Clinical Frailty Scale Score Before ICU Admission Is Associated With Mobility Disability in Septic Patients Receiving Early Rehabilitation

Hiroki Nakajima, PT1; Mitsuaki Nishikimi, MD2; Miho Shimizu, PT, MSc3; Kazuhiro Hayashi, PT, MSc3; Takayuki Inoue, PT, PhD1; Kazuki Nishida, MD4; Kunihiro Takahashi, PhD3; Shigeyuki Matsui, PhD5; Yoshihiro Nishida, MD, PhD1; Naoyuki Matsuda, MD, PhD2

Objectives: To clarify the relationship between mobility disability at the time of discharge from the ICU and clinical factors evaluated at ICU admission in septic patients.

Design: A single-center, retrospective, observational study.

Setting: Ten-bed, the emergency and medical ICU.

Patients: We analyzed the data of septic patients who were admitted to our ICU between September 2012 and September 2016 and received early rehabilitation.

Interventions: None.

Measurements and Main Results: The patients were categorized into two groups based on their scores on the ICU mobility scale at the time of discharge from the ICU: the mobility disability group (ICU mobility scale score < 9) and the no mobility disability group (ICU mobility scale score ≥ 9). Of the 110 eligible patients, 63 met the inclusion criteria; of these, 46 patients (73%) were classified into the mobility disability group, and 17 patients (27%) were classified into the no mobility disability group. The age (median, 72 vs 64 yr; p = 0.024), prevalence of patients with clinical frailty scale scores of greater than or equal to 5 (54% vs 12%; p = 0.003), Sequential Organ Failure Assessment score (median, 9.0 vs 6.0; p = 0.006) and rate of vasopressin use (26% vs 0%; p = 0.026) were significantly higher in the mobility disability group as compared with the no mobility disability group. Among the candidate variables for which values recorded before/at the time of ICU admission were available, the clinical frailty scale score was identified as the only independent, statistically significant predictor of mobility disability at ICU discharge (odds ratio, 7.77; 95% CI, 1.37–44.21; p = 0.021). The positive predictive value and negative predictive value of clinical frailty scale scores greater than or equal to 5 for mobility disability at ICU discharge were 92.6% and 41.7%, respectively.

Conclusions: The clinical frailty scale score was associated with increased mobility disability at ICU discharge in septic patients receiving early rehabilitation.

Key Words: clinical frailty scale; early rehabilitation; functional prognosis; intensive care unit mobility scale; mobility disability; sepsis

Sepsis is associated with the highest mortality among critically ill patients admitted to the ICU, with reported mortality rates in the range of 17% to 32% (1, 2). Although the survival rate may have improved with the recent improvements in the intensive care management techniques for sepsis (3, 4), the functional prognosis of these patients remains poor. Prevention of mobility disability is one of the important goals of treatment of sepsis (5, 6).
Numerous recent studies have shown the beneficial effect of early rehabilitation for obtaining a good functional prognosis in sepsis patients (7, 8). Based on the results of a double-blind, randomized controlled trial, Kayambu et al (7) reported that early rehabilitation, as compared with standard care, was associated with improved physical functioning of patients with sepsis, as assessed by the SF-36 medical short-form, at 6 months. Another study, a prospective observational study, reported that early rehabilitation in patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of greater than or equal to 10 were associated with improved scores on the modified Barthel Index and the Functional Independence Measure at hospital discharge (8). Therefore, the Japanese sepsis guidelines 2016 (9) suggest early rehabilitation for improving the functional prognosis of patients with sepsis admitted to the ICU.

Although several risk factors for the functional outcomes of ICU patients have been reported by previous studies (10–15), until date, there has been no study focusing on patients with sepsis admitted to the ICU, who often show worse functional outcomes than patients with other categories of illnesses (16). Furthermore, early rehabilitation is a new therapeutic strategy for improving the functional outcomes of sepsis patients admitted to the ICU, and there are few studies yet that have focused on patients receiving early rehabilitation (7, 8). In view of the likelihood of early rehabilitation becoming widespread for sepsis patients in the future, we considered it worthwhile to explore the risk factors for mobility disability in sepsis-3-defined (17) septic patients receiving early rehabilitation.

Therefore, the objective of this study was to investigate the relationships between newly developing mobility disability at ICU discharge and variables measured at the time of admission in sepsis-3-defined septic patients receiving early rehabilitation.

