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ORIGINAL ARTICLE

Nutritional screening based on the controlling nutritional status (CONUT) score at the time of admission is useful for long-term prognostic prediction in patients with heart failure requiring hospitalization

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Abstract The objective of the study was to clarify whether controlling nutritional status (CONUT) is useful for predicting the long-term prognosis of patients hospitalized with heart failure (HF). A total of 482 (57.5%) HF patients from the Ibaraki Cardiovascular Assessment Study-HF ($N = 838$) were enrolled (298 men, 71.7 ± 13.6 years). At admission, blood samples were collected and nutritional status assessed using CONUT. CONUT scores were defined as follows: 0–1, normal; 2–4, light; 5–8, moderate; and 9–12, severe undernutrition. Accordingly, 352 (73%) patients had light-to-severe nutritional disturbances. In the follow-up period [median 541.5 (range 354–786) days], 109 deaths were observed. A Kaplan–Meier analysis revealed that all-cause deaths occurred more frequently in HF patients with nutritional disturbances [$n = 93$ (26.4%)] than in those with normal nutrition [$n = 16$ (12.3%); log-rank $p < 0.001$]. The Cox proportional hazard analyses revealed that a per point increase in the CONUT score was associated with an increased risk of all-cause death (hazard ratio 1.142; 95% confidence interval, 1.044–1.249) after controlling simultaneously for age, sex, previous history of HF hospitalization, log brain natriuretic peptide, and use of therapeutic agents at admission (tolvaptan and aldosterone antagonists). This study suggests that nutritional screening using CONUT scores is helpful in predicting the long-term prognosis of patients hospitalized with HF in a multicenter registry setting.

Keywords CONUT score · Heart failure · Nutritional screening · Prognosis

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Introduction

Recently, advances in the treatment of heart failure (HF) have resulted in improved prognosis among patients. HF, however, is still associated with high morbidity and mortality. According to registry studies in Japan, the 1-year mortality rate in patients with HF was 7–9%, and the rate of hospital readmission due to an exacerbation of HF within 1 year of hospital discharge was 15–40% [1]. These data suggest that HF therapy is currently inadequate. Investigators have conducted research related to HF and identified several clinically significant prognostic factors. Data from this research can help healthcare providers to optimize patient management, which may help to decrease suboptimal HF outcomes. In recent years, evaluating and treating nutritional status in HF patients have emerged as an important area of research,

as undernutrition is associated with a suboptimal prognosis. Further study is needed, however, in order to confirm further details.

Researchers have promoted the use of various methods and indices for nutritional evaluation. Some of these methods and indices are used to predict unfavorable prognoses in patients with HF. In patients admitted for HF, Bonilla-Palomas et al. [2] used the Mini Nutritional Assessment (MNA) score. This study showed that malnutrition was present in 13% of the patients, which was found to be an independent predictor of mortality. The MNA, however, includes subjective data that are evaluated by medical staff; therefore, this index may not be convenient to use in a routine clinical setting.

The controlling nutritional status (CONUT) score [3] is calculated using serum albumin, total cholesterol level, and total lymphocyte count. A convenient indicator in laboratory analysis, CONUT, allows for the evaluation of protein reserves, calorie depletion, and immune parameters. A high CONUT score is related to an unfavorable prognosis in patients hospitalized with acute HF [4–6], in patients hospitalized with chronic HF [7], and in patients with HF classified as "stage B" according to American Heart Association/American College of Cardiology (AHA/ACC) guidelines [8]. Additionally, in patients with HF who needed hospitalization, a high CONUT score was related to in-hospital death [9].

A Japanese single-center registry study performed by Iwakami et al. [6] showed that malnutrition assessed based on the CONUT score upon admission was an independent determinant of long-term death among patients with acute HF. Multicenter trials are conducted at various locations and offer some advantages compared with single-center trials, which have potentially limited external validity [10–12]. Furthermore, the results of the research may vary if the number of deaths is small [13–18]. Thus, multicenter studies conducted among the Japanese population with higher number of deaths than the previous studies are needed to examine the association between malnutrition and long-term prognosis of patients with HF requiring hospitalization.

The present study aimed to clarify whether determining the CONUT score upon admission may be useful in predicting not only the short-term [9] but also the long-term prognosis of patients hospitalized with HF in a multicenter registry setting.

Materials and methods

Study population

A total of 838 patients with HF symptoms were hospitalized between June 2012 and March 2015 and were enrolled in the Ibaraki Cardiovascular Assessment Study-HF (ICAS-HF) registry. Follow-ups were conducted in the patients until March 31, 2016. The ICAS-HF is a multicenter registry study involving 11 hospitals in the Ibaraki Prefecture of Japan. The ICAS-HF registry inclusion criteria were patient age ≥20 years and the fulfillment of Framingham criteria for HF [19]. The registry exclusion criteria were patient age <20 years, patients who did not provide informed consent to the attending physician, patients with limited life expectancy due to malignant neoplasms, patients in whom the 2-year observation was predicted to be impossible, and patients who were medically judged as inappropriate by the attending physician. Written informed consent was obtained from all patients, and data collection for this study was approved by the institutional review boards of the 11 participating hospitals. Additionally, the ICAS-HF registry study was conducted in accordance with the ethical principles dictated by the Declaration of Helsinki.

