand partial weight standing	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 > 10 cm 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

The EM working group, includes ICU physicians, nurses, and physical therapists, discussed how to promote EM in the ICU and created an EM protocol.
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 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. Levels 0 and 1 were performed by physical therapists. Level 2 was done by nurses and physical therapists. Mobilization levels 3, 4, and 5 were performed by ICU physicians, nurses and physical therapists. At all rehabilitation sessions, the patient's hemodynamic and respiratory status and medical devices were monitored by ICU physicians.

Supplemental Table 3 Perceived barriers

List of barriers	Details of barrier
Consciousness factors	Consciousness disorder, RASS: ≤ –3 or ≥+2
Subjective symptoms	Respiratory distress, BPS or > 3 or NRS > 5, fatigue, patient refusal
Respiration factors	SpO_2: <90%; F_IO_2: >0.6; respiratory rate: >30 times/min, ventilator unsynchronized
Circulation factors	Systolic blood pressure: <90 or >180 mmHg; mean blood pressure: <65 or >110 mmHg; heart rate: <50 or >120 beats/min; new arrhythmias; additional administration of vasopressors

Device factors	Catheter, drain, dialysis etc.
Medical staff factors	Lack of staff[a], holidays, many examinations, poor time adjustment
Other	Non-predefined barriers in above, including vomiting, fever, and bleeding

RASS: Richmond Agitation Sedation Scale
NRS: numerical rating scale
BPS: behavioral pain scale
[a] Mobilization at the level of sitting on the edge of the bed or higher (levels 3, 4, and 5) were performed by a team consisting of ICU physicians, nurses, and physical therapists.

Supplemental Table 4 Adverse events

List of adverse events
Cardiopulmonary arrest
Fall to knees or the ground
Inadvertent removal of medical devices
Desaturation (<90%) or more than 10% decrease from the baseline
Bradypnea (<5 breaths/min) or tachypnea (>40 breaths/min)
Bradycardia (<40 beats/min) or tachycardia (>130 beats/min)
Hypotension (systolic blood pressure [SBP]<80 mmHg)
Hypertension (systolic blood pressure>200 mmHg)
New arrhythmia