**MATERIALS AND METHODS**

**Study Design**
A single-center, retrospective, observational study was performed to analyze the data of septic patients who were admitted to our emergency and medical ICU between September 2012 and September 2016. This study was conducted with the approval of the Ethics Committee of Nagoya University Hospital (approval number 0321). All eligible patients were more than 18 years old, were diagnosed as having sepsis at ICU admission, and received early rehabilitation. The diagnosis of sepsis was made in accordance with the criteria described in the Surviving Sepsis Campaign guidelines for the management of sepsis (17). The excluded cases are shown in Figure 1, and consisted of pediatric patients (< 18 yr old), patients who died before measurement of the ICU mobility scale (IMS) score at ICU discharge due to severe sepsis, patients who were unable to walk without assistance before ICU admission, and patients for whom records of the assessment of mobility disability at ICU discharge were not available.

**Data Collection**
Study data, including the clinical history, laboratory data, and data on the vital signs, clinical treatment, and outcomes, were collected retrospectively from the electronic medical records of Nagoya University Hospital. The degree of frailty of the subjects was routinely assessed at the time of admission to the ICU on a scale of 1 (very fit) to 9 (terminally ill) using the clinical frailty scale (CFS) (18). A CFS score of greater than or equal to 5 was used to designate a patient as frail (19, 20). A physical therapist (PT) who had received the relevant training at the Department of Geriatrics of our university hospital assigned the CFS scores, based on information obtained from the electronic medical records. The CFS score was determined 1 week prior to admission of the patient to the ICU (21). All the vital signs and laboratory variables were measured at ICU admission. The worst APACHE II score and Sequential Organ Failure Assessment (SOFA) scores calculated within 24 hours after ICU admission were used for the analysis.

**Outcome**
At the time of discharge from the ICU, the score on the IMS was calculated by the attending nurse and PT in early rehabilitation, and
the specialized PT assigned the IMS scores based on information obtained from the medical records. The IMS is a sensitive 11-point ordinal scale, with the score ranging from 0 (lying/pasive exercises in bed) to 10 (independent ambulation). Patients with IMS scores of less than 9 were classified into the mobility disability group, while those with IMS scores of greater than or equal to 9 were classified into the no mobility disability group (22). We used the IMS score cutoff of 9 in our study, because this cutoff has been shown to be clinically significant for discriminating between patients who can and cannot walk independently at ICU discharge (23, 24).

Rehabilitation Procedures During Hospitalization
In this study, we defined “early rehabilitation” as rehabilitation started within 48 hours after ICU admission, by reference to previous studies (25, 26). Early rehabilitation was performed according to our institutional protocol. In summary, our early rehabilitation protocol was instituted within 48 hours according to the ICU doctor’s approval without any clinical risks. Early rehabilitation was undertaken according to the functional ability grade (1 to 5) of the patients, as follows; grade 1 (patient unable to perform active movements): change of position and passive movements of each limb were performed; grade 2 (patient able to perform active movements): active range of motion of each limb; grade 3: sitting at the edge of the bed; grade 4: transferring from sitting to standing; grade 5: trial of ambulation. The PT sessions lasted for 20–40 minutes a day and were administered on 6 days of the week.

The following criteria were used to limit or withhold the early rehabilitation program: deteriorated hemodynamic or ventilatory status, defined as hypoxia with frequent desaturations to below 88%, hypotension, need for extracorporeal membrane oxygenation devices, need for increasing the doses of vaspressors, new documented myocardial infarction based on electrocardiographic and enzyme level changes, dysrhythmias requiring the use of new additional antiarrhythmic agents, and inspired oxygen fraction greater than 0.60 (27). The early rehabilitation program was resumed if/when the status recovered and continued until hospital discharge.

Statistical Analysis
Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables were performed. In order to identify independent risk factors for mobility disability at ICU discharge in the septic patients, we performed multivariate logistic regression analysis using all the candidate variables that were identified as being statistically significant by the univariate analyses. All the reported p values were two-sided, and a p value of less than 0.05 was regarded as denoting a statistically significant difference. All analyses were conducted using SPSS (Version 24.0 for Microsoft Windows; SPSS, Chicago, IL).

RESULTS
A total of 110 patients with sepsis were admitted to our ICU between September 2012 and September 2016. Of these, 47 patients were excluded because they were pediatric patients (age < 18 yr, n = 3), died before assessment of the IMS score at ICU discharge due to severe sepsis (n = 18), were unable to walk without assistance even prior to the ICU admission (n = 16), or their records of assessment of mobility disability at ICU discharge were unavailable (n = 10). The remaining 63 patients were included in this study (Fig. 1).

