Frailty and Neurologic Outcomes of Patients Resuscitated From Nontraumatic Out-of-Hospital Cardiac Arrest: A Prospective Observational Study

Ryo Yamamoto, MD, PhD*; Tomoyoshi Tamura, MD, PhD; Akina Haiden, MD; Jo Yoshizawa, MD; Koichiro Homma, MD, PhD; Nobuya Kitamura, MD, PhD; Kazuhiro Sugiyama, MD; Takashi Tagami, MD, PhD; Hideo Yasunaga, MD, PhD; Shotaro Aso, MD, PhD; Munekazu Takeda, MD, PhD; Junichi Sasaki, MD, PhD; on behalf of the SOS-KANTO 2017 Study Group

*Corresponding author. E-mail: ryo.yamamoto@gmail.com.

Study objective: To elucidate the clinical utility of the Clinical Frailty Scale score for predicting poor neurologic functions in patients resuscitated from out-of-hospital cardiac arrest (OHCA).

Methods: This was a prospective, multicenter, observational study conducted between 2019 and 2021. The study included adults with nontraumatic OHCA admitted to the intensive care unit after return of spontaneous circulation (ROSC). Pre-arrest high Clinical Frailty Scale score was defined as 5 or more. Favorable neurologic outcomes defined as a Cerebral Performance Category score of 2 or less at 30 days after admission were compared between patients with and without high Clinical Frailty Scale scores. Multivariable logistic regression analyses fitted with generalized estimating equations were performed to adjust for patient characteristics, out-of-hospital information, and resuscitation content and account for within-institution clustering.

Results: Of 9,909 patients with OHCA during the study period, 1,216 were included, and 317 had a pre-arrest high Clinical Frailty Scale score. Favorable neurologic outcomes were fewer among patients with high Clinical Frailty Scale scores. The high Clinical Frailty Scale score group showed a lower percentage of favorable neurologic outcomes after OHCA than the low Clinical Frailty Scale score group (6.1% vs 24.4%; adjusted odds ratio, 0.45 [95% confidence interval 0.22 to 0.93]). This relationship remained in subgroups with cardiogenic OHCA, with ROSC after hospital arrival, and without a high risk of dying (Clinical Frailty Scale score of 7 or less), whereas the neurologic outcomes were comparable regardless of pre-arrest frailty in those with noncardiogenic OHCA and with ROSC before hospital arrival.

Conclusions: Pre-arrest high Clinical Frailty Scale score was associated with unfavorable neurologic functions among patients resuscitated from OHCA. The Clinical Frailty Scale score would help predict clinical consequences following intensive care after ROSC. [Ann Emerg Med. 2023;■:1-10.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2023.02.009

INTRODUCTION

Background

Out-of-hospital cardiac arrest (OHCA) is a major cause of mortality worldwide.[1] Various treatments have improved OHCA clinical outcomes, including high-quality chest compression, immediate defibrillation, and targeted temperature management. However, 70% to 80% of patients with OHCA still suffer from unfavorable neurologic function.[2-4] Therefore, withholding or withdrawing intensive care, considering the dignity and quality of life, would be a management option in such cases and should be discussed even before a cardiac arrest event.[2,5,6] However, the appropriate evaluation of pre-arrest conditions of patients to predict neurologic outcomes after OHCA remains unclear.

Importance

Age is a simple and versatile parameter for estimating patient vulnerability.[7] However, several studies have reported that low physiologic reserve would be more appropriately defined using frailty.[8,9] The idea of frailty has been widely spread to capture physiological deterioration because of aging, comorbidities, and organ dysfunctions,[8] and the Clinical Frailty Scale 2.0 was developed as a 1 to 9 scaling system to objectively measure patient frailty.[9,10] The Clinical Frailty Scale score was shown to predict clinical outcomes in various diseases,[11,12] and the clinical feasibility of Clinical Frailty Scale score was examined to identify optimal candidates for major abdominal surgeries and allocate medical resources.[10,13]

The prognostic ability of the Clinical Frailty Scale score among patients with nontraumatic cardiac arrest was also

Editor's Capsule Summary

What is already known on this topic

Patient frailty influences outcomes after surgery and illness.

What question this study addressed

How does frailty influence outcomes after out-of-hospital cardiac arrest?

What this study adds to our knowledge

In 1,216 patients observed prospectively after resuscitation for at least 30 days in Japan, increasing frailty as measured by an existing score was associated with worse outcomes independently of other predictors.

How this is relevant to clinical practice

Clinical teams may measure and consider frailty when providing a prognosis for outcomes after out-of-hospital cardiac arrest.

analyzed in previous studies.[14-16] A recent systematic review of the association between frailty and postarrest outcomes that included 4 studies on inhospital cardiac arrest revealed that a Clinical Frailty Scale score more than or equal to 5 to 6 was associated with higher inhospital mortality.[16] Another similar systematic review that analyzed 7 retrospective studies evaluated patients with frailty who received cardiopulmonary resuscitation (CPR) and reported that those with a high Clinical Frailty Scale score had increased inhospital mortality.[14] However, most previous studies only retrospectively analyzed patients with inhospital cardiac arrest and examined mortality rather than neurologic outcomes.[14,16,17] Therefore, the prediction of unfavorable neurologic function using the Clinical Frailty Scale score among patients with OHCA has not been well evaluated.