Supplemental Table 5 Sequential Organ Failure Assessment Scores

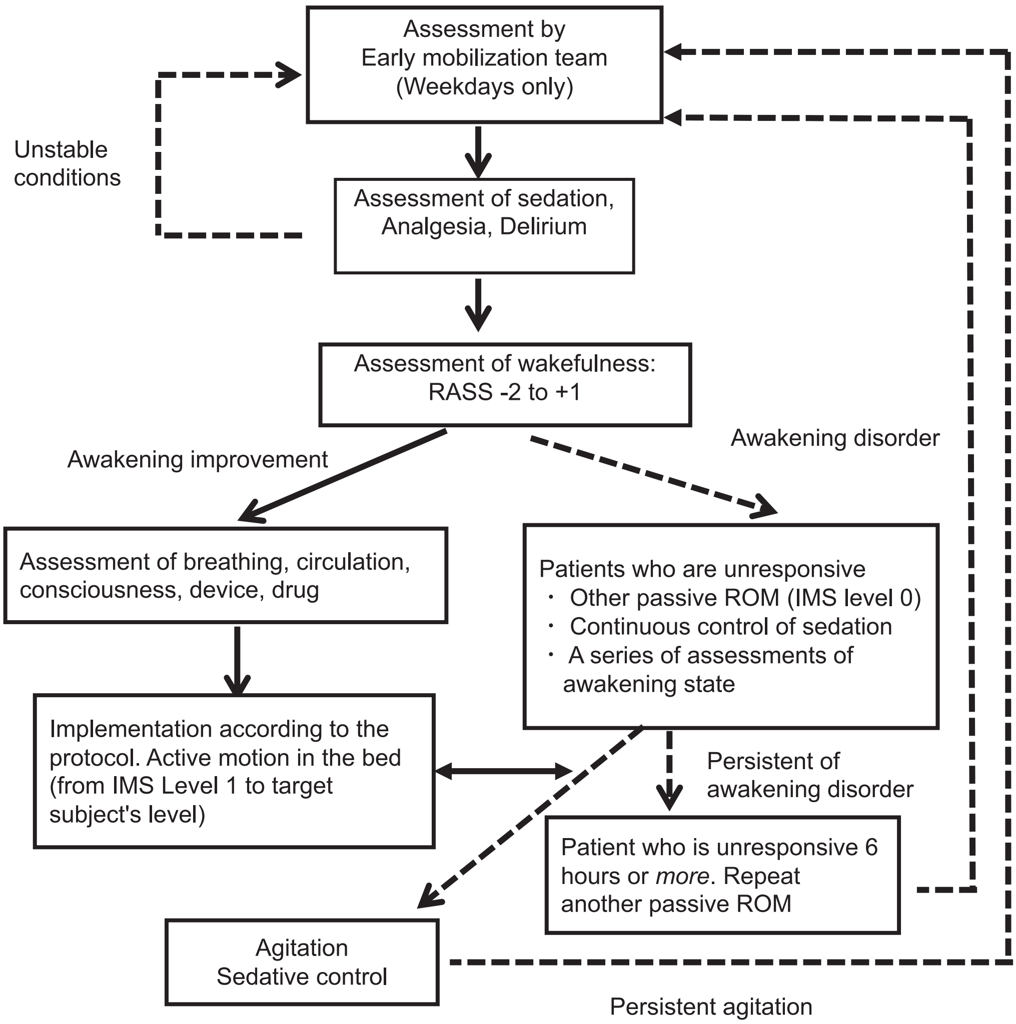
	At ICU admission
SOFA sum	7 [5–9]
SOFA respiratory system	2 [1–2]
SOFA cardiovascular system	3 [0–3]
SOFA liver	0 [0–1]
SOFA kidneys	1 [0–1]
SOFA coagulation	0 [0–1]
SOFA nervous system	1 [0–2]

Median (25th–75th percentile) or the number of patients.
SOFA: Sequential Organ Failure Assessment
ICU: intensive care unit

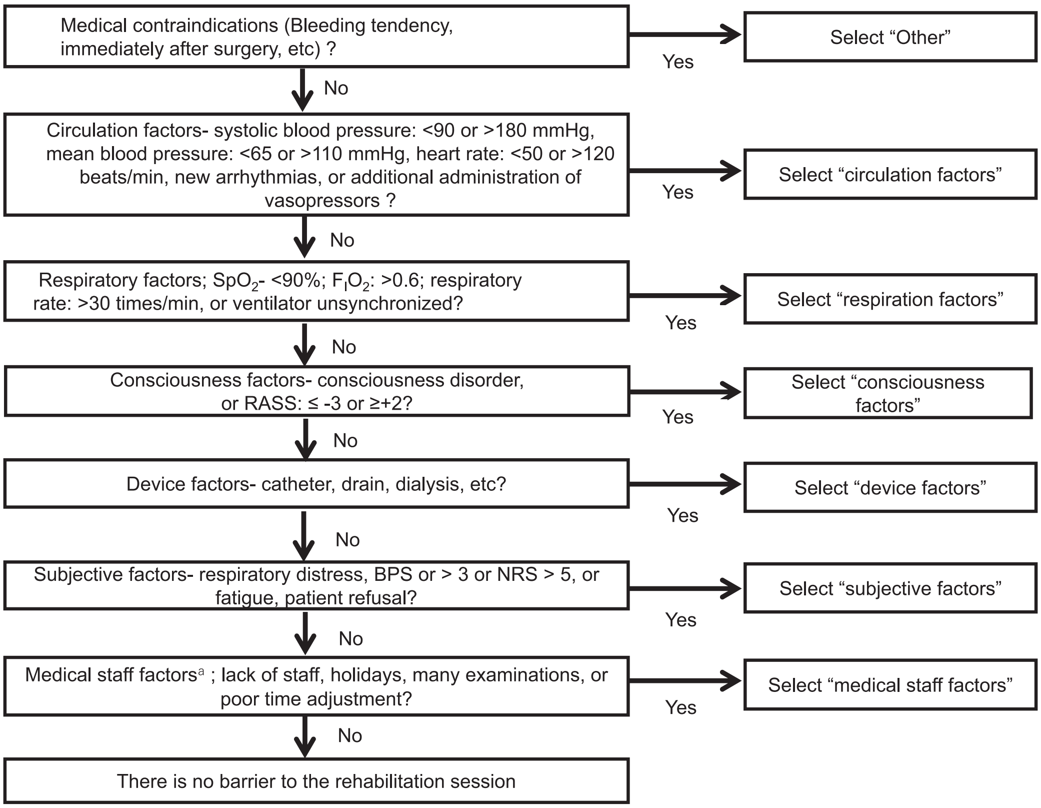
Supplemental Table 6 Changes in median day shift richmond agitation sedation scale from Day 1 to Day 7