The baseline characteristics of the 63 patients are summarized in Table 1. Most of the subjects were male (65%), with a median age of 70.0 years (interquartile range [IQR], 62.0–79.0 yr), median hospital stay of 4.0 days (2.0–12.0 d), median APACHE II score of 31.0 (24.0–33.0), and median SOFA score of 8.0 (6.0–10.0). Of the 63 patients, 46 (73%) were classified into the mobility disability

| TABLE 1. Characteristics of the Patients |
|----------------------|-------------------------|
| Characteristics before ICU admission | Total Patients (n = 63) |
| Age, yr, median (IQR) | 70.0 (62.0–79.0) |
| Body mass index, kg/m², median (IQR) | 21.3 (18.1–24.7) |
| Male gender, n (%) | 41 (65) |
| Source sepsis, n (%) | Respiratory 15 (24) |
| | Urinary 15 (24) |
| | Gastrointestinal 21 (33) |
| | Skin/soft tissue 6 (10) |
| | Bloodstream infection 5 (8) |
| | Bone/joint 3 (5) |
| | Clinical frailty scale score, median (IQR) 4.0 (4.0–5.0) |
| | Clinical frailty scale score ≥ 5, n (%) 27 (43) |
| Characteristics during ICU admission | Acute Physiology and Chronic Health Evaluation II score, median (IQR) 31.0 (23.5–33.0) |
| | Sequential Organ Failure Assessment score, median (IQR) 8.0 (6.0–10.0) |
| Septic shock, n (%) | 23 (37) |
| Medication, n (%) | Any dopamine use 2 (3) |
| | Any dobutamine use 2 (3) |
| | Any noradrenaline use 42 (67) |
| | Any epinephrine use 3 (5) |
| | Any vasopressin use 12 (19) |
| | Length of ICU stay, d, median (IQR) 4.0 (2.0–12.0) |
| Characteristics at ICU discharge | ICU mobility scale score, median (IQR) 5 (3–9) |
| | Length of hospital stay, d, median (IQR) 35.0 (18.0–57.0) |
| Transfer to another hospital, n (%) | 23 (44) |

IQR = interquartile range.
group, and the remaining 17 patients (27%) were classified into the no mobility disability group (Tables 2 and 3). The percentages of patients discharged to return to their homes/ transferred to another hospital in the mobility ability group were as follows: 32% (n = 15)/46% (n = 21). The hospital mortality was 22% (n = 10). The percentages of patients discharged to return to their homes/ transferred to another hospital in the no mobility disability group were as follows: 88% (n = 15)/12% (n = 2), and the hospital mortality was 0% (n = 0).

Univariate analysis was performed for identifying the candidate variables (Tables 2 and 3). The median age, prevalence of patients with CFS scores of greater than or equal to 5, SOFA score, and rate of vasopressin use were all higher in the mobility disability group as compared with the no mobility disability group. Multivariate logistic regression analysis was performed using these 4 variables. Only the CFS score measured before ICU admission was identified as an independent risk factor for mobility disability at ICU discharge (odds ratio, 7.77; 95% CI, 1.37–44.21; p = 0.021) (Table 4). We performed the Hosmer-Lemeshow goodness-of-fit test for the logistic regression model; the p value was determined to be 0.511. Post hoc power analysis was calculated as 89.5% based on the observed odds ratio (or effect size) of 8.929 on the association between mobility disability and the CFS score (< 5 or ≥ 5), when a chi-square test was performed with a two-sided alpha error of 5%.

### DISCUSSION

Sepsis is defined as a pathophysiological state of organ failure caused by infection, according to the Sepsis-3 definition (17); this definition of sepsis was used in this retrospective observational research, which was conducted to identify predictors of mobility ability at ICU discharge in septic patients. Several studies have been conducted to investigate the risk factors for mortality in septic patients (28–31), however, no study has been conducted to identify the predictors of mobility disability at ICU discharge in septic patients (as defined according to the Sepsis-3 definition of organ failure). Multivariate analysis in this study identified the CFS score was an independent associated with mobility disability at ICU discharge in septic patients receiving early rehabilitation.