Data from the ICAS-HF registry were retrospectively analyzed. Three parameters are used to calculate the CONUT score: serum albumin level, total cholesterol level, and total lymphocyte count (Table 1). Among the 838 patients enrolled in the registry, serum albumin level was unavailable for 25 patients, total cholesterol level was unavailable for 146 patients, and total lymphocyte count was unavailable for 267 patients. Registry patients for whom CONUT scores could not be estimated were excluded ($n = 356$), and a total of 482 patients with CONUT scores were ultimately enrolled in this study. The patient characteristics of the excluded patients were comparable to characteristics of the enrolled patients. Most study variables were similar, with the exception of the serum albumin level and therapeutic agents prescribed. In addition, the Kaplan–Meier analysis revealed that all-cause deaths did not occur more frequently in a group of patients that had a CONUT score [$n = 109$ (22.6%)] compared to a group of patients that did not have a CONUT score [$n = 75$ (21.1%)] (log-rank $p = 0.96$).

Table 1 Assessment of undernutrition degree by CONUT score

Parameter	Undernutrition degree			
	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3.0–3.49	2.5–2.99	<2.5
Score	0	2	4	6
Total lymphocytes (/μL)	≥1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3
Total CONUT score	0–1	2–4	5–8	9–12

CONUT controlling nutritional status

Data collection and definition of nutritional impairment

Baseline clinical data were collected for each patient. All patient-related information collected at enrollment, including medical history, laboratory test results, and echocardiographic findings, was recorded in a computer database. Essentially, blood sampling and echocardiographic examinations were performed within 72 h of admission. Blood tests were performed to determine total lymphocyte counts, hemoglobin, albumin, total cholesterol, serum creatinine, C-reactive protein, and plasma brain natriuretic peptide (BNP) levels. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR = 194 × serum creatinine$^{-1.094}$ × age in years$^{-0.287}$ for male patients. The adjusted eGFR value for female patients was calculated using the following formula: eGFR female = eGFR × 0.739 [20]. As edema is known to significantly affect patient body weight at admission, the patients' body weights were measured after their condition stabilized. The body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters.

Assessment of nutritional status using CONUT scores

The CONUT score is a sum of 3 parameters: the serum albumin level (g/dL), total cholesterol level (mg/dL), and the total lymphocyte count (/μL) (Table 1). The serum albumin level serves as an indicator of protein reserves, while the total cholesterol level is an indicator of caloric depletion. The total lymphocyte count is used as an indicator of undernutrition-mediated impaired immune defense. Patients with CONUT scores of 0–1 have a normal nutritional status, those with CONUT scores of 2–4 have a light degree of undernutrition, those with CONUT scores of 5–8 have a moderate degree of undernutrition, and those with CONUT scores of 9–12 have a severe degree of undernutrition (Table 1).

Assessment of long-term prognosis using CONUT scores

We divided the present study patients into two groups: (1) HF patients with normal nutrition (patients with CONUT scores of 0–1), and (2) HF patients with nutritional disturbances (patients with CONUT scores of 2–12).

We examined whether nutritional status assessed using the CONUT score was associated with all-cause death, cardiovascular death, and aged HF patients (≥75 years old). Cardiovascular death was defined as a death attributable to cardiovascular origin, and a noncardiovascular death was defined as a death attributable to reasons of noncardiovascular origin (e.g., respiratory, gastrointestinal, renal, cancer-related, or infectious).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if normally distributed, and as median (interquartile range) if non-normally distributed. Differences between two groups were compared using an unpaired Student's *t* test or a Mann–Whitney *U* test, as appropriate. A Chi square test was used to compare categorical variables.

The Kaplan–Meier analysis with log-rank test was performed to determine whether nutritional assessment using CONUT scores is useful in predicting long-term prognosis in patients hospitalized with HF. In addition, a Cox proportional hazards model analysis was performed to determine the significant predictors of long-term prognosis. In the univariate analysis, we mainly defined the covariates as those variables that showed a statistically significant correlation with long-term prognosis. First, to evaluate the influence of the CONUT score on all-cause death, the following four Cox proportional hazard regression models were constructed: model 1, unadjusted; model 2, age and sex adjusted; model 3; and model 4. In model 3, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, logarithmic transformation BNP (log BNP), and use of therapeutic agents at admission (carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 4, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, log BNP, and use of therapeutic agents at admission (tolvaptan and aldosterone antagonists). Second, the following four Cox proportional hazard regression models were constructed to evaluate the effect of the CONUT score on cardiovascular death: model 1, unadjusted; model 2, age and sex adjusted; model 5; and model 6. In model 5, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, log BNP, and use of therapeutic agents at admission (positive inotropic action agents or phosphodiesterase inhibitor, carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 6, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, eGFR, log BNP, and use of aldosterone antagonists at admission.

Finally, the following four Cox proportional hazard regression models were constructed to evaluate the influence of the CONUT score on noncardiovascular or unknown death: model 1, unadjusted; model 2, age and sex adjusted; model 7; and model 8. In model 7, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, hemoglobin level, and use of tolvaptan at admission. In model 8, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, and use of tolvaptan at admission.

A p value <0.05 was considered statistically significant. All statistical analyses were performed using StatView 5.0 for Windows.