	Median RASS
Day 1	–4 [–1 – –4]
Day 2	–3 [–1 – –4]
Day 3	–2 [–1 – –3]
Day 4	–2 [–1 – –3]
Day 5	–2 [–1 – –3]
Day 6	–1 [–2 – 1]
Day 7	0 [–1 – 0]

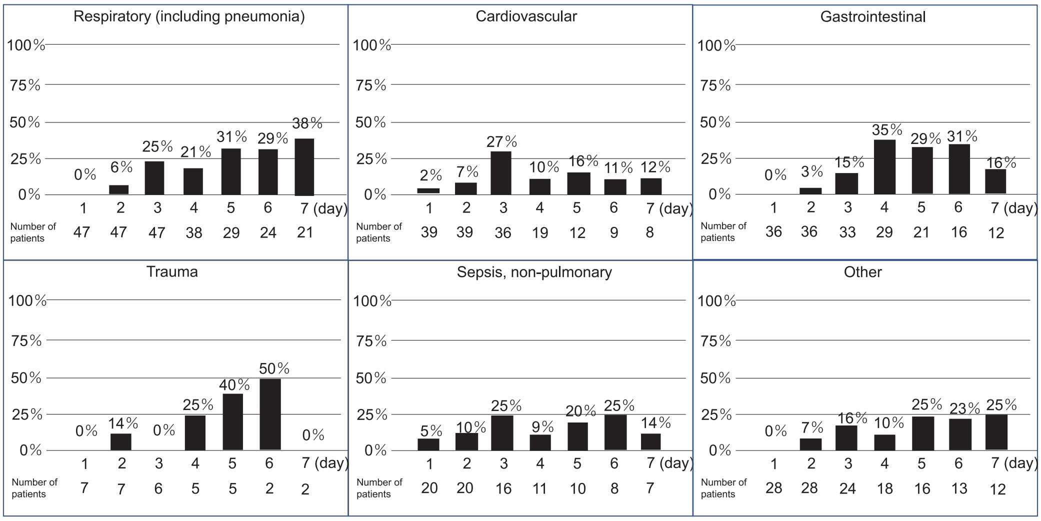
Median (25th–75th percentile) or the number of patients.
RASS: Richmond Agitation Sedation Scale



Supplemental Fig. 1 Early mobilization protocol level decision flowchart
RASS: Richmond Agitation Sedation Scale
ICU: intensive care unit
IMS: ICU mobility scale
ROM: range of motion



Supplemental Fig. 2 Algorithm to determine the primary barrier preventing mobilization
SpO_2: oxygen saturation of peripheral artery
FiO_2: fraction of inspiratory oxygen
RASS: Richmond Agitation Sedation Scale
BPS: behavioral pain scale
NRS: numerical rating scale
The barrier to mobilization was determined by the intensivist in charge of the patient following this algorithm. At every rehabilitation session, only one selected barrier is recorded on the medical records.



Supplemental Fig. 3 Changes in the rate of mobilization by intensive care unit admission diagnosis
We investigated the tendency of rate of mobilization by ICU admission diagnosis.