### TABLE 2. Comparison With No Mobility Disability and Mobility Disability Groups Before ICU Admission

| Variables                              | No Mobility Disability (n = 17) | Mobility Disability (n = 46) | p    |
|----------------------------------------|---------------------------------|------------------------------|------|
| Age, yr, median (IQR)                  | 64.0 (58.5–70.5)                | 72.0 (64.0–80.0)             | 0.026|
| Body mass index, kg/m², median (IQR)   | 22.1 (18.5–25.2)                | 21.6 (17.9–24.6)             | 0.562|
| Male gender, n (%)                     | 10 (59)                         | 31 (67)                      | 0.488|
| Comorbidity, n (%)                     |                                 |                              |      |
| Diabetes                               | 5 (29)                          | 11 (24)                      | 0.747|
| Respiratory disease                    | 3 (18)                          | 12 (26)                      | 0.740|
| Cancer                                 | 3 (18)                          | 18 (39)                      | 0.139|
| Chronic kidney disease                 | 2 (12)                          | 10 (22)                      | 0.487|
| Cardiac disease                        | 3 (18)                          | 8 (17)                       | 1.000|
| Neurologic disease                     | 2 (12)                          | 10 (22)                      | 0.487|
| Clinical frailty scale score ≥ 5, n (%)| 2 (12)                          | 25 (54)                      | 0.003|
| Source of sepsis, n (%)                |                                 |                              |      |
| Respiratory                            | 3 (18)                          | 12 (26)                      | 0.740|
| Urinary                                | 5 (29)                          | 10 (22)                      | 0.523|
| Gastrointestinal                       | 6 (35)                          | 15 (33)                      | 1.000|
| Skin/soft tissue                       | 2 (12)                          | 4 (9)                        | 0.657|
| Bloodstream infection                  | 1 (6)                           | 4 (9)                        | 1.000|
| Bone/joint                             | 0 (0)                           | 3 (7)                        | 0.557|

IQR = interquartile range.

p values less than 0.05 are indicated in bold.
The CFS is an effective and easily available measure of frailty, consisting of various clinical items, including the patients’ cognition, mobility, physical functioning, and comorbidities (18). Several studies have reported the usefulness of the CFS for predicting the functional prognosis in ICU patients (13, 19, 20). However, all these studies included all critical care patients, regardless of the underlying disease, and none of the studies was conducted on sepsis patients alone. In addition, the CFS is a useful

### TABLE 3. Comparison With No Mobility Disability and Mobility Disability Groups During ICU Admission

| Variables                        | No Mobility Disability (n = 17) | Mobility Disability (n = 46) | p    |
|----------------------------------|---------------------------------|-----------------------------|------|
| Mean blood pressure, mm Hg       | 67.0 (60.5–79.5)                | 62.0 (49.8–75.3)            | 0.116|
| \(\text{Pao}_2\), mm Hg          | 86.3 (77.7–100)                 | 97.9 (79.9–140)             | 0.234|
| \(\text{pH}\)                    | 7.43 (7.38–7.46)                | 7.33 (7.35–7.44)            | 0.084|
| Creatinine, mg/dL                | 1.25 (0.87–2.00)                | 1.93 (0.83–3.14)            | 0.193|
| Hematocrit, %                    | 29.7 (26.3–36.7)                | 30.9 (27.5–36.6)            | 0.969|
| WBC, \(\times 10^9/\mu\text{L}\) | 12.7 (7.6–22.2)                 | 13.7 (5.28–20.0)            | 0.481|
| Glasgow Coma Scale               | 15 (14–15)                      | 14 (11–15)                  | 0.290|
| Sequential Organ Failure Assessment score | 6.0 (4.5–9.0)  | 9.0 (7.0–10.3)               | 0.006|
| \(\text{Pao}_2/\text{FiO}_2\)   | 357 (275–397)                   | 254 (176–372)               | 0.091|
| Platelet, \(\times 10^4/\mu\text{L}\) | 124 (88–223)                 | 116 (57–175)                | 0.154|
| Total bilirubin, mg/dL           | 0.9 (0.6–1.6)                   | 1.1 (0.6–1.9)               | 0.669|
| Albumin, g/dL                    | 2.6 (2.2–2.9)                   | 2.6 (2.0–2.9)               | 0.514|
| Blood glucose, mg/dL             | 137 (106–180)                   | 115 (91–148)                | 0.100|
| C-reactive protein, mg/dL        | 18.9 (13.9–23.9)                | 18.6 (9.3–22.7)             | 0.775|
| Hemoglobin, g/dL                 | 9.5 (8.5–11.4)                  | 10.1 (8.8–10.7)             | 0.883|
| Lactate, g/dL                    | 1.7 (1.0–3.2)                   | 1.8 (1.1–3.3)               | 0.711|
| International normalized ratio   | 1.3 (1.2–1.4)                   | 1.4 (1.2–1.6)               | 0.255|
| Procalcitonin, ng/mL             | 18.9 (3.5–41.4)                 | 20.5 (4.3–62.9)             | 0.804|
| \(\text{Paco}_2\), mm Hg        | 32.6 (29.5–35.8)                | 32.2 (26.7–37.5)            | 0.670|
| Septic shock                     | 5 (8)                           | 18 (29)                     | 0.567|