Results

Baseline characteristics of study patients

The mean age of the included patients was 71.7 ± 13.6 years. Male patients accounted for 61.8% (n = 298) of the study population. At the time of admission, based on the New York Heart Association Functional Classification, 50 patients were classified as class II, 174 patients as class III, and 253 patients were classified as class IV. The median plasma BNP level of the study population was 741.5 (387.0–1257.8) pg/mL, and as the distribution of BNP levels was highly skewed, the data were normalized through a logarithmic transformation. The mean visual left ventricular ejection fraction (LVEF), as measured using echocardiography, was 40.5 ± 15.2%. The median CONUT score of the study population was 3 (1–5). Of the 482 enrolled HF patients for whom CONUT scores could be calculated, 352 (73%) had light-to-severe nutritional disturbances (light, 46.1%; moderate, 23.9%; severe, 3.1%).

Evaluation of long-term prognosis by CONUT assessment

In the present study, the 482 HF included patients were divided into two groups: (1) HF patients with normal nutrition (n = 130), and (2) HF patients with nutritional disturbances (n = 352). The clinical characteristics of the patients enrolled in the two groups are shown in Table 2. Between these two groups, there was a significant difference in age, BMI, systolic blood pressure, heart rate, previous history of HF hospitalization, hemoglobin, eGFR, plasma BNP, serum albumin, total cholesterol, total lymphocytes counts, C-reactive protein, the use of carperitide, and the use of tolvaptan.

Impact of nutritional screening using CONUT scores on all-cause death

In the follow-up period [541.5 (354–786) days], 109 deaths were observed. Of these, 74 patients (67.9%) had a cardiovascular death: HF death (n = 54, 49.5%), sudden death (n = 15, 13.8%), and others (n = 5, 4.6%). Thirty-five patients (32.1%) experienced noncardiovascular (n = 30) or unknown (n = 5) deaths.

The Kaplan–Meier analysis revealed that all-cause deaths occurred more frequently in HF patients with nutritional disturbances [n = 93 (26.4%)] compared to patients with normal nutrition [n = 16 (12.3%)] (log-rank $p < 0.001$) (Fig. 1). Table 3 shows the impact of nutritional screening using CONUT scores on all-cause death. The Cox proportional hazard analyses revealed that a per point increase in the CONUT score was associated with an increased risk of all-cause death [hazard ratio (HR) and 95% confidence interval (CI): 1.169 and 1.088–1.256, respectively, for model 1; 1.163 and 1.081–1.251, respectively, for model 2; and 1.142 and 1.044–1.249, respectively, for model 4]. The analysis also revealed that HF patients with nutritional disturbances had an increased risk for all-cause death compared to patients in the normal nutrition group ($p < 0.01$; HR and 95% CI: 2.627 and 1.544–4.469, respectively, for model 1; 2.378 and 1.393–4.060, for model 2, respectively) (Table 3). Table 4 presents the univariate and multivariate associations between nutritional status and all-cause deaths.

The Kaplan–Meier analysis revealed that cardiovascular deaths occurred more frequently in HF patients with nutritional disturbances than in those with normal nutrition (p = 0.003 by the log-rank test). The Cox proportional hazard analyses revealed that a per point increase in the CONUT score was associated with an increased risk of cardiovascular deaths in model 1 (unadjusted) and model 2 (age and sex adjusted), but not in model 6 (HR and 95% CI: 1.136 and 1.039–1.241, respectively, for model 1; 1.132 and 1.035–1.239, respectively, for model 2; and 1.087 and 0.977–1.209, respectively, for model 6) (Table 5). Table 6 presents the univariate and multivariate associations between nutritional status and cardiovascular deaths. Additionally, the Kaplan–Meier curves for the noncardiovascular or unknown death end point differed significantly between HF patients with nutritional disturbances and those with normal nutrition (p = 0.024 by the log-rank test). A per point increase in the CONUT score was correlated with an increased risk of noncardiovascular or unknown deaths in model 1 (unadjusted), model 2 (age and sex adjusted), and model 8 based on the Cox proportional hazard analyses (HR and 95% CI: 1.239 and 1.095–1.401, respectively, for model 1; 1.230 and 1.086–1.393, respectively, for model 2; and 1.180 and 1.034–1.346, respectively, for model 8)