Goals of This Investigation

This prospective cohort study involving 41 institutions was conducted to test whether the Clinical Frailty Scale score provides independent information about the outcome of patients after OHCA. This study aimed to reveal the relationship between pre-arrest frailty and favorable neurologic outcomes in patients resuscitated from OHCA. We hypothesized that a high Clinical Frailty Scale score before cardiac arrest was associated with low cerebral performance function 30 days after resuscitation from OHCA.

METHODS

Study Design and Setting

This was a prospective, multicenter, observational study conducted by the SOS-KANTO 2017 study group. The study included patients with OHCA who were transported to 41 emergency hospitals in the Kanto area, including Tokyo and its suburbs, between September 2019 and March 2021. The SOS-KANTO study group has investigated multiple clinical issues related to OHCA since 2002 and regularly performs prospective observational studies with preregistered research hypotheses.[18] SOS-KANTO has been maintained with support from the Kanto chapter of the Japanese Association for Acute Medicine. Before the study initiation, all collaborating hospitals obtained individual local institutional review board approvals for conducting research on human subjects. This study was approved by the institutional review board of Keio University School of Medicine (approval number: 20210006). The requirement for informed consent was waived because of the anonymous nature of the data used.

In Japan, the emergency medical service (EMS) personnel performs CPR according to the Japanese CPR guidelines, which follow the International Liaison Committee on Resuscitation guidelines and the American Heart Association guidelines for cardiac arrest.[18,19] Most EMS crews have an emergency life-saving technician certified to obtain intravenous access and use a supraglottic airway device, whereas only a specially trained emergency life-saving technician can administer medications and perform endotracheal intubation under instructions from a medical director in each region. A physician-staffed ambulance/helicopter is also available and usually dispatched from a tertiary care center in a city and covers both the city and rural areas.[20] The availability of out-of-hospital physicians and out-of-hospital medical systems considerably differs between regions.

Selection of Participants

The study included patients who met the following inclusion criteria: (1) nontraumatic OHCA that was diagnosed by EMS or out-of-hospital physicians and confirmed by treating physicians based on the history of OHCA and/or clinical findings, (2) at least 18 years of age, and (3) intensive care unit (ICU) admission after return of spontaneous circulation (ROSC). Patients were excluded if the pre-arrest Clinical Frailty Scale score was not recorded.

Data Collection and Definitions

Out-of-hospital information regarding OHCA was prospectively collected by EMS providers in the

standardized Utstein style, and inhospital information was collected by treating physicians at each institution. Demographic information, including the Clinical Frailty Scale score (Table E1, available at http://www.annemergmed.com), was collected by physicians or registered nurses and confirmed by the treating physicians. The Clinical Frailty Scale score was determined using a scoring sheet provided by Rockwood K. et al who developed the Clinical Frailty Scale score,[10] which includes concrete examples with visual guidance for each score of the Clinical Frailty Scale. Physicians at study institutions had been notified to record the Clinical Frailty Scale scores and to learn Clinical Frailty Scale scoring as needed before the study initiation. Survival status and neurologic function were collected by treating physicians and evaluated using the Cerebral Performance Category, a 1 through 5 scaling system for neurologic function (Table E2, available at http://www.annemergmed.com).[21] If patients were discharged or transferred to another hospital, information to determine the Cerebral Performance Category score was obtained by phone survey on a patient or a caregiver. Data were registered at an online data portal in which variables had been predefined based on preregistered hypotheses.

Available data included demographics, including age, sex, comorbidities for Charlson Comorbidity Index, and Clinical Frailty Scale score; out-of-hospital information, including place of cardiac arrest, witness status, presence of bystander CPR, defibrillation by bystander automated external defibrillator, ROSC on EMS arrival, initial cardiac rhythm on EMS arrival, and out-of-hospital physician presence; out-of-hospital treatment, including airway device, defibrillation, intravenous access, medications, and mechanical CPR use; inhospital information, including presence of spontaneous circulation, Glasgow Coma Scale score, and cardiac rhythm on arrival; inhospital resuscitation, including defibrillation, intubation, mechanical CPR use, and extracorporeal membrane oxygenation use before ROSC; information after ROSC, including Glasgow Coma Scale score and laboratories; post-ROSC treatment, including extracorporeal membrane oxygenation use, coronary angiography and revascularization, and targeted temperature management; time variables, including time of witness of cardiac arrest, emergency call, CPR initiation, and ROSC, and cause of cardiac arrest that was determined by treating physicians. The survival status and Cerebral Performance Category score for neurologic function were available at hospital discharge and 30 and 90 days after admission. The length of hospital stay and days to do-not-attempt-resuscitation (DNAR) order were also available.

Based on previous studies, a high Clinical Frailty Scale score was defined as a Clinical Frailty Scale score ≥ 5 out of a 1 to 9 scale.[9,14] No-flow time was defined as the interval between the witness of cardiac arrest and CPR initiation, in which the time of the emergency call was used for the time of cardiac arrest when witness time was unavailable. Low-flow time was defined as the interval between CPR initiation and ROSC, in which the time of ROSC at the hospital was used when the time of ROSC before and after hospital arrival was recorded. Detailed information on the frailty degree, such as the activities of daily living, was unavailable in the database.

