Original Article

Acta Medica Okayama

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Frailty at 1 Month before ICU Admission Poses a Hospital Mortality Risk in Cancer Survivors whose Condition Has Deteriorated due to Medical Factors

Junya Matsumi*, and Tetsufumi Sato

Department of Anesthesiology and Intensive Care Medicine, National Cancer Center Hospital, Chuo-ku, Tokyo 104-0045, Japan

The optimal indications for intensive care unit (ICU) treatment for critically ill cancer survivors whose condition has deteriorated due to medical factors are unclear. To test our hypothesis that frailty before deterioration was associated with hospital mortality in this patient population, we retrospective analyzed the cases of the patients admitted to the ICU at the National Cancer Center Hospital, Japan (April 2014-March 2022). We excluded patients who underwent surgery within 28 days or were denied critical care within 24 h or admitted after cardiopulmonary arrest. Their Clinical Frailty Scale (CFS) scores at 1 month before ICU admission (Pre-ICU) were obtained. Frailty was defined as CFS scores ≥ 4 points. We analyzed 298 admissions and observed that the mortality rate at hospital discharge was significantly higher in the frailty group (n = 119). A multivariate analysis demonstrated that the following factors were significantly associated with hospital mortality: Pre-ICU frailty (OR 2.00, 95%CI: 1.19-3.36, p = 0.009), cancer type (hematological: OR 2.93, 95%CI: 1.42-6.05, p=0.004), and Sequential Organ Failure Assessment score at ICU admission (OR 0.88, 95%CI: 0.82-0.95, p = 0.0008). Frailty retrospectively assessed using the CFS at 1 month pre-ICU admission is a risk factor for hospital mortality in these cancer survivors.

Key words: frailty, cancer survivor, clinical frailty scale, cancer, critically ill

ancer survivors are defined as individuals who ✓ had cancer and are still alive, regardless of whether they still have cancer: we referenced this definition from National Cancer Institute: Definitions, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, https://cancercontrol.cancer. gov/ocs/definitions> (last accessed 9.17.2025). Although the indications for intensive care unit (ICU) for patients just after surgery have been discussed, the optimal indications for ICU care of critically ill cancer survivors whose condition has deteriorated due to medical factors are not know. Historically, patients with cancer were considered ineligible for critical care in an

ICU because of their poor prognoses [1], but nowadays long-term survival can often be expected for cancer survivors [2]. Nevertheless, since cancer treatment may cause long-lasting complications (e.g., immuno-related adverse events and graft versus host diseases [GVHD]), the health of some cancer survivors might be impaired. It is thus crucial to identify the ICU indications for critically ill cancer survivors whose health is impaired due to medical factors.

Several research groups have reported that (i) cancerrelated factors such as the pathological diagnosis and cancer stage were not associated with ICU prognosis, but (ii) the cancer patients' general condition before deterioration was associated with their ICU prognoses

[3-9]. The Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) is commonly used for assessing the general conditions of cancer patients, but since patient evaluations using the ECOG-PS are commonly done by oncologists seeking to identify the appropriate cancer treatment, it is possible that the general conditions of survivors of cancer may be better evaluated by intensivists.

Frailty, an aging-related syndrome of physiological decline, is one indicator of a person's general condition [10]. The presence of frailty is associated with poor outcomes in various diseases [11]. Although the original targets of frailty examinations were limited to the elderly, the concept is now also applied to the nonelderly in critical care fields [12]. The Clinical Frailty Scale (CFS) is used to evaluate frailty [13], and it has been established that frailty assessed with the CFS at a patient's admission to an ICU was associated with shortand long-term mortality in patients who were critically ill due to various causes [14-19]. However, most of those studies' patient populations included both surgical and medical patients, and few studies have examined frailty in critically ill cancer survivors whose health has worsened due to medical factors. Moreover, the assessments conducted at a patient's admission to an ICU (including assessments of the patient's frailty status) were mainly simply interviews with the patients' next of kin, which may provide inaccurate information since patients' family members are not always in a reliable state of mind as their loved ones are admitted to an ICU, especially in emergencies. An assessment of patient conditions by another method might be preferable. We speculated that frailty evaluated with the CFS and recorded in a patient's medical records before deterioration could be used retrospectively, but the feasibility of doing this has not been determined.

