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Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure

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ABSTRACT

Background: The prognostic value of nutritional status is poorly understood and evidence-based nutritional assessment indices are required in acute heart failure (AHF). We investigated the prognostic value of malnutrition assessed by the Controlling Nutritional Status (CONUT) score (range 0–12, higher = worse, consisting of serum albumin, cholesterol and lymphocytes) in AHF patients.

Methods: The CONUT score was measured on admission in 635 consecutive AHF patients. The primary outcome was all-cause death.

Results: Median CONUT score was 3 (interquartile range 2 to 5). During the median follow-up of 324 days, CONUT score was independently associated with death (HR 1.26, 95% CI 1.11–1.42, $P < 0.001$) after adjustment for confounders in a multivariate Cox model. The CONUT score demonstrated the best C-statistic for predicting death (0.71) among other common nutritional markers in HF. Furthermore, addition of the CONUT score to an established risk prediction model from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure study significantly increased the C-statistic from 0.75 to 0.77 ($P = 0.02$). The net reclassification improvement afforded by CONUT score was 21% for all-cause death, 27% for survival and 49% overall ($P < 0.001$).

Conclusion: Malnutrition assessed by the CONUT score on admission was an independent determinant of long-term death in AHF, and its prognostic value outweighed that of other nutritional indices. Moreover, addition of the score to the existing risk prediction model significantly increased the predictive ability for death, indicating beneficial clinical application of the CONUT score in AHF patients.

1. Introduction

Although evidence-based management of heart failure (HF) has improved outcomes, the absolute mortality of HF remains as high as 50% within 5 years of diagnosis [1,2]. HF not only decreases the health-related quality of life for patients, but also loads a heavy annual economic burden of >30 billion dollars in the United States [3]. The need for a multidisciplinary approach is greater than ever in order to achieve better clinical outcomes and cost effectiveness [4–6].

Nutritional management is one of the non-pharmacological approaches with high expectations in HF. It is listed as a component of the management program for patients with HF in the recent updated guidelines for HF [4,6]. It is expected that early identification of malnutrition may lead to early nutritional intervention and a better clinical outcome [7]; nevertheless, a universally accepted definition of malnutrition and evidence-based methodology for nutritional assessment of HF patients have not been established.

Various nutritional indices have been examined, and Controlling Nutritional Status (CONUT) score is reported to be one of the most promising [8,9]. It was originally proposed by Ignacio de Ulíbarri et al. as a screening tool for undernutrition in hospitalized patients [10] and the score consists of three indices; serum albumin, total cholesterol, and lymphocyte count.

In view of the importance of earlier identification of malnutrition, an appropriate nutritional assessment tool that can be used in the decompensated phase of HF might be useful [7]. Although malnutrition assessed by CONUT score has been shown to be related to worse clinical outcomes in chronic HF patients [8,9] the usefulness of the score in acute HF (AHF) patients remains unclear.

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Hence, the purpose of this study was first to investigate the prognostic significance of malnutrition status assessed by CONUT score on admission in AHF patients, and second to validate the clinical application of the score by comparing it with other nutritional indices and by adding it to the existing outcome prediction model for AHF.

2. Methods

2.1. Study design

Data from the NaDEF (National cerebral and cardiovascular center acute DEcompensated heart Failure) registry, which were obtained between January 2013 and March 2015, were retrospectively analyzed. The NaDEF registry is a single-center, observational, on-going, prospective cohort that includes all consecutive patients aged above 20 requiring hospitalization to our institution from January 2013 for the first episode of rapid onset or worsening symptoms and/or signs of heart failure which were compatible with the Framingham criteria [11] and were also confirmed by chest X-ray, laboratory assessment and echocardiography. Patients with both preserved and reduced HF were included. At least two experienced cardiologists confirmed the diagnosis of AHF including de novo HF and decompensation of chronic HF. Follow-up was performed at 3, 6, 12, and 24 months after discharge by direct contact with patients or their physicians at the hospital or outpatient clinic, telephone interview of patients or, if deceased, of family members, and mail, by dedicated coordinators and investigators. In this study, because patient information was anonymized and de-identified prior to analyses, written informed consent was not obtained from each patient. However, we publicized the study by posting a summary of the protocol (with an easily understood description) on the website of the National Cerebral and Cardiovascular Center, and noticed the enrolled patients by showing the explanation form (the same form as on the website) during hospitalization; the notice clearly informed patients of their right to refuse enrollment. These procedures for informed consent and enrollment are in accordance with the detailed regulations regarding informed consent described in the Japanese Ministry of Health, Labor and Welfare guidelines [12], and this study, including the procedure for enrollment, has been approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M22-025), and registered under the Japanese UMIN Clinical Trials Registration (UMIN000017024).