**Medication**

| Variables                      | No Mobility Disability | Mobility Disability | p    |
|--------------------------------|------------------------|---------------------|------|
| Any dopamine use               | 1 (6)                  | 1 (2)               | 0.470|
| Any dobutamine use             | 0 (0)                  | 2 (4)               | 1.000|
| Any noradrenaline use          | 9 (53)                 | 33 (72)             | 0.229|
| Noradrenaline dose             | 0.02 (0.00–0.06)        | 0.07 (0.00–0.17)    | 0.056|
| Any epinephrine use            | 0 (0)                  | 3 (7)               | 0.557|
| Any vasopressin use            | 0 (0)                  | 12 (26)             | 0.026|
| Any midazolam use              | 0 (0)                  | 6 (13)              | 0.178|
| Any corticosteroid use         | 2 (12)                 | 14 (30)             | 0.195|
| Any muscle relaxant use        | 0 (0)                  | 4 (9)               | 0.567|
| Use of mechanical ventilation  | 4 (24)                 | 18 (39)             | 0.354|
| Duration of mechanical ventilation, d | 5.0 (2.8–9.5)   | 13.0 (4.0–24.0)     | 0.373|
| Use of renal replacement therapy | 3 (18)                | 18 (39)             | 0.139|
| Use of extracorporeal membrane oxygenation | 0 (0)      | 1 (2)               | 1.000|

Data are presented as median values (interquartile range) or n (%). p values less than 0.05 are indicated in bold.
we did not evaluate whether early rehabilitation itself improved the functional decline of septic patients. Such objective information about a high risk for poor functional outcomes and allow more appropriate rehabilitation plans to be devised for such patients in the early phase after ICU admission, during the ICU stay, after ICU discharge and after hospital discharge.

TABLE 4. Binary Logistic Regression Analysis for the Mobility Disability Group

| Variables                                | OR (95% CI)      | p     |
|------------------------------------------|------------------|-------|
| Age, yr                                  | 0.99 (0.93–1.05) | 0.622 |
| Clinical frailty scale score ≥ 5         | 7.77 (1.37–44.21) | 0.021a|
| Sequential Organ Failure Assessment score | 0.80 (0.63–1.01)  | 0.061 |
| Any vasopressin use                      | 0.999            |       |

OR = odds ratio.
aClinical frailty scale score was identified as an independent statistically significant variable.

Four before ICU admission and during ICU admission variables that were identified as being significant by univariate analysis with \(p < 0.05\) (i.e., age, clinical frailty scale score, Sequential Organ Failure Assessment score, any vasopressin use) were entered into the binary logistic regression models. Boldface value indicates \(p < 0.05\).

scale to determine the risk of mobility disability at the time of discharge from the ICU in septic patients who were able to walk independently prior to ICU admission.

Frailty is characterized by a loss of physiologic reserves, and consequently, an inability to maintain homeostasis to combat disease or injury (32, 33). According to previous studies, the overall prevalence of frailty in a community-dwelling population was 6.9% (32), whereas that in patients with critical illness was 23–30% (14, 15). In another study, frailty in critically ill patients before ICU admission was associated with increased disability after discharge from the ICU (12), which may suggest the importance of early recognition of frailty in critically ill patients for predicting their future functional prognosis (34). Our results suggested that the CFS score recorded prior to ICU admission may be useful for estimating the risk of mobility disability at the time of a patient’s discharge from the ICU. We excluded any patients who were not able to walk independently prior to admission to the ICU in our study. Although it may be meaningless to show that those who were not able to walk independently prior to ICU admission were still unable to walk at the time of discharge from the ICU, we considered it worthwhile to illustrate that the CFS score was independently associated with mobility disability at the time of discharge from the ICU, even after we excluded patients who were unable to walk independently prior to admission to the ICU, consistent with previous reports (35, 36). Besides, it is also noteworthy that our multivariate logistic regression analysis showed that the CFS score was a stronger risk factor than age or severity of illness, which are also known as predictors of mobility disability in ICU patients. Early recognition of frailty using the CFS score may help identify targets for interventions to reduce the functional decline of septic patients.