We suspected that frailty assessed with the CFS might be a factor in the indications for ICU admission among cancer survivors, and we hypothesized that the presence of frailty evaluated with the CFS could be associated with hospital mortality in critically ill cancer survivors whose health has deteriorated due to medical factors. The present study was performed to test this hypothesis.

Patients and Methods

Study goals, design, and setting. The goal of this

study was to determine whether frailty assessed with the CFS at 1 month before ICU admission was associated with hospital mortality in critically ill cancer survivors whose condition had worsened due to medical factors. This retrospective study was performed at National Cancer Center Hospital (NCCH) in Tokyo, Japan and was approved by the NCCH Institutional Review Board for Human Clinical Studies. The requirement for patients' informed consent was waived in light of the study's design as a noninvasive retrospective analysis. The study was conducted in accord with the Declaration of Helsinki. The ICU at the NCCH is a mixed surgical and medical ICU with semi-closed management provided by the hospital's Department of Anesthesiology and Intensive Care Medicine.

Eligible patients. We included patients admitted to the ICU at the NCCH during the period from April 2014 through May 2022. To limit the study's patient population to critically ill cancer survivors whose health had worsened due to medical factors, we excluded the cases of the patients who underwent surgery within 28 days of their admission to the ICU. We also excluded the cases of patients who were denied critical care at the ICU within 24 h of their ICU admission and those who were admitted just after resuscitation or just after the recovery of spontaneous circulation from cardiopulmonary arrest (post-CPA), since the purpose of this study was to identify appropriate indications for the ICU. Among the patients with more than one ICU admission during the study period, we used the first admission for the same hospitalization, and we considered each admission for a separate hospitalization.

Measurement. The same study investigator (JM) obtained each patient's CFS score that had been recorded approx. 30 days before their ICU admission (Pre-ICU) from the patients' medical records and/or medical information letter. Frailty was defined as a CFS score ≥ 4 points. We collected the patients' characteristics including age, sex, Charlson Comorbidity Index (CCI), cancer type (solid, hematological), and cancer state (complete remission [CR], CR with GVHD [GVHD], partial response [PR], stable disease [SD], progressive disease [PD], during treatment, and before treatment). We also collected the available information regarding the patients' critical care, including the main cause for ICU admission, i.e., sepsis, central nerve dysfunction, respiratory dysfunction, circulatory dysfunction, acute kidney injury, and others; the Sequential Organ Failure Assessment (SOFA) score on the day of ICU admission, the use of a ventilator, and the use of renal replacement therapy.

Outcomes. The primary outcome of the study was hospital mortality, and the secondary outcomes were mortality at 6 months and 1 year after ICU admission.

Statistical analyses. The variables are summarized using the mean \pm standard deviation (SD) or number (n) and percentage. We divided the patients into two groups according to the presence of frailty at the Pre-ICU timepoint. Comparisons between groups were assessed using Student's t-test or the χ^2 -test as appropriate. To identify factors associated with the patients' hospital mortality, we performed a multivariable logistic regression using age, sex, CCI, cancer type, SOFA at ICU admission, main cause of ICU admission, and frailty at Pre-ICU.

All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [20]. Confidence intervals (CIs) of odds ratio (OR) were estimated at 95%. Statistical significance was set at a p-value < 0.05.

Results

Patients. As illustrated in the patient flowchart in Fig. 1, during the study period there were a total of 7,237 admissions. We excluded the cases of the 6,910 admissions that were followed by surgery within 28 days. Among the remaining 327 admissions, 29 were excluded for the following reasons: denial of critical care within 24 h from ICU admission (n=5), more than one ICU admission during the study period at the same hospitalization (n=18), admission post-CPA (n=5), and a single case in which the CFS could not be assessed for emergent ICU admission from another hospital due to inadequate information in the medical form from the referring hospital. A final total of 298 admissions were included in the study (Fig. 1).