Outcome Measures

The primary outcome was a favorable neurologic function at 30 days after admission, which was defined as a Cerebral Performance Category score ≤ 2.[22] The secondary outcomes included survival at 30 days, favorable neurologic function at discharge and 90 days, hospital-free days up to day 90, and length of hospital stay. Days to the DNAR order were also included in the secondary outcomes.

Statistical Analysis

Patient data were classified into no-to-mild frailty (Clinical Frailty Scale score ≤ 4) and moderate-to-high frailty (Clinical Frailty Scale score ≥ 5) groups.[14,16] Unadjusted analysis was performed on the primary outcome using the Chi-square test.

Multivariable logistic regression analyses fitted with generalized estimating equations (GEE) were performed to adjust for patient characteristics, out-of-hospital information, and resuscitation content and account for within-institution clustering.[23] Before GEE model development, missing non outcome values were replaced with a set of substituted plausible values by creating 5 filled-in complete data sets using multiple imputation by chained equation method. Estimated associations in each of the imputed data sets were averaged together to give overall estimated associations.

Besides high Clinical Frailty Scale score, relevant covariates were selected from known or possible predictors for favorable neurologic outcomes in patients with OHCA,[1,3-5,17-19,] including age, sex, comorbidities for Charlson Comorbidity Index, cause of cardiac arrest (cardiogenic vs noncardiogenic), place of cardiac arrest (home vs public space), witness status, presence of bystander CPR, defibrillation (no defibrillation, before EMS arrival, on route, and on hospital arrival), cardiac rhythm (shockable vs nonshockable) at the scene and on hospital arrival, out-of-hospital physician presence, out-of-hospital treatment

(defibrillation, epinephrine, supraglottic airway device, intubation, and mechanical CPR use), no- and low-flow time, and ROSC on hospital arrival. The number of covariates in the model followed standard upper limits for a multivariate logistic regression model with at least 10 outcomes for each potential predictor analyzed in the model. Moreover, additional GEE models were developed incorporating variables of inhospital resuscitation (mechanical CPR and extracorporeal membrane oxygenation use before ROSC) and post-ROSC treatment (extracorporeal membrane oxygenation use, coronary angiography and revascularization, and targeted temperature management), as well as laboratories on admission.

The secondary outcomes were similarly examined using GEE models with the same covariates of the model for the primary outcome or were evaluated with median differences between the no-to-mild frailty and moderate-to-high frailty groups using the Hodges–Lehmann estimator. The length of hospital stay and days to DNAR order were examined in patients who survived more than a day after admission.

Three sensitivity analyses, which were not predefined before the study initiation, were performed to examine the robustness of the primary results. A GEE model using all covariates from the primary and 2 additional models were developed to validate the association between high Clinical Frailty Scale score and poor neurologic function after OHCA. Multivariate logistic regression analysis with a backward stepwise method was also performed using the same variables of the GEE model to avoid overestimating the effects of within-institution clustering. Furthermore, inverse probability weighting analysis with propensity scores was performed using the date before imputation,[24] adjusting for patient and resuscitation characteristics other than Clinical Frailty Scale score between the two groups. The propensity score was developed using the same variables of the GEE model, and the effect of a high Clinical Frailty Scale score on primary outcomes was examined after weighting. Additionally, 4 and 6 of the Clinical Frailty Scale score were used to redefine high clinical frailty to examine whether a score of 5 on the Clinical Frailty Scale was an appropriate cut-off, in which the same primary GEE analysis was repeated.

In addition, to consider the potential bias because of missing data on the Clinical Frailty Scale score, patient characteristics were compared between patients with and without available Clinical Frailty Scale data, using the original dataset of SOS-KANTO 2017 in which the exclusion criterion (missing Clinical Frailty Scale data) was not applied.

Subgroup analyses, which were not predefined before the study initiation, were performed to examine the association between high Clinical Frailty Scale score (Clinical Frailty Scale score equal to or more than 5), clinical characteristics, and neurologic outcomes. The GEE analyses were repeated in patient subgroups determined by the cause of cardiac arrest (cardiogenic vs. noncardiogenic), age (less than 65 vs. 65 or more years), and the timing of ROSC (before vs. after hospital arrival). Patients without a high risk of dying (Clinical Frailty Scale score equal to or less than 7) were also defined as another subgroup.[9] The same covariates of the primary GEE models were used.

Descriptive statistics are presented as median (interquartile range [IQR]) or number (percentage). The hypothesis was tested only on the primary outcome in which an α error rate of 0.05 was considered statistically significant in a 2-sided test. The secondary outcomes were shown with an odds ratio (OR) and 95% confidence interval (CI) or median (IQR). All statistical analyses were performed using IBM SPSS Statistics for Windows version 28.0 (IBM Corp., Armonk, NY).

RESULTS

Characteristics of the Study Subjects

Of 9,909 patients with OHCA in the SOS-KANTO 2017 database, 1,216 adult patients with nontraumatic OHCA were admitted to the ICU and had available pre-arrest Clinical Frailty Scale data. Therefore, they were eligible for inclusion in this study (Figure). A total of 317 (26.1%) patients had moderate-to-severe frailty (Clinical Frailty Scale score equal to or more than 5).