The results of this study identified the CFS score as an independent risk factor for mobility disability at ICU discharge in septic patients, even if they received early rehabilitation. Such objective information about a poor functional prognosis would be very important for the ICU staff, including ICU doctors, nurses, and PTs engaged in the management of patients with sepsis. Although we did not evaluate whether early rehabilitation itself improved the functional outcomes of these patients or not, we believe that early rehabilitation is beneficial for septic patients with frailty, consistent with previous reports (37–39). CFS scores greater than or equal to 5 is a good predictor for identifying septic patients at risk of mobility disability at ICU discharge. In regard to specific plans, for patients with CFS scores greater than or equal to 5, early rehabilitation plus electrical muscle stimulation and/or exercises using a cycle ergometer of the leg muscles would be considered. In a previous study, it was shown that electrical muscle stimulation (40, 41) and exercises using a cycle ergometer (42) may improve the muscle function in critically ill patients. Therefore, these intervention plans may prevent mobility disability via improved muscle function. But, on the other hand, CFS scores of less than 5 cannot sufficiently predict the possibility of mobility disability at ICU discharge. In patients with CFS scores of less than 5, the risk would need to be evaluated more precisely with a combination of risk factors, including the CFS score. In the future, the development of an intervention strategy based on the CFS score information is expected in septic patients receiving early rehabilitation.

As sepsis is one of the most common diagnoses in critically ill patients, to investigate the relationship between sepsis and frailty may be important. The pathologic condition of "sepsis" can influence the patients’ frailty via many pathophysiological mechanisms, including via causing muscle atrophy by inducing a hypercatabolic state during the acute phase of systemic inflammatory response to infection (43–45), via causing prolonged immobility due to the large amounts of sedatives and muscle relaxant drugs used in intensive care (46), via direct attack of the CNS and muscle by the pathogen, via endotoxin-induced multiple organ failure (47), via causing decline in cognitive function caused by sepsis-associated encephalopathy (the pathophysiology of which is not yet completely understood) (48), and so on. In order to prevent deterioration of the functional outcome by these factors, it may be useful to devise a rehabilitation plan and optimize it to suit individual patients. Our results suggest the possibility that sharing the objective information about a high CFS would enable ICU physicians to identify patients with sepsis in the ICU who are at a high risk for poor functional outcomes and allow more appropriate rehabilitation plans to be devised for such patients in the early phase after ICU admission, during the ICU stay, after ICU discharge and after hospital discharge.

There were several limitations of this study. First, the primary endpoint was the outcome at ICU discharge, and it may be better to set a longer-term endpoint (13, 19, 20). Second, the results of this study identified the CFS score as an independent risk factor for mobility disability at ICU discharge even in patients who received early rehabilitation. However, we did not evaluate whether early rehabilitation by itself improved the functional outcome or not in frail patients. Also, although large multicenter research is expected, the adaptation and protocols of early rehabilitation vary among studies in the present conditions (49–51). Formal rehabilitation protocols may be necessary to perform a large multicenter study for septic patients receiving early rehabilitation. Third, our study was a retrospective study conducted on a small sample at a single medical center. Although the sample size and the power were sufficient, there is a possibility of potential loss of generalizability. Fourth, we did not adopt other frailty measures such as the Fried frailty index (32) or the Total Kihon checklist.
score (52) because this study was designed as a retrospective study and CFS was the only information that we could gather as a scale for the frailty. We believe that the CFS is the most suitable scale for evaluating the severity of morbidity because the score on this scale is the easiest and simplest to calculate (18). But, it remains one of the limitations of our study that we did not examine other scales to determine the patients’ morbidity in our study, and it would be interesting to compare the predictive accuracy of CFS versus other scales in the future. Fifth, we did not monitor the IMS score during follow-up. It would be of great interest to investigate, in the future, functional trajectories of the CFS score measured before ICU admission and of the IMS score measured after ICU admission. Clarification of this point would help in predicting the recovery process toward mobility in septic patients receiving early rehabilitation.