2.2. Study population

From the 651 consecutive patients enrolled in the NaDEF registry, 16 patients without CONUT data on admission were excluded. There was no patient who turned out not to have HF or who refused to participate. Finally, the study population consisted of 635 patients.

2.3. Nutritional score and index

The CONUT score was first developed and validated by Ignacio de Ulíbarri et al. in 2005 as a screening tool for undernutrition in a hospital population [10] and has recently been applied to patients with heart failure [8,9]. It is calculated from three variables: albumin, total cholesterol, and lymphocyte count scores (Table 1). The range of the CONUT scores is 0 to 12; a person with normal nutritional status would correspond to zero, and a higher score indicates worse nutritional status. In this study, baseline information including the CONUT score on admission was obtained within 2 h after hospital arrival.

Nutritional risk index (NRI) was also calculated based on previous studies [13–15].

$$\mathrm{NRI} = [1.519 \times \text{serum albumin (g/dL)}] + [41.7 \times \text{present weight (kg)}/\text{ideal body weight (kg)}]$$

Table 1
CONUT score [10].

Parameter	Score			
Serum albumin, g/mL	≥3.5	3.00–3.49	2.50–2.99	<2.50
Albumin score	0	2	4	6
Total cholesterol, mg/dL	>180	140–180	100–139	<100
Cholesterol score	0	1	2	3
Lymphocyte count, count/mL	≥1600	1200–1599	800–1199	<800
Lymphocyte score	0	1	2	3

CONUT = Controlling Nutritional Status.

2.4. Clinical outcomes

The primary outcome was all-cause death. This included in-hospital and post-discharge death; i.e. death after initial nutritional assessment on admission. Secondary outcomes were cardiovascular death and worsening HF after initial nutritional assessment. Cardiovascular death was defined as death attributable to cardiovascular origin. Worsening HF consisted of in-hospital worsening HF and re-admission for HF. We defined in-hospital worsening HF as worsening of symptoms and signs of HF requiring intensification of intravenous therapy or initiation of mechanical therapy during hospitalization [16,17]. We defined worsening HF after discharge as worsening of symptoms and signs of HF requiring re-admission for treatment. Re-admission was judged by two experienced cardiologists independently of this study, just as for the initial admission.

2.5. Outcome prediction model

We examined whether addition of nutritional assessment might improve the predictive ability of the existing prognostic model for AHF. As an existing representative prognostic model, the risk prediction nomogram from the OPTIMIZE-HF (the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) was utilized [18,19]. The OPTIMIZE-HF trial is one of the largest hospital-based registries for new or worsening HF, and the risk prediction nomogram for all-cause death derived from this trial is a representative risk model, having most of the variables in common with others [20,21]. There are two different OPTIMIZE-HF nomograms predicting in-hospital death [18] or post-discharge death [19]. The latter nomogram was used in this study. Briefly, the nomogram consists of age, weight, systolic blood pressure, serum sodium and creatinine levels on admission combined with baseline risk factors such as history of liver disease, depression and reactive airway disease.

2.6. Statistical analysis

All continuous variables were shown as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. Patients were simply stratified by the CONUT score as 0–1, 2–3, 4–5, and ≥6 for comparison. Comparisons of differences between the groups were performed by unpaired Student's *t*-test or ANOVA with Bonferroni post-hoc testing for continuous variables, and by Fisher's exact test for dichotomous variables. Ischemic cardiomyopathy (ICM) was defined as myocardial disorders with reduced ejection fraction and with the presence of >75% stenosis in any coronary artery, or any history of MI or coronary revascularization [22]. Non-ischemic cardiomyopathy (NICM) was defined as myocardial disorders with reduced ejection fraction and without obvious ischemic or valvular etiology. Cumulative overall event-free survival rates were plotted using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was performed to evaluate the influence of nutritional assessment by the CONUT score on all-cause death. Four models were constructed and the Cochran-Armitage trend test was performed across the CONUT score strata also with analysis using the CONUT score as a continuous

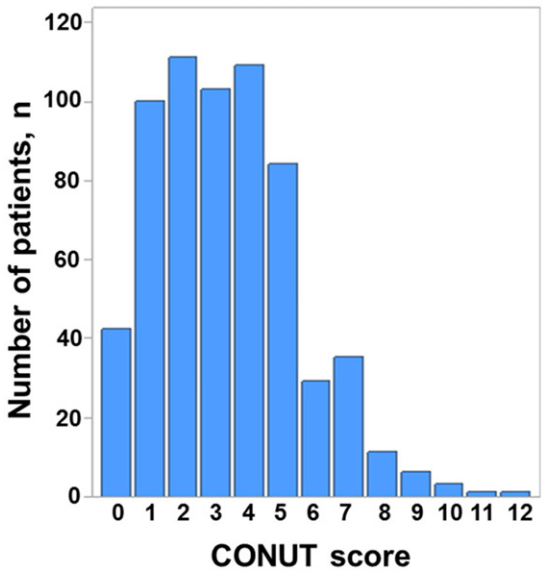


Fig. 1. Distribution of CONUT score. CONUT, Controlling Nutritional Status.