Table 1 shows the patient characteristics. Patients with moderate-to-severe frailty were older and had a higher Charlson Comorbidity Index, higher partial pressure of carbon dioxide, potassium, and D-dimer after ROSC, and lower hemoglobin and albumin after ROSC than those with no-to-low frailty. Additionally, fewer patients with high Clinical Frailty Scale score suffered from cardiogenic OHCA rather than noncardiogenic one, underwent bystander CPR and defibrillation at the scene, on route, and on hospital arrival, had shockable rhythm on EMS arrival and hospital arrival, and underwent most of the post-ROSC invasive treatments, compared with those without high Clinical Frailty Scale score. Conversely, more patients with moderate-to-severe frailty suffered from cardiac arrest at home, underwent out-of-hospital intubation and received intravenously administered fluid and epinephrine before hospital arrival compared with those with no-to-low frailty. The median no- and low-flow times were comparable between the 2 groups: 9 to 10 and 34 to 35 min,

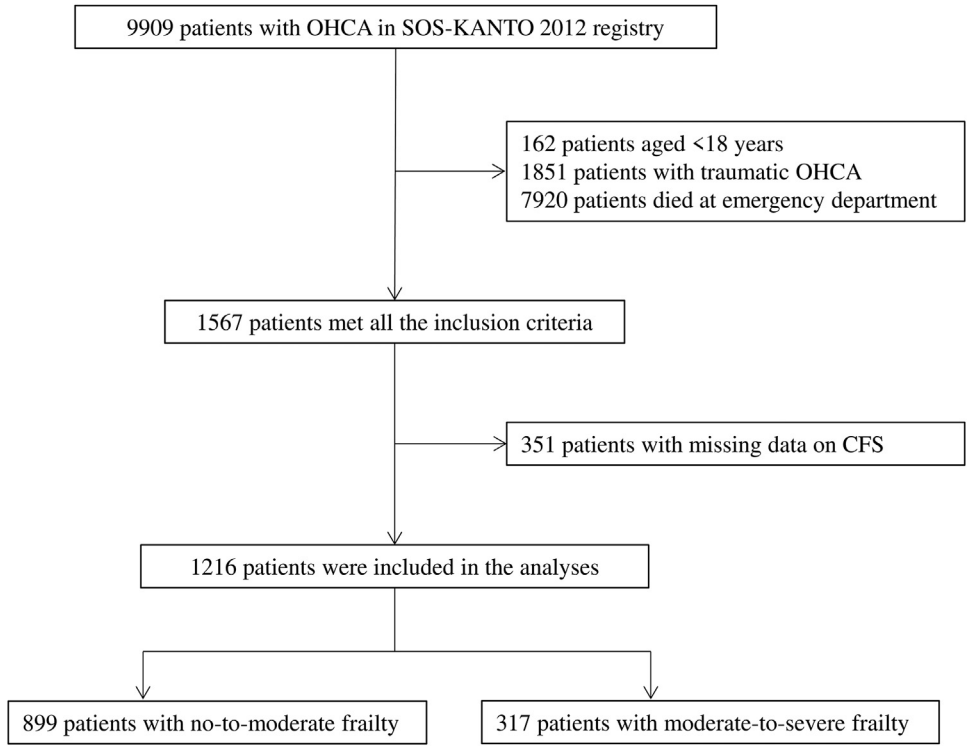

Figure. Patient flow diagram. Of 9,909 patients with OHCA in the SOS-KANTO 2017 database, 1216 adult patients with nontraumatic OHCA were admitted to intensive care units and had available pre-arrest Clinical Frailty Scale data. Therefore, they were eligible for inclusion in this study. A total of 317 (26.1%) patients had moderate-to-severe frailty (Clinical Frailty Scale score $\geq$ 5). *CFS*, Clinical Frailty Scale.

respectively. Patient characteristics between those with and without available Clinical Frailty Scale data are shown in Table E3 (available at http://www.annemergmed.com), in which no obvious differences were identified in any variables.

Favorable Neurologic Outcomes and Secondary Outcomes

The rate of favorable neurologic function (Cerebral Performance Category score equal or less than 2) at 30 days after ROSC from OHCA was significantly lower in patients with high Clinical Frailty Scale score than in those without high Clinical Frailty Scale score in unadjusted analysis (18 [6.1%] vs 202 [24.4%]; OR, 0.20 [95% CI 0.12 to 0.33]; Table 2).

A GEE model for adjusted OR was developed with Clinical Frailty Scale score and OHCA-related variables (Table E4, available at http://www.annemergmed.com). The adjusted analysis using the GEE model showed that a high Clinical Frailty Scale score was associated with a lower rate of favorable neurologic function at 30 days (adjusted OR, 0.45 [95% CI 0.24 to 0.82]; Table 2). Moreover, the additional GEE models incorporating treatments after ROSC and laboratories on admission that were replaced with some OHCA-related variables in the primary GEE model revealed similar results (adjusted OR, 0.54 [95% CI 0.26 to 0.97] and adjusted OR, 0.44 [95% CI 0.20 to 0.96], respectively; Table 2).

