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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, MSc¹;
Kazuhiro Hayashi, PT, MSc³; Takayuki Inoue, PT, PhD¹; Kazuki Nishida, MD⁴;
Kunihiko Takahashi, PhD⁴; Shigeyuki Matsui, PhD⁴; 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 \geq 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

¹Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan.

²Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan.

³Department of Rehabilitation, Aichi Medical University Hospital, Nagakute, Japan.

⁴Department of Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan.

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For information regarding this article, E-mail: nkjmx1121@med.nagoya-u.ac.jp
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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

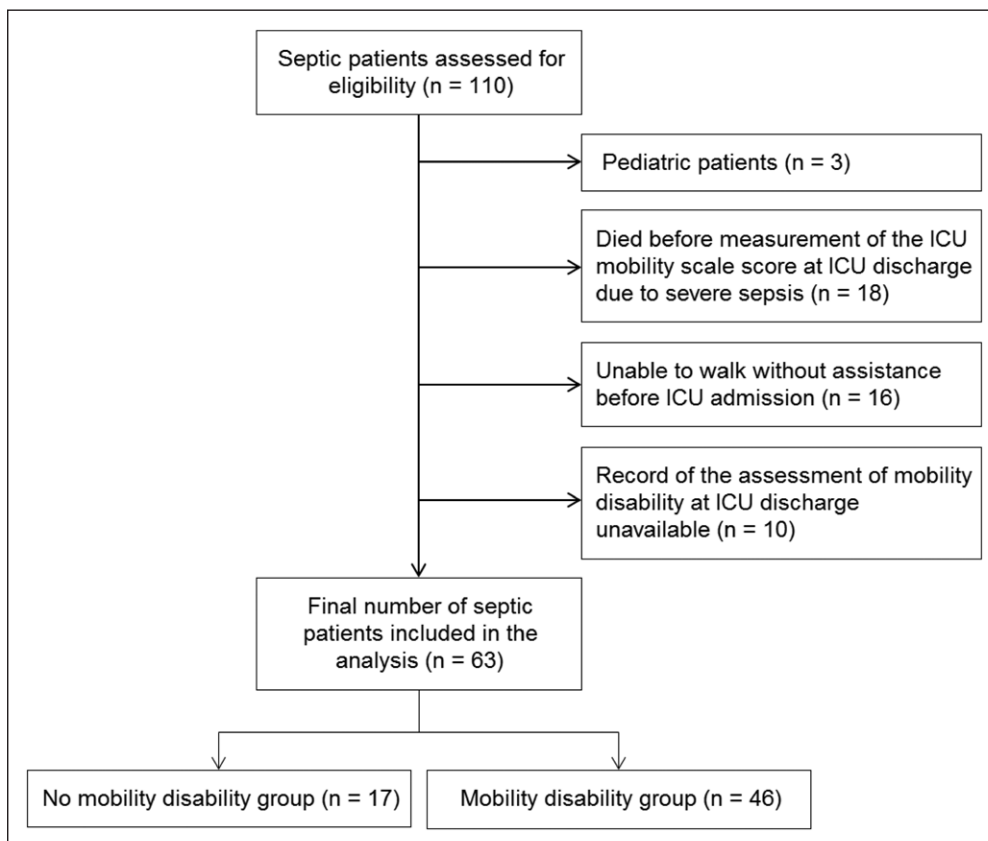


Figure 1. Patients' flow in this study.

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/passive 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 vasopressors, 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 *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	Total Patients (<i>n</i> = 63)
Characteristics before ICU admission	
Age, yr, median (IQR)	70.0 (62.0–79.0)
Body mass index, kg/m ² , median (IQR)	21.3 (18.1–24.7)
Male gender, <i>n</i> (%)	41 (65)
Source sepsis, <i>n</i> (%)	
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, <i>n</i> (%)	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, <i>n</i> (%)	23 (37)
Medication, <i>n</i> (%)	
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, <i>n</i> (%)	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%.

CFS scores greater than or equal to 5 were associated with a sensitivity and specificity for the prediction of mobility disability at ICU discharge of 54.3% and 88.2%, respectively. The positive predictive value and negative predictive value were 92.6% (25/27) and 41.7% (15/36), respectively. The overall prevalence of patients with CFS scores greater than or equal to 5 was 43% (27/63). The prevalence of patients with CFS scores greater than or equal to 5 was 54% (25/46) in the mobility ability group, but only 12% (2/17) in the no mobility disability group.

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/m ² , 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.

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
Pao ₂ , mm Hg	86.3 (77.7–100)	97.9 (79.9–140)	0.234
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, × 10 ³ /μL	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
Pao ₂ /Fio ₂	357 (275–397)	254 (176–372)	0.091
Platelet, × 10 ⁴ /μL	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, mg/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
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			
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.

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 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 \geq 5	7.77 (1.37–44.21)	0.021^a
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.

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