CONCLUSIONS

The CFS score was independently associated with increased mobility disability at ICU discharge in septic patients receiving early rehabilitation. Patients with a high CFS score are needed to provide a more comprehensive plan.

ACKNOWLEDGMENTS

We express our gratitude to Dr. Atsushi Numaguchi (Department of Emergency and Critical Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan) for his clinical assistance.

REFERENCES

1. Stevenson EK, Rubenstein AR, Radin GT, et al: Two decades of mortality trends among patients with severe sepsis: A comparative meta-analysis. Crit Care Med 2014; 42:625–631
2. Fleischmann C, Scherag A, Adhikari NK, et al; International Forum of Acute Care Trials: Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193:259–272
3. Kaukonen KM, Bailey M, Suzuki S, et al: Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 2014; 311:1308–1316
4. Iwashyna TJ, Cooke CR, Wunsch H, et al: Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc 2012; 60:1070–1077
5. Heyland DK, Hopman W, Coo H, et al: Long-term health-related quality of life in survivors of sepsis. Short form 36: A valid and reliable measure of health-related quality of life. Crit Care Med 2000; 28:3599–3605
6. Borges RC, Carvalho CR, Colombo AS, et al: Physical activity, muscle strength, and exercise capacity 3 months after severe sepsis and septic shock. Intensive Care Med 2015; 41:1433–1444
7. Kayambu G, Boots R, Paratz J: Early physical rehabilitation in intensive care patients with sepsis syndromes: A pilot randomised controlled trial. Intensive Care Med 2015; 41:865–874
8. Ahn JY, Song JE, Ann HW, et al: Effects of early exercise rehabilitation on functional recovery in patients with severe sepsis. Yonsei Med J 2018; 59:843–851
9. 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; 5:3–89
10. Wilson ME, Barwise A, Heise KJ, et al: Long-term return to functional baseline after mechanical ventilation in the ICU. Crit Care Med 2018; 46:562–569
11. Fan E, Dowdy DW, Colantuoni E, et al: Physical complications in acute lung injury survivors: A two-year longitudinal prospective study. Crit Care Med 2014; 42:849–859
12. Baldwin MR, Reid MC, Westlake AA, et al: The feasibility of measuring frailty to predict disability and mortality in older medical intensive care unit survivors. J Crit Care 2014; 29:401–408
13. Bagshaw SM, Stelfox HT, McDermid RC, et al: Association between frailty and short- and long-term outcomes among critically ill patients: A multicentre prospective cohort study. CMAJ 2014; 186:E95–102
14. Brummel NE, Bell SP, Girard TD, et al: Frailty and subsequent disability and mortality among patients with critical illness. Am J Respir Crit Care Med 2017; 196:64–72
15. Le Maguet P, Roquilly A, Lasocki S, et al: Prevalence and impact of frailty on mortality in elderly ICU patients: A prospective, multicenter, observational study. Intensive Care Med 2014; 40:674–682
16. Solverson KJ, Grant C, Doig CJ: Assessment and predictors of physical functioning post-hospital discharge in survivors of critical illness. Ann Intensive Care 2016; 6:92
17. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016; 315:801–810
18. Rockwood K, Song X, MacKnight C, et al: A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173:489–495
19. Bagshaw SM, Stelfox HT, Johnson JA, et al: Long-term association between frailty and health-related quality of life among survivors of critical illness: A prospective multicenter cohort study. Crit Care Med 2015; 43:973–982
20. Bagshaw M, Majumdar SR, Rolfsen DB, et al: A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care 2016; 20:175
21. Shears M, Takaoka A, Rochwerg B, et al; Canadian Critical Care Trials Group: Assessing frailty in the intensive care unit: A reliability and validity study. J Crit Care 2018; 45:197–203
22. Hodgson C, Needham D, Haines K, et al: Feasibility and inter-rater reliability of the ICU mobility scale. Heart Lung 2014; 43:19–24
23. Rockwood K, Stadnyk K, MacKnight C, et al: A brief clinical instrument to classify frailty in elderly people. Lancet 1999; 353:205–206
24. Mahoney JE, Sager MA, Jalaluddin M: New walking dependence associated with hospitalization for acute medical illness: Incidence and significance. J Gerontol A Biol Sci Med Sci 1998; 53:M307–M312
25. Hodgson CL, Berney S, Harrold M, et al: Clinical review: Early patient mobilization in the ICU. Crit Care 2013; 17:207
26. Cameron S, Ball I, Cepinskas G, et al: Early mobilization in the critical care unit: A review of adult and pediatric literature. J Crit Care 2015; 30:664–672
27. 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; 36:2238–2243
28. Drewry AM, Fuller BM, Skrupky LP, et al: The presence of hypothermia within 24 hours of sepsis diagnosis predicts persistent hypothermia. Crit Care Med 2015; 43:1165–1169
29. Sakhija A, Kumar G, Gupta S, et al: Acute kidney injury requiring dialysis in severe sepsis. Am J Respir Crit Care Med 2015; 192:951–957
30. Houwink AP, Rijkenberg S, Bosman RJ, et al: The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: A retrospective cohort analysis. Crit Care 2016; 20:56
31. Ho KM, Lee KY, Dobb GJ, et al: C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: A prospective cohort study. Intensive Care Med 2008; 34:481–487
32. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group: Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56:M146–M156
33. Clegg A, Young J, Illife S, et al: Frailty in elderly people. Lancet 2013; 381:752–762
34. Muscedere J, Waters B, Varambally A, et al: The impact of frailty on intensive care unit outcomes: A systematic review and meta-analysis. Intensive Care Med 2017; 43:1105–1122
35. Ferrante LE, Pisani MA, Murphy TE, et al: Functional trajectories among older persons before and after critical illness. *JAMA Intern Med* 2015; 175:523–529.