Lower survival at 30 days and lower incidences of Cerebral Performance Category score of 2 or less at hospital discharge and at 90 days after ROSC were also associated with high Clinical Frailty Scale score (58 [19.1%] vs 337 [39.2%]; OR, 0.52 [95% CI 0.28 to 0.98], 24 [7.6%] vs 233 [26.8%]; OR, 0.41 [95% CI 0.21 to 0.82], and 13 [4.5%] vs 203 [25.6%]; OR, 0.24 [95% CI 0.11 to 0.50], respectively; Table 2). Median differences in hospital-free days, length of hospital stay, and days to DNAR order were insignificant between the 2 groups.

The sensitivity analysis using all covariates from the primary and 2 additional models revealed a relationship between high Clinical Frailty Scale score and fewer frequency of favorable neurologic outcomes (OR, 0.10 [95% CI 0.03 to 0.33]; Table E5, available at http://www.annemergmed.com). In addition, multivariate logistic regression and inverse probability weighting with propensity score similarly revealed that moderate-to-high frailty as a pre-arrest condition was associated with decreased favorable neurologic outcomes (OR, 0.14 [95% CI 0.02 to 0.86] and OR, 0.36 [95% CI 0.27 to 0.47], respectively; Table E5).

Table 1. Characteristics of patients with nontraumatic OHCA.

	Moderate-To-Severe Frailty		No-To-Mild Frailty	
Case	**317**		**899**	
Demographics				
Clinical Frailty Scale score, median (IQR)	6	(5–7)	3	(2–3)
Age, y; median (IQR)	79	(71–85)	66	(54–76)
Sex, male, n (%)	191	(60.3)	650	(72.3)
Comorbidity, Charlson Comorbidity Index, median (IQR)	1	(0–3)	0	(0–1)
Cause, cardiogenic, n (%)	152	(47.9)	657	(73.1)
Out-of-hospital information before EMS arrival, n (%)				
Cardiac arrest at home	221	(69.7)	487	(54.2)
Witness presence	207	(65.3)	646	(71.9)
Bystander CPR	138	(43.5)	481	(53.)
Bystander AED	8	(2.5)	89	(9.9)
Out-of-hospital information after EMS arrival, n (%)				
ROSC on EMS arrival	15	(4.7)	76	(8.5)
Shockable rhythm on EMS arrival*	20	(6.3)	289	(32.1)
Cardiac arrest on route	31	(9.8)	122	(13.6)
ROSC on route	123	(38.8)	340	(37.8)
Out-of-hospital treatment, n (%)				
Supraglottic airway device	135	(42.6)	341	(37.9)
Intubation	54	(17.0)	107	(11.9)
Defibrillation	31	(9.8)	346	(38.5)
Intravenous line	171	(53.9)	383	(42.6)
Epinephrine	147	(46.4)	321	(35.7)
Mechanical CPR	22	(6.9)	58	(6.5)
Out-of-hospital physician presence	52	(16.4)	108	(12.0)
Inhospital information				
ROSC on arrival, n (%)	123	(38.8)	370	(41.2)
GCS on arrival, median (IQR)	3	(3-3)	3	(3-3)
Shockable rhythm on arrival, n (%)	13	(4.1)	116	(12.9)
Defibrillation after arrival, n (%)	36	(11.4)	222	(24.7)
Intubation after arrival, n (%)	252	(79.5)	770	(85.7)
Mechanical CPR after arrival, n (%)	31	(9.8)	105	(11.7)
Extracorporeal CPR, n (%)	3	(0.9)	157	(17.5)
No-flow time, min, median (IQR)	10	(7–14)	9	(6–13)
Low-flow time, min, median (IQR)	34	(24–43)	35	(26–46)
Treatment after ROSC, n (%)				
ECMO	8	(2.5)	55	(6.1)
Coronary angiography	25	(7.9)	394	(43.8)
Coronary revascularization	12	(3.8)	203	(22.6)
TTM	41	(12.9)	355	(39.5)
GCS on admission, median (IQR)	3	(3–3)	3	(3–3)
Laboratory on admission, median (IQR)				
PaO_2, mmHg	152	(83–291)	145	(76–302)
$PaCO_2$, mmHg	61	(40–84)	48	(36–70)
Base excess, mEq/L	−13	(−20 to −7)	−13	(−19 to −7)
Lactate, mmol/L	10.2	(6.9–14.2)	9.4	(6.2–13.3)
WBC, $10^3/\mu L$	10.7	(8.0–14.5)	10.4	(7.8–13.5)

Table 1. Continued.

	Moderate-To-Severe Frailty		No-To-Mild Frailty	
Case	**317**		**899**	
Hemoglobin, g/dL	11.1	(9.4–12.7)	12.9	(11.1–14.6)
Na, mEql/L	140	(136–143)	140	(138–143)
K, mEql/L	5.2	(4.2–6.3)	4.2	(3.6–5.2)
Albumin, g/dL	2.8	(2.4–3.3)	3.4	(3.0–3.9)
D-dimer, μg/mL	17.5	(8.4–29.9)	9.8	(3.8–25.1)

IQR, interquartile range; *AED*, automated external defibrillator; *GCS*, Glasgow Coma Scale; *ECMO*, extracorporeal membrane oxygenation; *TTM*, targeted temperature management; PaO_2, arterial oxygen pressure; $PaCO_2$, partial pressure of carbon dioxide; *WBC*, white blood cell count.
*Shockable rhythm includes ventricular fibrillation and pulseless ventricular tachycardia.