Patient characteristics. The patients' overall characteristics are summarized in Table 1. The mean age of the study population was 57.1 ± 18.7 years, and 67.4% of the patients were male. Solid and hematological tumors were present in 53% and 47% of the patients, respectively. The most common causes for ICU admission were respiratory dysfunction (33.9%) and sepsis (32.9%). Mechanical ventilation and renal replacement therapy were utilized in 140 (47.0%) and 61 (20.5%)

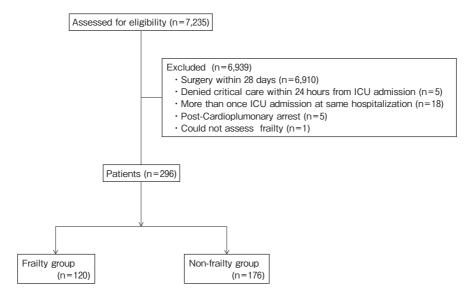


Fig. 1 Flowchart of the patients' enrollment. Among a total of 7,237 admissions, 6,910 were excluded for surgery within 28 days, and 29 were excluded owing to the following reasons: five cases were denied critical care within 24 h from ICU admission, 18 cases had more than one admission at the same hospitalization, five cases were after cardiopulmonary arrest, and one urgently admitted to the ICU from another hospital could not be assessed using the clinical frailty scale owing to poor information. Thus, 298 admissions were included in this study.

Age (years)		57.1 ± 18.7
	Female	97 (32.6)
Sex (%)	Male	201 (67.4)
Charlson comorbidity index		3.3 ± 2.1
0	Hematological	140 (47.0)
Cancer type (%)	Solid	158 (53.0)
Frailty 1 month before ICU admission	(%)	119 (39.9)
	Before treatment	28 (9.4)
	During treatment	111 (37.2)
	Complete remission	58 (19.5)
Cancer state at ICU admission (%)	Hematological Solid Soli	42 (14.1)
	Partial remission	10 (3.4)
	Sustained disease	13 (4.4)
	Progressive disease Sepsis	36 (12.1)
	Sepsis	98 (32.9)
	Hematological Solid Ssion (%) Before treatment During treatment Complete remission GVHD Partial remission Sustained disease Progressive disease Sepsis Central nerve dysfunction Respiratory dysfunction Circulatory dysfunction Acute kidney injury Others admission J discharge	15 (5.0)
Cause for ICLL admission (9/)		101 (33.9)
Cause for ICU admission (%)		32 (10.7)
		27 (9.1)
		25 (8.4)
SOFA score on the day of ICU admission		8.0 ± 3.0
Mechanical ventilation (%)		140 (47.0)
Renal replacement therapy (%)		61 (20.5)
Length of ICU stay		8.7 ± 8.9
Length of hospital stay after ICU discharge		37.1 ± 48.6
Mortality at hospital discharge (%)		107 (35.9)
Mortality at 6 month (%)		152 (51.0)
Mortality at 1 year (%)		168 (56.4)
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ICU, intensive care unit; GVHD , graft versus host disease; SOFA , sequential organ failure assessment.

Frailty was assessed by Clinical Frailty Scale score 4 or higher.

cases, respectively. Among the 298 admissions of the patients, 107 (35.9%) had not survived until discharge; 152 (51.0%) had not survived 6 months after the ICU admission, and 168 (56.4%) had not survived at 1 year after the admission.

Comparison of the Frailty and Non-frailty groups. The Frailty group and the Non-frailty group were comprised of 119 and 179 patients, respectively. As shown

in Table 2, the parameters before the initiation of critical care were not significantly different between the groups without a cancer state at ICU admission (p = 0.002) or between those with a SOFA score at ICU admission (Frailty group: 8.6 ± 3.8 , Non-frailty group: 7.6 ± 3.8 , p = 0.019). During the ICU stay, the patients in the Frailty group were more significantly in need of mechanical ventilation: n = 67 (56.3%) vs. Non-frailty,