Table 2 Clinical characteristics of the patients by CONUT score

	HF patients with normal nutrition ($n = 130$)	HF patients with nutritional disturbances ($n = 352$)	p value
Age (years)	68.8 ± 14.0	72.8 ± 13.3	0.004
Male, *n* (%)	79 (60.8%)	219 (62.2%)	0.83
NYHA (2/3/4/unknown)	14/42/73/1	36/132/180/4	
NYHA (3 or 4), *n* (%)	115 (89.1%)	312 (89.7%)	
BMI (kg/m^2) at stable state	23.1 ± 3.5	21.9 ± 4.0	0.003
Systolic blood pressure (mmHg)	154 [125–190]	136 [116–162]	<0.001
Heart rate (beats/min)	107 ± 31	96 ± 27	<0.001
Medical history			
Current or past smoker, *n* (%)	74 (56.9%)	174 (49.4%)	0.152
Readmission count for HF (0/1/2/≥3)	105/9/8/8	246/38/24/44	0.085
Previous history of HF hospitalization, *n* (%)	25 (19.2%)	106 (30.1%)	0.021
Hypertension, *n* (%)	67 (51.5%)	202 (57.4%)	0.26
Dyslipidemia, *n* (%)	42 (32.3%)	106 (30.1%)	0.66
Cerebrovascular disease, *n* (%)	5 (3.8%)	22 (6.3%)	0.38
Laboratory measurement			
Hemoglobin (g/dL)	13.8 ± 2.3	11.8 ± 2.4	<0.001
Estimated GFR (mL min^{-1} 1.73 m^{-2})	54.2 [42.7–70.8]	45.0 [30.1–65.1]	<0.001
BNP (pg/mL)	658.5 [328.5–997.6]	770.1 [398.7–1513.0]	<0.001
log BNP	2.72 ± 0.45	2.87 ± 0.43	0.003
Albumin (g/dL)	3.90 [3.70–4.20]	3.40 [3.10–3.80]	<0.001
Total cholesterol (mg/dL)	190.8 ± 34.3	154.7 ± 37.8	<0.001
Total lymphocytes (count/μL)	2374 [1858–3715]	1152 [757–1608]	<0.001
C-reactive protein (mg/dL)	0.35 [0.16–1.07]	0.68 [0.21–2.29]	<0.001
Visual LVEF (%)	37.5 [27.5–47.5]	42.5 [27.5–52.5]	0.46
Medication at admission			
Positive inotropic action agents or phosphodiesterase inhibitor, *n* (%)	54 (41.5%)	136 (38.6%)	0.6
Carperitide, *n* (%)	90 (69.2%)	193 (54.8%)	0.005
Tolvaptan, *n* (%)	5 (3.8%)	55 (15.6%)	<0.001
Aldosterone antagonist, *n* (%)	21 (16.2%)	77 (21.9%)	0.2
ACEIs/ARBs, *n* (%)	42 (32.3%)	147 (41.8%)	0.074
β-blocker, *n* (%)	36 (27.7%)	120 (34.1%)	0.19
Statin, *n* (%)	25 (19.2%)	90 (25.6%)	0.185

Results are expressed as mean ± standard deviation or the median [inter-quartile range]

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CONUT* controlling nutritional status, *GFR* glomerular filtration ratio, *HF* heart failure, *LVEF* left ventricular ejection fraction, *n* number of patients, *NYHA* New York Heart Association. Data were missing for the following characteristics: *BMI* for 1 patient in HF patients with normal nutrition and 14 in HF patients with nutritional disturbances, *BNP* for 18 patients in HF patients with normal nutrition, and 44 in HF patients with nutritional disturbances, *C-reactive protein* for 1 patient in HF patients with normal nutrition, *LVEF* for 5 patients in HF patients with normal nutrition and 19 in HF patients with nutritional disturbances

(Table 7). Table 8 shows the univariate and multivariate associations between nutritional status and noncardiovascular or unknown deaths.

In the older HF patients (≥75 years old), the Kaplan–Meier analysis revealed that all-cause deaths occurred more frequently in the group with nutritional disturbances than in those with normal nutrition ($p = 0.002$ by the log-rank test). In the non-aged HF patients (<75 years old), however, the Kaplan–Meier curves for the end point of all-cause deaths did not differ significantly between HF patients with nutritional disturbances and those with normal nutrition ($p = 0.088$ by the log-rank test).

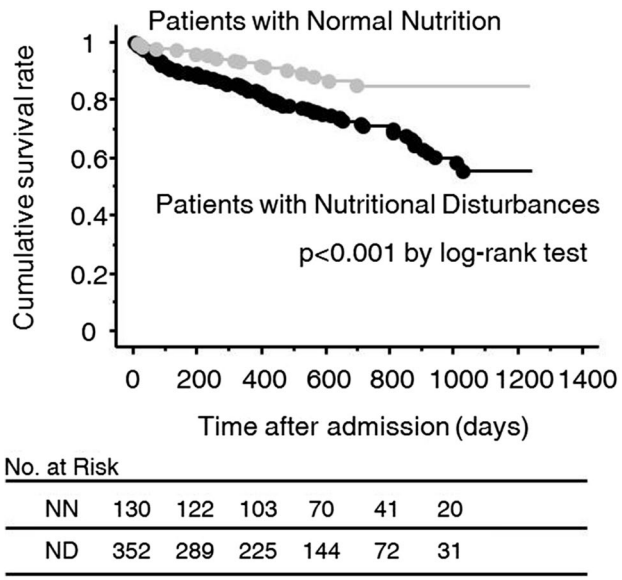

Fig. 1 Kaplan–Meier estimates of all-cause deaths. Among the 482 HF patients with CONUT scores who were followed for a median of 541.5 days, 93 HF patients (26.4%) died in the group with nutritional disturbances, whereas 16 HF patients (12.3%) died in the group with normal nutrition (hazard ratio 2.627; 95% confidence interval 1.544–4.469). *CONUT* controlling nutritional status, *HF* heart failure, *ND* group of HF patients with nutritional disturbances, *NN* group of HF patients with normal nutrition

Discussion

In the present study, patient nutritional status, assessed using CONUT scores, was examined to determine its usefulness in predicting the long-term prognosis of patients hospitalized with HF in a multicenter registry setting. Our results show that all-cause deaths occurred more frequently in HF patients with nutritional disturbances than in those with normal nutrition. Evidence that a higher CONUT score is a significant predictor of the occurrence of all-cause death in patients hospitalized with HF is as follows: (1) a per point increase in the CONUT score was associated with increased risk of all-cause death, and (2) HF patients with nutritional disturbances had an increase in the risk for all-cause death as compared with those with normal nutrition (Table 3). A per point increase in the CONUT score was found to be an independent predictor of all-cause mortality, as well as advanced age, previous history of HF hospitalization, higher log BNP, and use of tolvaptan or aldosterone antagonists at admission (Table 4). These results of the present study indicate that screening nutritional status using a CONUT score further refines risk assessment in patients hospitalized with HF.