Furthermore, repeated GEE analyses with other cut-offs in the Clinical Frailty Scale score for high clinical frailty revealed that a Clinical Frailty Scale score of 6 or more was similarly related to fewer incidences of favorable neurologic function at 30 days, whereas a Clinical Frailty Scale score of 4 or more did not (Table E5).

Subgroup Analysis

Subgroup analyses (Table 3) revealed a relationship between unfavorable neurologic function at 30 days after ROSC and high Clinical Frailty Scale score (Clinical Frailty Scale score of 5 or more) in several subgroups, namely, patients with cardiogenic OHCA, elderlies (65 years or older) and nonelderly adults (younger than 65 years), those with ROSC after hospital arrival, and those without a high risk of dying (Clinical Frailty Scale score of 7 or less).

Patients with noncardiogenic OHCA had a comparable incidence of favorable neurologic outcomes regardless of pre-arrest frailty.

LIMITATIONS

The study results must be interpreted within the context of the study design. First, the pre-arrest frailty was evaluated using only the Clinical Frailty Scale score, and other types of scaling, such as the Study of Osteoporotic Fractures index[25] and Fatigue, Resistance, Ambulation,

Table 2. Neurologic and other clinical outcomes.

	Moderate-To-Severe Frailty	No-To-Mild Frailty	OR (95 CI)		Difference In Median (95 CI)	
Cerebral Performance Category ≤ 2 at 30 days						
Unadjusted, n/total (%)	18/294 (6.1)	202/827 (24.4)	0.20	(0.12 to 0.33)		
Adjusted with GEE model			0.45	(0.24 to 0.82)		
Additional model with treatments after ROSC			0.54	(0.26 to 0.97)		
Additional model with laboratories on admission			0.44	(0.20 to 0.96)		
Survival at 30 days, n/total (%)	58/303 (19.1)	337/859 (39.2)	0.52	(0.28 to 0.98)		
Cerebral Performance Category ≤2 at discharge, n/total (%)	24/314 (7.6)	233/868 (26.8)	0.41	(0.25 to 0.86)		
Cerebral Performance Category ≤2 at 90 days, n/total (%)	13/288 (4.5)	203/794 (25.6)	0.26	(0.15 to 0.48)		
Hospital-free-days up to 90 days, days, mean, median (IQR)	10, 0 (0–0)	23, 0 (0–59)			0	(0 to 0)
Length of hospital stay, days, mean, median (IQR)*	21, 13 (3–34)	16, 8 (3–23)			2	(-1 to 7)
Days to DNAR order, days, mean, median (IQR)*	8, 4 (2–10)	5, 3 (1–6)			1	(0 to 2)

OR, odds ratio.
*Patients who survived for >1 day were included.

Table 3. Favorable neurologic outcomes in subgroup analyses.

				CFS ≥ 5	
		Moderate-To-Severe Frailty	No-To-Mild Frailty	OR	95% CI
Cause					
	Cardiogenic	6.3% (2.3%–10.3%)	31.4% (27.7%–35.2%)	0.24	0.11 to 0.51
	Noncardiogenic	6.0% (2.2%–9.7%)	6.1% (3.0%–9.2%)	0.95	0.26 to 3.43
Age					
	<65 y	7.1% (0.0%–16.7%)	29.3% (24.8%–33.8%)	0.29	0.09 to 0.88
	≥65 y	6.0% (3.2%–8.9%)	20.0% (16.3%–23.8%)	0.19	0.07 to 0.50
ROSC					
	Before hospital arrival	14.0% (7.4%–20.6%)	50.3% (44.8%–55.8%)	0.72	0.34 to 1.56
	After hospital arrival	1.6% (0.0%–3.4%)	7.9% (5.6%–10.3%)	0.14	0.04 to 0.47
Patients without a high risk of dying (CFS ≤ 7)		6.6% (3.6%–9.6%)	24.4% (21.5%–27.4%)	0.46	0.24 to 0.87

CFS, Clinical Frailty Scale. Generalizing estimating equations were performed in each subgroup.

Illness, and Loss of Weight index, were not recorded.[26] Therefore, the results may differ if the frailty is assessed with other methods. Second, the details of pathophysiological changes during ICU stay, such as daily vital signs and the degree of organ dysfunction, were unavailable. Although suboptimal recovery because of limited homeostatic response would introduce an unfavorable neurologic function in patients with high frailty, it cannot be validated based on objective data. Third, unmeasured biases because of endogeneity, including differences in management strategies and the termination of invasive treatment depending on the frailty, would conclude another result. However, considering the potential difference in treatment intensity between patients with and without high frailty, GEE analyses with and without covariates for post-ROSC treatment were conducted and validated the relationship between high Clinical Frailty Scale score and a lower rate of favorable neurologic outcomes. Finally, as this study investigated only patients who were resuscitated and then obtained ROSC, the results did not suggest the usefulness of the Clinical Frailty Scale in predicting the successful recovery of spontaneous circulation from OHCA. The pre-arrest frailty should be assessed using the Clinical Frailty Scale in patients with OHCA only to predict favorable neurologic function after ROSC.