Table 2 Comparison of the two groups

		One month be	fore admission	P-value
		Frailty n=119	Non-frailty n=179	
Age (years)		57.6 ± 18.0	56.7 ± 19.2	0.70
Sex (%)	Female	40 (33.6)	57 (31.8)	0.85
	Male	79 (66.4)	122 (68.2)	
Charlson comorbidity in	ndex	3.5 ± 2.1	3.2 ± 2.1	0.21
0	Hematological	58 (48.7)	82 (45.8)	
Cancer type (%)	Solid	61 (51.3)	97 (54.2)	0.71
Cancer state at ICU admission (%)	Before treatment	4 (3.4)	24 (13.4)	
	During treatment	37 (31.1)	74 (41.3)	0.002
	Complete remission	24 (20.2)	34 (19.0)	
	GVHD	26 (21.8)	16 (8.9)	
	Partial remission	19 (16.0)	17 (9.5)	
	Sustained disease	6 (5.0)	7 (3.9)	
	Progressive disease	3 (2.5)	7 (3.9)	
Cause for ICU admission (%)	Sepsis	37 (31.1)	61 (34.1)	0.05
	Central nerve dysfunction	6 (5.0)	9 (5.0)	
	Respiratory dysfunction	52 (43.7)	49 (27.4)	
	Circulatory dysfunction	11 (9.2)	21 (11.7)	
	Acute kidney injury	7 (5.9)	20 (11.2)	
	Others	6 (5.0)	19 (10.6)	
SOFA score at ICU ad	mission	8.6 ± 3.8	7.6 ± 3.8	0.019
Mechanical ventilation (%)		67 (56.3)	73 (40.8)	0.012
Renal replacement therapy (%)		23 (19.3)	38 (21.2)	0.80
Length of ICU stay (days)		8.8 ± 6.1	8.7 ± 10.3	0.97
Length of hospital stay after ICU discharge (days)		39.7 ± 52.3	35.4 ± 46.0	0.46
Mortality at hospital discharge (%)		57 (47.9)	50 (27.9)	0.001
Mortality at 6 month (%)		74 (62.2)	78 (43.6)	0.004
Mortality at 1 year (%)		79 (66.4)	89 (49.7)	0.005

ICU, intensive care unit; GVHD, graft versus host disease; SOFA, sequential organ failure assessment. Frailty was assessed by Clinical Frailty Scale score 4 or higher. The parameters before starting critical care were not significantly different between groups without cancer state at ICU admission and SOFA at ICU admission. During ICU stay, the patients with frailty were more significantly in need of mechanical ventilation.

n = 73 (40.8%), p = 0.012.

The mortality at hospital discharge was significantly higher in the Frailty group (n = 57, 47.9%) compared to the Non-frailty group (n = 50, 27.9%, p = 0.001). The mortality rates at 6 months and 1 year were also significantly higher in the Frailty group versus the Non-frailty group: at 6 months, n = 74 (62.2%) vs. n = 78 (43.6%), p = 0.004; at 1 year, n = 79 (66.4%) vs. n = 89 (49.7%), p = 0.005.

Multivariate analysis of potential risk factors for hospital mortality. The data presented in Table 3 demonstrated that in the multivariable linear regression, frailty at the Pre-ICU timepoint was significantly associated with hospital mortality (OR 2.00, 95%CI: 1.19-3.36, p = 0.009). In addition, the cancer type (hematological: OR 2.93, 95%CI: 1.42-6.05, p = 0.004) and the SOFA score at ICU admission (OR 0.88, 95%CI: 0.82-0.95, p = 0.0008) were significantly associated with hospital mortality. However, the following other parameters were not associated with hospital mortality: age (OR 0.99, 95%CI: 0.97-1.00, p=0.16); female sex (OR 0.78, 95%CI: 0.44-1.37, p = 0.39); CCI (OR 0.91, 95%CI: 0.78-1.06, p = 0.22), and the main cause of ICU admission (p = 0.81).

Discussion

Our analyses revealed that in a population of nearly 300 critically ill cancer survivors whose health had deteriorated due to medical factors, the patients who showed frailty at 1 month before ICU admission had significantly worse mortality at hospital discharge compared to those without frailty, which indicates that frailty assessed with the CFS might help assess indications for ICU admission. Several studies have evaluated the usefulness of CFS-evaluated frailty in association with the outcomes of critically ill patients. Elderly and non-elderly adult critically ill patients with frailty assessed based on CFS had higher mortality than that of

similar patients without frailty [12,15-19]. Another study indicated that CFS-assessed frailty was associated with ICU and hospital mortality in patients with cancer [14]. These results are similar to our present findings.

However, most of the prior studies included both surgical and medical patients [12, 14, 15, 17-19]. Since indications for invasive treatments (including critical care) for patients who are going to undergo surgery are generally discussed when the decision concerning surgery is made, the indications for critical care in patients who have already undergone surgery are rarely discussed in the clinical setting. Discussions about indications for critical care are mainly occurred in the patients with a status that has worsened due to medical factors. Earlier studies' evaluations of patients' frailty were based mainly or solely on interviews of the patients' next of kin at the patients' admission to the ICU [15,18,19], which may not be accurate. A better method appears to be the use of the frailty information obtained ~30 days before the patient's ICU admission, which the present study indicates is significantly associated with hospital mortality.