Some studies [7, 8, 21] have shown the independent predictive value of nutritional status using CONUT scores in patients with HF, or in patients with structural heart

Table 3 Impact of nutritional screening using CONUT scores on all-cause death

	No. of events/at risk (%)	Model 1: unadjusted		Model 2: age and sex adjusted		No. of events/at risk (%)	Model 3		No. of events/at risk (%)	Model 4	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value		HR	*p* value		HR (95% CI)	*p* value
CONUT score as continuous variable	109/482 (22.6)	1.169 (1.088–1.256)	<0.001	1.163 (1.081–1.251)	<0.001	97/405 (24.0)	1.138	0.005	99/420 (23.6)	1.142 (1.044–1.249)	0.004
CONUT score 0–1 vs. 2–12		2.627 (1.544–4.469)	<0.001	2.378 (1.393–4.060)	0.002		–	–		–	–

Data were missing for the following characteristics: *BMI* for 15 patients, *BNP* for 62 patients. In model 3, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, logarithmic transformation BNP (log BNP), and use of therapeutic agents at admission (carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 4, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, log BNP, and use of therapeutic agents at admission (tolvaptan and aldosterone antagonists)

BMI body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CONUT* controlling nutritional status, *eGFR* estimated glomerular filtration ratio, *HF* heart failure, *HR* Hazard ratio

Table 4 Univariate and multivariate Cox regression analysis for all-cause death

	Univariate analysis		Multivariate analysis, model 3		Multivariate analysis, model 4	
	HR (95% CI)	*p* value	HR	*p* value	HR (95% CI)	*p* value
Age (years)	1.042 (1.024–1.061)	<0.001	1.027	0.006	1.025 (1.006–1.045)	0.009
Male	0.778 (0.532–1.136)	0.194	0.954	0.82	0.906 (0.599–1.370)	0.64
CONUT score as continuous variable	1.169 (1.088–1.256)	<0.001	1.138	0.005	1.142 (1.044–1.249)	0.004
CONUT score as categorical variable (nutritional disturbances)	2.627 (1.544–4.469)	<0.001				
BMI (kg/m^2) at stable state	0.898 (0.850–0.949)	<0.001	–	–		
Systolic blood pressure (mmHg)	0.990 (0.985–0.996)	<0.001				
Heart rate (beats/min)	0.993 (0.986–0.999)	0.028				
Medical history						
Current or past smoker	0.799 (0.548–1.164)	0.24				
Previous history of HF hospitalization	2.445 (1.676–3.568)	<0.001	1.848	0.007	1.824 (1.169–2.846)	0.008
Hypertension	0.861 (0.591–1.255)	0.44				
Dyslipidemia	1.025 (0.688–1.528)	0.9				
Cerebrovascular disease	0.970 (0.426–2.210)	0.94				
Laboratory measurement						
Hemoglobin (g/dL)	0.860 (0.798–0.926)	<0.001	–	–		
Estimated GFR (ml min^{-1} 1.73 m^{-2})	0.986 (0.977–0.994)	0.001	–	–		
log BNP	2.298 (1.376–3.839)	0.002	1.801	0.031	1.749 (1.034–2.959)	0.037
Albumin (g/dL)	0.657 (0.472–0.915)	0.013				
Total cholesterol (mg/dL)	0.994 (0.990–0.999)	0.024				
log Total lymphocytes	0.249 (0.138–0.448)	<0.001				
C-reactive protein (mg/dL)	1.016 (0.966–1.069)	0.53				
Visual LVEF (%)	1.008 (0.995–1.022)	0.2				
Medication at admission						
Positive inotropic action agents or phosphodiesterase inhibitor	1.253 (0.858–1.830)	0.24				
Carperitide	0.656 (0.450–0.957)	0.028	–	–		
Tolvaptan	2.898 (1.846–4.549)	<0.001	1.806	0.021	1.794 (1.089–2.955)	0.022
Aldosterone antagonists	1.984 (1.322–2.976)	<0.001	1.663	0.028	1.664 (1.060–2.612)	0.027
ACEIs or ARBs	1.372 (0.940–2.002)	0.101				
β-blocker	1.549 (1.058–2.269)	0.025	–	–		
Statin	1.164 (0.761–1.780)	0.48				

Data were missing for the following characteristics: *BMI* for 15 patients, *BNP* for 62 patients, *C-reactive protein* for 1 patient, *LVEF* for 24 patients. In model 3, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, logarithmic transformation BNP (log BNP), and use of therapeutic agents at admission (carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 4, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, log BNP, and use of therapeutic agents at admission (tolvaptan and aldosterone antagonists)