DISCUSSION

In this prospective observational study, a high Clinical Frailty Scale score before a cardiac arrest was associated with unfavorable neurologic outcomes in patients resuscitated from nontraumatic OHCA. Importantly, this relationship remained after adjusting for patient background and resuscitation characteristics, and multiple sensitivity analyses also confirmed the robustness of our results.

Based on the study results, several clinical benefits of using the Clinical Frailty Scale for patients with OHCA can be considered. First, given that a high Clinical Frailty Scale score was independently associated with neurologic outcomes after adjusting for patient demographics, the Clinical Frailty Scale score can be applied as an integrated score that manifests both preservation and deprivation in homeostatic functions due to each disease and condition. Although the frailty was determined by various physiological deteriorations, including aging, the existence of comorbidities, and loss of activity in daily living,[8-10] physicians would categorize patients using the 1 to 9 scale of Clinical Frailty Scale only with limited information regarding the patient background, rather than using details in the severity of comorbidities.[27] Second, a high Clinical Frailty Scale score of 5 or more would predict unfavorable neurologic function after OHCA. As a considerable number of patients with OHCA would suffer from neurologic disabilities even after the return of circulation,[1,4] Clinical Frailty Scale score would be feasible to forecast clinical consequences relevant to well-being after ROSC. Third, considering that the Clinical Frailty Scale score was a pre-arrest parameter and not affected by any resuscitation characteristic related to prognosis, the Clinical Frailty Scale score would help determine advanced care planning on intensive care after ROSC. Notably, a high Clinical Frailty Scale score might be useful even for patients without obvious risks of dying (Clinical Frailty Scale score of less than 8) based on the subgroup analysis.

A high Clinical Frailty Scale score was also associated with increased mortality at 30 days and unfavorable

neurologic outcomes at discharge and at 90 days after admission. These results were similar to those of previous studies, which reported that high frailty was associated with mortality after inhospital cardiac arrest.[28-30] Considering that this study targeted OHCA, the usefulness of the Clinical Frailty Scale would be generalized regardless of the place of cardiac arrest. Moreover, days to DNAR order were not different between patients with no-to-low and moderate-to-high frailty, which indicates that the unfavorable neurologic function at 30 days of patients with high Clinical Frailty Scale score would not be from an early termination of intensive care. In addition, although possible endogeneity between high Clinical Frailty Scale score and low tendency to provide invasive treatment would be expected, GEE models both with and without treatment variables after ROSC similarly revealed the relationship between high Clinical Frailty Scale score and neurologic outcomes, suggesting that a high Clinical Frailty Scale score would be an independent predictor of neurologic functions after OHCA.

Patients with noncardiogenic OHCA had similar clinical outcomes regardless of the frailty in the subgroup analyses, suggesting that the Clinical Frailty Scale score would not be useful in patients with high baseline risks for devastating neurologic outcomes. However, as the sample size was limited in each subgroup, the interpretation of these results should be cautioned. Regarding patients who obtained ROSC before hospital arrival, the association between high Clinical Frailty Scale score and unfavorable outcomes was not evaluated because of the wide CI of OR. Moreover, although the cut-off value for a high Clinical Frailty Scale score was set as 5 in this study based on previous studies,[9,14,16] Clinical Frailty Scale score of 6 or more would be another option for defining high frailty to predict unfavorable outcomes. Further studies are needed to examine the appropriate cut-offs.

High frailty, defined as a Clinical Frailty Scale score of 5 or more, was associated with a lower frequency of favorable neurologic outcomes, a Cerebral Performance Category score of 2 or less 30 days after admission in resuscitated patients from OHCA. The assessment of pre-arrest frailty using the Clinical Frailty Scale would be useful for considering advanced care planning on intensive care after ROSC.

Supervising editor: Clifton Callaway, MD, PhD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency and Critical Care Medicine, Keio University School of Medicine (Yamamoto, Tamura, Haiden, Yoshizawa, Homma, Sasaki), Tokyo, Japan; the Department of Emergency and Critical Care Medicine, Kimitsu Chuo Hospital (Kitamura), Chiba, Japan; the Tertiary Emergency Medical Center, Tokyo Metropolitan Bokutoh Hospital (Sugiyama), Tokyo, Japan; the Department of Emergency and Critical Care Medicine, Nippon Medical School Musashikosugi Hospital (Tagami), Kanagawa, Japan; the Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo (Yasunaga), Tokyo, Japan; the Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo (Aso), Tokyo, Japan; the Department of Critical Care and Emergency Medicine, Tokyo Women's Medical University (Takeda), Tokyo, Japan.

Authors' contributions: RY, TT, HK, KS, and JS designed the study. RY, AH, JY, and TT performed data collection. NK, MT, and JS managed quality control. RY and TT performed data analysis. RY, TT, HY, and SA conducted data interpretation. RY, TT, HK, KS, and JS performed writing and critical revision. All authors revised the article. RY and TT contributed equally to this work. RY takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors do not have any conflict of interest to declare. This study was not supported by any funding.

Publication dates: Received for publication November 15, 2022. Revisions received January 9, 2023, and February 1, 2023. Accepted for publication February 9, 2023.

Availability of data and materials: Data used in this study are available from the SOS-KANTO 2017 study group. However, restrictions apply to the availability of these data, which were used under the license for the current study and so are not publicly available. Data are available from the authors upon reasonable request and with the permission of the SOS-KANTO 2017 study group.