Another difference between the previous studies and our present analyses is the CFS cut-off value used. We defined frailty as a CFS score ≥ 4 points, but other studies used ≥ 5 points [14-18]. The CFS score 4 points is referred to as 'vulnerable' or 'very mild frailty.' We used ≥ 4 points to evaluate CFS scores as a risk factor for hospital mortality among cancer survivors, taking into account that even the vulnerable state or very mild frailty could have significant impacts on the outcomes of

Table 3 Multivariable analysis

	Odds ratio	95% CI	P-value
Female	0.78	0.44 to 1.37	0.39
Age	0.99	0.97 to 1.00	0.16
Charlson comorbidity index	0.91	0.78 to 1.06	0.22
Hematological tumor	2.93	1.42 to 6.05	0.004
SOFA score on the day of ICU admission	0.88	0.82 to 0.95	0.0008
Cause for ICU admission			0.81
Frailty 1 month before ICU admission	2.00	1.19 to 3.36	0.009

SOFA, sequential organ failure assessment; ICU, intensive care unit; CI, confidence interval. Frailty was assessed by Clinical Frailty Scale score 4 or higher. The frailty at pre (OR 2.00 [95%CI 1.19–3.36], p=0.009), cancer type (hematological: OR 2.93 [95%CI 1.42–6.05], p=0.004) and SOFA score at ICU admission (OR 0.88 [95%CI 0.82–0.95], p=0.0008) were associated with hospital mortality.

the present cancer survivors. Critical care is a highly invasive medical intervention, and post-intensive care syndrome has become a focus of interest. In addition, it was reported that among elderly patients taken to a hospital's emergency department, the outcomes differed between those with a CFS score of 1-3 points and those with a score of 4-5 points [21]. Although that patient group is different from our present population, both emergency medicine and critical care are acutecare departments. We thus believe that it is reasonable to define frailty as CFS score ≥ 4 in the present evaluation of outcomes after critical (ICU) care.

Study limitations. This study has several limitations to address. First, a sufficiently long prognostic period for identifying ICU indications for cancer survivors has not been established. It was proposed that an assumed prognosis of 1 year could be used as the cutoff for clinical decision-making with full-code status, and it thus seems that ICU indications for patients with cancer might be assessed by using a 1-year prognosis [22]. However, the primary endpoints applied in the studies assessing CFS regarding ICU admission varied [14-19]. The NCCH is a cancer-specialized hospital, and a considerable number of the patients treated at the NCCH have complicated cancer-related conditions, e.g., standard-treatment failures. Since we suspected that the prognosis of the present cancer survivors might be poorer than that of the overall cancer population, we set the present study's primary endpoint as hospital mortality. The relatively high mortality rates in our series of cancer survivors at 6 months and 1 year could be explained by this characteristic of the NCCH. We thus speculate that the adequate ICU prognostic period at the NCCH is hospital mortality. However, the diseases that were the basis of the patients' ICU admissions on the mortality at 6 months and 1 year might have had an impact on the mortality rate; an example is a delay and/or discontinuation of anti-cancer therapy due to a patient's decreased performance status after critical care. Second, the severity of the present patients' cancer, such as the cancer stage, was not considered in this study. However, a comparison of stages between different types of cancer is not meaningful, because the cancer stages are classified differently for various cancer types. Moreover, at the NCCH, a criterion for ICU indication is the patient's prognosis over the upcoming 6 months as predicted by the attending physician. The differences among cancer types may thus not strongly

affect hospital mortality. A third study limitation is that since our patient population was limited to patients admitted to the ICU, we did not evaluate the cases of critically ill patients not admitted to the ICU. The usefulness of the CFS in decisions about critical care for cancer survivors was thus not purely elucidated. Lastly, we included the cases of patients who were treated during a 9-year period, and heterogeneity due to medical advances might exist.

In conclusion, the frailty of cancer survivors assessed with the Clinical Frailty Scale at 1 month before ICU admission was associated with the patients' hospital mortality. This finding reaffirms the importance of preventing frailty in similar patient populations. From the intensivist perspective, this result suggests the importance of frailty in the indications for critical care for cancer survivors.

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