variable: model 1, unadjusted; model 2, age- and sex-adjusted; model 3, fully adjusted by major confounders; and model 4, fully adjusted by all potential confounders using the OPTIMIZE-HF nomogram. Among the predictors of outcome, we defined major confounders as those that showed a statistically significant correlation with the CONUT score that had biological plausibility, which included age, systolic blood pressure, hemoglobin, estimated glomerular filtration rate, serum sodium, body mass index, and statin use. Other confounders included history of malignancy, liver disease, reactive airway disease, and depression. Model 3 consisted of major confounders. Model 4 consisted of all potential confounders, some of which such as age, weight, systolic blood pressure, serum sodium, renal function, and history of liver disease, reactive airway disease, and depression were substituted by the OPTIMIZE-HF nomogram in order to avoid overfitting. Accordingly, model 4 consisted of the OPTIMIZE-HF nomogram score, hemoglobin, statin use, and history of malignancy. Furthermore, sensitivity analyses for the association of the CONUT score with all-cause death were performed, with addition or exclusion of covariates regardless of biological and statistical plausibility as confounders in order to investigate the robustness of the results.

The prognostic value of the CONUT score was compared with that of its components (serum albumin, total cholesterol and lymphocyte count) and other nutritional indices, such as body mass index (BMI)

Table 2
Baseline characteristics of total population.

Variable	Overall ($N = 635$)	CONUT score				*P* value
		0–1 ($N = 142$)	2–3 ($N = 214$)	4–5 ($N = 193$)	≥6 ($N = 86$)	
Age, years	75 ± 12	71 ± 13	75 ± 13	78 ± 10	77 ± 11	<0.001
Male, *n* (%)	392 (62)	82 (58)	126 (59)	125 (65)	59 (69)	0.24
Body mass index, kg/m^2	23.0 ± 4.2	23.7 ± 4.7	23.5 ± 4.0	22.2 ± 3.9	22.6 ± 3.7	0.005
Past history, n (%)						
Hypertension	448 (71)	101 (71)	158 (72)	137 (71)	52 (60)	0.14
Diabetes	226 (36)	47 (33)	76 (36)	72 (37)	31 (36)	0.90
Dyslipidemia	326 (51)	73 (51)	118 (55)	104 (54)	31 (36)	0.019
CKD	348 (55)	54 (38)	117 (55)	128 (66)	49 (57)	<0.001
Prior MI	147 (23)	27 (19)	55 (26)	52 (27)	13 (15)	0.08
Atrial fibrillation	311 (49)	49 (35)	102 (48)	104 (54)	56 (65)	<0.001
HF admission	283 (45)	40 (28)	86 (40)	111 (58)	46 (53)	<0.001
ICD	57 (9)	10 (7)	21 (10)	19 (10)	7 (8)	0.80
CRTP/D	42 (7)	5 (4)	20 (9)	13 (7)	4 (5)	0.15
Malignancy	98 (15)	17 (12)	33 (15)	34 (18)	14 (16)	0.57
Liver disease	7 (1)	2 (1)	0 (0)	3 (2)	2 (2)	0.25
Depression	18 (3)	6 (4)	5 (2)	5 (3)	2 (2)	0.73
Reactive airway disease	51 (8)	10 (7)	19 (9)	13 (7)	9 (10)	0.69
NYHA III, *n* (%)	227 (36)	39 (27)	86 (41)	69 (37)	33 (38)	0.10
NYHA IV, *n* (%)	302 (48)	81 (57)	88 (42)	91 (48)	42 (49)	0.02
Heart rate, /min	92 ± 29	102 ± 30	91 ± 29	86 ± 26	91 ± 29	<0.001
Systolic BP, mmHg	138 ± 32	151 ± 35	137 ± 30	136 ± 29	124 ± 28	<0.001
LVEF, %	38 ± 17	38 ± 18	36 ± 16	40 ± 17	39 ± 16	0.13
Nutritional risk index	48.6 ± 7.9	50.3 ± 9.1	49.6 ± 7.6	47.0 ± 7.2	46.9 ± 7.0	<0.001
Etiology, n (%)						
ICM	137 (22)	28 (20)	44 (21)	49 (25)	16 (19)	0.18
NICM	215 (34)	57 (40)	78 (36)	50 (26)	30 (35)	
Valvular	147 (23)	23 (16)	49 (23)	52 (27)	23 (27)	
Other	136 (21)	34 (24)	43 (20)	42 (22)	17 (20)	
Oral medication, n (%)						
Loop diuretic	337(53)	45 (32)	118 (55)	125 (65)	49 (57)	<0.001
Hydrochlorothiazide	58 (9)	10 (7)	15 (7)	21 (11)	12 (14)	0.17
Aldosterone antagonist	152 (24)	23 (16)	54 (25)	51 (26)	24 (28)	0.10
ACE-I or ARB	325 (51)	60 (42)	118 (55)	106 (55)	41 (48)	0.06
Beta blocker	321 (51)	59 (42)	107 (50)	111 (58)	44 (51)	0.039
Digoxin	79 (12)	14 (10)	27 (13)	23 (12)	15 (17)	0.41
Statin	225 (35)	38 (27)	90 (42)	75 (39)	22 (26)	0.004