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CONUT* controlling nutritional status, *GFR* glomerular filtration ratio, *HF* heart failure, *HR* hazard ratio, *LVEF* left ventricular ejection fraction

disease that lack signs or symptoms of HF. Nochioka et al. [8] reported that poor nutritional status was associated with increased incidence of death in HF patients classified as stage B in the AHA/ACC guidelines. In patients hospitalized with chronic HF, Narumi et al. [7] also reported that a severe CONUT score was independently associated with cardiovascular events. In acute HF patients, Agra Bermejo et al. [5] reported that malnutrition as determined by the CONUT score is associated with a poor outcome in terms of HF and non-HF readmissions, independent of BMI score. Moreover, Iwakami et al. [6] reported that malnutrition assessed by the CONUT score on admission was an independent determinant of long-term death in acute HF. These reports

Table 5 Impact of nutritional screening using CONUT scores on cardiovascular death

	No. of events/at risk (%)	Model 1: unadjusted		Model 2: age and sex adjusted		No. of events/at risk (%)	Model 5		No. of events/at risk (%)	Model 6	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value		HR	*p* value		HR (95% CI)	*p* value
CONUT score as continuous variable	74/482 (15.4)	1.136 (1.039–1.241)	0.005	1.132 (1.035–1.239)	0.007	67/405 (16.5)	1.079	0.17	69/420 (16.4)	1.087 (0.977–1.209)	0.127

Data were missing for the following characteristics: *BMI* for 15 patients, *BNP* for 62 patients. In model 5, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, log BNP, and use of therapeutic agents at admission (positive inotropic action agents or phosphodiesterase inhibitor, carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 6, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, eGFR, log BNP, and use of aldosterone antagonists at admission

BMI body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CONUT* controlling nutritional status, *eGFR* estimated glomerular filtration ratio, *HF* heart failure, *HR* hazard ratio

[5–8, 21] support the present study, which demonstrates that a higher CONUT score is a significant predictor of the occurrence of all-cause death in patients hospitalized with HF.

Suzuki et al. [4] reported that the HF patients with higher CONUT scores tended to have a longer hospital stay. Previous study [9] showed that a high CONUT score is a significant predictor of in-hospital deaths among patients hospitalized with HF. The present study demonstrates that all-cause deaths occurred more frequently in HF patients with nutritional disturbances than in those with normal nutrition. These results suggest that even if patients hospitalized with HF can be discharged through HF treatment alone, the prognosis was not sufficiently improved in HF patients that had nutritional disturbances at the time of admission.

As HF and undernutrition can each influence one another, once patients develop severe HF, their nutritional status deteriorates further. HF patients with undernutrition thus enter a vicious cycle of inflammation, catabolic drive, undernutrition, and HF exacerbation [22]. Strategies to improve nutritional status in the early stages of HF are thus a crucial component of HF management and are important in preventing HF exacerbations and improving patient long-term prognosis.

In the present study, we also demonstrated that nutritional screening using CONUT scores is helpful in predicting noncardiovascular or unknown deaths among patients hospitalized with HF. Recently, Desai et al. [23] have reported that a substantial portion of morbidities and mortality risks of patients with HF was related to noncardiovascular hospitalizations. These findings suggest the need for the development of HF disease management approaches that focus more comprehensively on the treatment of both cardiovascular and noncardiovascular comorbidities, rather than on HF exclusively [23]. Therefore, comprehensive approaches, including not only HF but also nutritional management, are required in improving the prognosis of patients with HF.

In cases of HF, standard treatment must not only be initiated, but nutritional treatment must also be implemented to improve nutritional status and other parameters. The recently updated ESC guidelines for the diagnosis and treatment of acute and chronic HF [24], however, do not specifically address nutritional issues except in the context of cachexia and sarcopenia. Given the lack of available evidence on the benefits and safety of treating undernutrition using therapeutic interventions, the ESC guidelines did not provide recommendations on the use of potential nutritional treatments. In their review, Rahman et al. [25] described that the best intervention appears to be optimization of HF therapy. It is important to understand the potential survival benefits of dietary and

Table 6 Univariate and multivariate Cox regression analysis for cardiovascular death

	Univariate analysis		Multivariate analysis, model 5		Multivariate analysis, model 6	
	HR (95% CI)	*p* value	HR	*p* value	HR (95% CI)	*p* value
Age (years)	1.028 (1.007–1.049)	0.008	1.007	0.55	1.006 (0.984–1.027)	0.61
Male	0.792 (0.500–1.256)	0.32	0.935	0.79	0.873 (0.532–1.434)	0.59
CONUT score as continuous variable	1.136 (1.039–1.241)	0.005	1.079	0.17	1.087 (0.977–1.209)	0.127
CONUT score as categorical variable (nutritional disturbances)	2.529 (1.331–4.803)	0.005				
BMI (kg/m^2) at stable state	0.913 (0.855–0.976)	0.007	–	–		
Systolic blood pressure (mmHg)	0.986 (0.980–0.993)	<0.001				
Heart rate (beats/min)	0.989 (0.981–0.997)	0.009				
Medical history						
Current or past smoker	0.856 (0.543–1.351)	0.51				
Previous history of HF hospitalization	3.671 (2.321–5.808)	<0.001	2.761	<0.001	2.657 (1.558–4.532)	<0.001
Hypertension	0.682 (0.432–1.077)	0.1				
Dyslipidemia	1.205 (0.750–1.934)	0.44				
Cerebrovascular disease	0.701 (0.221–2.226)	0.55				
Laboratory measurement						
Hemoglobin (g/dL)	0.874 (0.798–0.956)	0.003	–	–		
Estimated GFR (ml min^{-1} 1.73 m^{-2})	0.982 (0.971–0.993)	<0.001	0.985	0.026	0.985 (0.972–0.998)	0.028
log BNP	3.395 (1.788–6.446)	<0.001	2.476	0.012	2.306 (1.156–4.603)	0.018
Albumin (g/dL)	0.765 (0.509–1.150)	0.2				
Total cholesterol (mg/dL)	0.994 (0.988–1.000)	0.041				
log Total lymphocytes	0.241 (0.119–0.487)	<0.001				
C-reactive protein (mg/dL)	1.001 (0.935–1.071)	0.98				
Visual LVEF (%)	1.003 (0.987–1.019)	0.75				
Medication at admission						
Positive inotropic action agents or phosphodiesterase inhibitor	1.675 (1.062–2.644)	0.027	–	–		
Carperitide	0.586 (0.371–0.926)	0.022	–	–		
Tolvaptan	2.594 (1.485–4.532)	<0.001	–	–		
Aldosterone antagonists	2.788 (1.748–4.448)	<0.001	2.241	0.003	2.224 (1.317–3.755)	0.003
ACEIs or ARBs	1.407 (0.890–2.225)	0.144				
β-blocker	2.069 (1.311–3.264)	0.002	–	–		
Statin	1.101 (0.654–1.856)	0.72				