REFERENCES

1. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: current concepts. *Lancet*. 2018;391:970-979.
2. Andersen LW, Holmberg MJ, Berg KM, et al. In-hospital cardiac arrest: a review. *JAMA*. 2019;321:1200-1210.
3. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus Normothermia after out-of-hospital cardiac arrest. *N. Engl. J. Med*. 2021;384:2283-2294.
4. Jentzer JC, Clements CM, Wright RS, et al. Improving survival from cardiac arrest: a review of contemporary practice and challenges. *Ann. Emerg. Med*. 2016;68:678-689.
5. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. *Lancet*. 2021;398:1269-1278.

6. Yates EJ, Schmidbauer S, Smyth AM, et al. Out-of-hospital cardiac arrest termination of resuscitation with ongoing CPR: an observational study. *Resuscitation*. 2018;130:21-27.
7. Steptoe A, Deaton A, Stone AA. Subjective wellbeing, health, and ageing. *Lancet*. 2015;385:640-648.
8. Dent E, Martin FC, Bergman H, et al. Management of frailty: opportunities, challenges, and future directions. *Lancet*. 2019;394:1376-1386.
9. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489-495.
10. Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. *Can Geriatr J*. 2020;23:210-215.
11. Elliott A, Taub N, Banerjee J, et al. Does the clinical frailty scale at triage predict outcomes from emergency care for older people? *Ann. Emerg. Med*. 2021;77:620-627.
12. Kaeppeli T, Rueegg M, Dreher-Hummel T, et al. Validation of the clinical frailty scale for prediction of thirty-day mortality in the emergency department. *Ann. Emerg. Med*. 2020;76:291-300.
13. O'Mahony M, Mohammed K, Kasivisvanathan R. Cardiopulmonary exercise testing versus frailty, measured by the clinical frailty score, in predicting morbidity in patients undergoing major abdominal cancer surgery. *World J. Surg*. 2021;45:116-125.
14. Hamlyn J, Lowry C, Jackson TA, et al. Outcomes in adults living with frailty receiving cardiopulmonary resuscitation: a systematic review and meta-analysis. *Resusc Plus*. 2022;11:100266.
15. Jonsson H, Piscator E, Israelsson J, et al. Is frailty associated with long-term survival, neurological function, and patient-reported outcomes after in-hospital cardiac arrest? - a Swedish cohort study. *Resuscitation*. 2022;179:233-242.
16. Mowbray FI, Manlongat D, Correia RH, et al. Prognostic association of frailty with post-arrest outcomes following cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2021;167:242-250.
17. Sulzgruber P, Sterz F, Poppe M, et al. Age-specific prognostication after out-of-hospital cardiac arrest - The ethical dilemma between 'life-sustaining treatment' and 'the right to die' in the elderly. *Eur Heart J Acute Cardiovasc Care*. 2017;6:112-120.
18. SOS-KANTO 2012 Study Group. Changes in pre- and in-hospital management and outcomes for out-of-hospital cardiac arrest between 2002 and 2012 in Kanto, Japan: the SOS-KANTO 2012 Study. *Acute Med Surg*. 2015;2:225-233.
19. Hayashida K, Suzuki M, Yonemoto N, et al. Early lactate clearance is associated with improved outcomes in patients with postcardiac arrest syndrome: a prospective, multicenter observational study (SOS-KANTO 2012 Study). *Crit. Care Med*. 2017;45:e559-e566.
20. Yamamoto R, Suzuki M, Yoshizawa J, et al. Physician-staffed ambulance and increased in-hospital mortality of hypotensive trauma patients following prolonged prehospital stay: a nationwide study. *J Trauma Acute Care Surg*. 2021;91:336-343.
21. Grossestreuer AV, Abella BS, Sheak KR, et al. Inter-rater reliability of post-arrest cerebral performance category (CPC) scores. *Resuscitation*. 2016;109:21-24.
22. Balouris SA, Raina KD, Rittenberger JC, et al. Development and validation of the cerebral performance categories-extended (CPC -E). *Resuscitation*. 2015;94:98-105.
23. Bible J, Albert PS, Simons-Morton BG, et al. Practical issues in using generalized estimating equations for inference on transitions in longitudinal data: what is being estimated? *Stat. Med*. 2019;38:903-916.
24. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat. Methods Med. Res*. 2017;26:1654-1670.
25. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J. Gerontol. A Biol. Sci. Med. Sci*. 2007;62:744-751.
26. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle-aged African Americans. *J. Nutr. Health Aging*. 2012;16:601-608.
27. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. *Eur. J. Intern. Med*. 2016;31:3-10.
28. Fernando SM, McIsaac DI, Rochwerg B, et al. Frailty and associated outcomes and resource utilization following in-hospital cardiac arrest. *Resuscitation*. 2020;146:138-144.
29. Hu FY, Streiter S, O'Mara L, et al. Frailty and survival after in-hospital cardiopulmonary resuscitation. *J. Gen. Intern. Med*. 2022.
30. Wharton C, King E, MacDuff A. Frailty is associated with the adverse outcome from in-hospital cardiopulmonary resuscitation. *Resuscitation*. 2019;143:208-211.