36. Ferrante LE, Pisani MA, Murphy TE, et al: The association of frailty with post-ICU disability, nursing home admission, and mortality: A longitudinal study. *Chest* 2018; 153:1378–1386.

37. Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, et al: Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: A randomized clinical trial. *JAMA Intern Med* 2019; 179:28–36.

38. Ferrante LE, Pisani MA, Murphy TE, et al: The association of frailty with post-ICU disability, nursing home admission, and mortality: A longitudinal study. *Chest* 2018; 153:1378–1386.

39. Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, et al: Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: A randomized clinical trial. *JAMA Intern Med* 2019; 179:28–36.

40. Goldfarb M, Afilalo J, Chan A, et al: Early mobility in frail and non-frail older adults admitted to the cardiovascular intensive care unit. *J Crit Care* 2018; 47:9–14.

41. Joseph B, Jehan FS: The mobility and impact of frailty in the intensive care unit. *Surg Clin North Am* 2017; 97:1199–1213.

42. Rodriguez PO, Setten M, Maskin LP, et al: Muscle weakness in septic patients requiring mechanical ventilation: Protective effect of transcutaneous neuromuscular electrical stimulation. *J Crit Care* 2012; 27:319–e1–e8.

43. Burtin C, Clerckx B, Robbeets C, et al: Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009; 37:2499–2505.

44. Callahan LA, Supinski GS: Sepsis-induced myopathy. *Crit Care Med* 2009; 37:S354–S367.

45. Tennilä A, Salmi T, Pettilä V, et al: Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. *Intensive Care Med* 2000; 26:1360–1363.

46. Latronico N, Bolton CF: Critical illness polyneuropathy and myopathy: A major cause of muscle weakness and paralysis. *Lancet Neurol* 2011; 10:931–941.

47. Needham DM: Mobilizing patients in the intensive care unit: Improving neuromuscular weakness and physical function. *JAMA* 2008; 300:1685–1690.

48. Witt NJ, Zochodne DW, Bolton CF, et al: Peripheral nerve function in sepsis and multiple organ failure. *Chest* 1991; 99:176–184.

49. Iacobone E, Bailly-Salin J, Polito A, et al: Sepsis-associated encephalopathy and its differential diagnosis. *Crit Care Med* 2009; 37:S331–S336.

50. Bakhrui RN, Wiebe DJ, McWilliams DJ, et al: An environmental scan for early mobilization practices in U.S. ICUs. *Crit Care Med* 2015; 43:2360–2369.

51. Taito S, Sanui M, Yasuda H, et al: Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group: Current rehabilitation practices in intensive care units: A preliminary survey by the Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group. *J Intensive Care* 2016; 4:86.

52. 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:e744–e752.

53. Satake S, Shimokata H, Senda K, et al: Validity of total Kihon checklist score for predicting the incidence of 3-year dependency and mortality in a community-dwelling older population. *J Am Med Dir Assoc* 2017; 18:552.e1–552.e6.