Data were missing for the following characteristics: *BMI* for 15 patients, *BNP* for 62 patients; *C-reactive protein* for 1 patient, *LVEF* for 24 patients. In model 5, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, previous history of HF hospitalization, hemoglobin level, eGFR, log BNP, and use of therapeutic agents at admission (positive inotropic action agents or phosphodiesterase inhibitor, carperitide, tolvaptan, aldosterone antagonists, and β-blockers). In model 6, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, previous history of HF hospitalization, eGFR, log BNP, and use of aldosterone antagonists at admission

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CONUT* controlling nutritional status, *GFR* glomerular filtration ratio, *HF* heart failure, *HR* hazard ratio, *LVEF* left ventricular ejection fraction

nutritional supplementation in malnourished HF patients. In a recent study, malnourished and hospitalized older patients ($N = 652$) with congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease were randomized to a high protein nutritional supplement (HP-HMB) or a placebo supplement [26]. No between-group differences were observed for the 90-day readmission rate. The 90-day mortality rate, however, was significantly lower with an HP-HMB relative to placebo (4.8 vs. 9.7%; relative risk 0.49, 95% CI 0.27–0.90, $p = 0.018$). In addition, an ongoing study is assessing the efficacy of a nutritional intervention on morbidity and mortality in hospitalized HF patients who are malnourished [27].

Table 7 Impact of nutritional screening using CONUT scores on noncardiovascular or unknown deaths

	No. of events/at risk (%)	Model 1: unadjusted		Model 2: age and sex adjusted		No. of events/at risk (%)	Model 7		No. of events/at risk (%)	Model 8	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value		HR	*p* value		HR (95% CI)	*p* value
CONUT score as continuous variable	35/482 (7.3)	1.239 (1.095–1.401)	<0.001	1.230 (1.086–1.393)	0.001	35/467 (7.5)	1.182	0.013	35/482 (7.3)	1.180 (1.034–1.346)	0.014

Data were missing for the following characteristics: *BMI* for 15 patients. In model 7, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, hemoglobin level, and use of tolvaptan at admission. In model 8, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, and use of tolvaptan at admission

BMI body mass index, *CI* confidence interval, *CONUT* controlling nutritional status, *HR* hazard ratio

Many factors can alter nutritional status in HF patients, including decreased intake (due both to malabsorption from intestinal edema, and to symptoms affecting food intake such as tiredness and dyspnea) and increased catabolism triggered by the effects of inflammatory cytokines and neurohormonal activation [22]. Thiamine, riboflavin, pyridoxine, L-carnitine, coenzyme Q10, creatine, and taurine levels are also reduced in HF populations [28]. There is no universally accepted definition, however, of malnutrition or a gold-standard methodology for nutritional assessment. In patients with HF, as multiple causes induce undernutrition, nutrition management cannot be standardized and may require tailor-made treatment. Thus, further research is required to determine whether dietary and nutritional supplementation can slow progression of HF and reduce mortality among these patients.

Because the CONUT score is a relatively new index, it needs to be validated with established scores. A validation study of the screening tool, however, was not examined. Indeed, it has been shown that the CONUT score is in good agreement with two other classical methods: the Subjective Global Assessment and the Full Nutritional Assessment [3]. Moreover, in previous studies [7, 8], investigators also examined the prognostic impact of the CONUT score and the Nutritional Risk Index (NRI) [8], or the CONUT score, the prognostic nutritional index (PNI) [7], and the geriatric nutritional risk index (GNRI) [7]. These scores were determined to have comparable prognostic significance. Furthermore, Iwakami et al. [6] reported that malnutrition assessed by the CONUT score on admission was an independent determinant of long-term death in acute HF, and its prognostic value outweighed that of other nutritional indices, including albumin, total cholesterol, BMI, and NRI.

In the aged HF patients (≥75 years old), screening of nutritional disturbances using the CONUT score was associated with occurrence of all-cause deaths. In the non-aged HF patients (<75 years old); however, there tended to be association. This result suggests that the CONUT score is a more useful predictor in aged HF patients. It is reasonable to note that undernutrition, which is more commonly observed in aged HF patients, was associated with an increased occurrence of all-cause deaths. Even in the non-aged HF patients (<75 years old), a further long-term follow may have detected a significant association between nutritional disturbances and occurrence of all-cause deaths.

In the present study, all-cause deaths occurred more frequently in HF patients who were administered with tolvaptan at admission [$n = 25$ (41.7%)] than in those who were not [$n = 84$ (19.9%); log-rank $p < 0.001$]. However, Konstam et al. [29] reported that the initiation of tolvaptan for the acute treatment of patients hospitalized with HF had no effect on long-term mortality or HF-related morbidity. In the present study, significant differences in the previous

Table 8 Univariate and multivariate Cox regression analysis for noncardiovascular or unknown deaths

	Univariate analysis		Multivariate analysis, model 7		Multivariate analysis, model 8	
	HR (95% CI)	*p* value	HR	*p* value	HR (95% CI)	*p* value
Age (years)	1.081 (1.042–1.121)	<0.001	1.079	<0.001	1.079 (1.039–1.120)	<0.001
Male	0.747 (0.383–1.459)	0.39	1.016	0.96	1.014 (0.514–2.000)	0.97
CONUT score as continuous variable	1.239 (1.095–1.401)	<0.001	1.182	0.013	1.180 (1.034–1.346)	0.014
CONUT score as categorical variable (nutritional disturbances)	2.846 (1.102–7.347)	0.031				
BMI (kg/m^2) at stable state	0.865 (0.782–0.957)	0.005	–	–		
Systolic blood pressure (mmHg)	0.998 (0.989–1.006)	0.58				
Heart rate (beats/min)	0.999 (0.989–1.010)	0.92				
Medical history						
Current or past smoker	0.688 (0.352–1.345)	0.27				
Previous history of HF hospitalization	0.910 (0.413–2.006)	0.82				
Hypertension	1.440 (0.717–2.896)	0.31				
Dyslipidemia	0.706 (0.331–1.508)	0.37				
Cerebrovascular disease	1.572 (0.481–5.138)	0.45				
Laboratory measurement						
Hemoglobin (g/dL)	0.831 (0.728–0.948)	0.006	–	–		
Estimated GFR (ml min^{-1} 1.73 m^{-2})	0.993 (0.978–1.008)	0.36				
log BNP	1.070 (0.465–2.462)	0.87				
Albumin (g/dL)	0.483 (0.275–0.850)	0.012				
Total cholesterol (mg/dL)	0.996 (0.987–1.004)	0.3				
log Total lymphocytes	0.269 (0.094–0.773)	0.015				
C-reactive protein (mg/dL)	1.042 (0.967–1.123)	0.28				
Visual LVEF (%)	1.020 (0.998–1.044)	0.079				
Medication at admission						
Positive inotropic action agents or phosphodiesterase inhibitor	0.641 (0.308–1.336)	0.24				
Carperitide	0.836 (0.427–1.637)	0.6				
Tolvaptan	3.642 (1.688–7.859)	0.001	2.649	0.021	2.737 (1.200–6.246)	0.017
Aldosterone antagonists	0.747 (0.290–1.926)	0.55				
ACEIs or ARBs	1.298 (0.664–2.540)	0.45				
β-blocker	0.777 (0.364–1.659)	0.51				
Statin	1.304 (0.626–2.715)	0.48				

Data were missing for the following characteristics: *BMI* for 15 patients, *BNP* for 62 patients, *C-reactive protein* for 1 patient, *LVEF* for 24 patients. In model 7, the following covariates were included after controlling simultaneously for age, sex, and nutritional status based on the CONUT score as a continuous variable and using forward stepwise selection: BMI, hemoglobin level, and use of tolvaptan at admission. In model 8, the following covariates were included using simultaneous selection: age, sex, CONUT scores as a continuous variable, and use of tolvaptan at admission

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CI* confidence interval, *CONUT* controlling nutritional status, *GFR* glomerular filtration ratio, *HF* heart failure, *HR* hazard ratio, *LVEF* left ventricular ejection fraction

history of HF hospitalization, hemoglobin level, eGFR, and CONUT score (data not shown) were observed between the two groups. Thus, instead of the effect of tolvaptan itself, the characteristics of patients contributed to worse outcomes among those who were administered with tolvaptan at admission than those who were not [30–32].

Several limitations should be mentioned for the present study. Nutritional status was only assessed on admission. A reassessment of nutritional status at discharge, however, may provide useful information during follow-up. Due to the number of HF patients in the present study, data were not evaluated by further stratification (0–1, 2–4, 5–8, and ≥9, by Ignacio de Ulíbarri et al. [3]) of CONUT score. In our study, nutritional management was conducted according to usual practice. It is possible that patients with a worse nutritional status might have received more intensive

nutritional care. In addition, we did not exclude comorbid diseases such as nephrotic syndrome, the presence of infectious diseases, and blood disorders, which can affect the levels of albumin and cholesterol, and also the lymphocyte count.

In conclusion, the present study suggests that nutritional screening using CONUT scores is helpful in predicting the long-term prognosis of patients hospitalized with HF in a multicenter registry setting, especially among the aged populations (≥75 years old).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest or financial relationships relevant to this study.

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