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CKD = chronic kidney disease; CONUT = Controlling Nutritional Status; CRTP/D = cardiac resynchronization therapy pacemaker/defibrillator; ICD = implantable cardioverter defibrillator; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NICM = non-ischemic cardiomyopathy; NYHA = New York Heart Association.
Continuous variables are presented as mean ± SD if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).

and nutritional risk index (NRI), using C-statistics. C-statistics were compared using the method described by DeLong et al. [23]. We added the CONUT score to the OPTIMIZE-HF nomogram and compared the C-statistics and the category-free net re-classification improvement described by Penicina et al. [24,25]. We performed all analyses using JMP Pro® 11 (SAS Institute Inc., Cary, NC). The alpha (α) level of significance was set at 0.05.

3. Results

3.1. Patient characteristics

The distribution of the CONUT score on admission is shown in Fig. 1. The median value (IQR) was 3 (3 to 5). The baseline clinical characteristics categorized by the CONUT score of the total 635 patients on admission are shown in Tables 2 and 3. Mean age was 75 years and 62% were male. Patients with a higher CONUT score had higher age, lower systolic blood pressure, lower hemoglobin, impaired renal function, and a state of malnutrition assessed with other indices such as BMI and NRI. Patients with a higher CONUT score also had a more frequent history of HF admission and accordingly were receiving more oral medication for HF. Initial intravenous treatment and medication at discharge are shown in Table 3 and Supplemental Table 1, respectively.

3.2. CONUT score and clinical outcomes

During the median follow-up of 324 (IQR 106 to 554) days, the primary outcome occurred in 64 (10%) patients. Kaplan-Meier curves revealed that the risk of all-cause and cardiovascular death significantly increased in accordance with the CONUT score stratum (Fig. 2A and B), whereas the risk of worsening HF did not show a significant association (Figure 2C). Cox proportional hazard analyses indicated that per point increase in the CONUT score was associated with an increased risk of all-cause death even after full adjustment by major confounders with HR 1.26 (95% CI 1.11–1.42, $P < 0.001$), and patients with a CONUT score ≥6 had a 3.67-fold increase in the risk as compared with those with a CONUT score of 0–1 (Table 4). As for cardiovascular death, HR after full adjustment by major confounders was 1.24 (95% CI 1.05–1.47, $P = 0.016$), and the risk tended to increase according to the score stratum (Table 5). Worsening HF showed no association with CONUT score (Table 5).

Sensitivity analysis showed that the results were robust even after addition or exclusion of covariates for adjustment (Supplemental Table 2).

3.3. Comparison with other nutritional indices

C-statistics of CONUT score were compared with those of other nutritional indices in order to assess its validity as a nutritional risk assessment tool in AHF (Figure 3). CONUT score showed the highest C-statistics at 0.71 (95% CI 0.64–0.77) among others including albumin (0.68, 95% CI 0.61–0.74), total cholesterol (0.61, 95% CI 0.53–0.69), BMI (0.66, 95% CI 0.59–0.73), and NRI (0.68, 95% CI 0.60–0.75).

3.4. Addition of CONUT score to the existing outcome prediction model

Fig. 4 demonstrates a comparison of the risk prediction models for all-cause death; one being the original score from the OPTIMIZE-HF nomogram, and one being addition of the CONUT score to the OPTIMIZE-HF nomogram. The C-statistic of the OPTIMIZE-HF nomogram was 0.75 (95% CI 0.68–0.80), and increased to 0.77 (95% CI 0.70–0.81) in the OPTIMIZE-HF nomogram plus CONUT score ($P = 0.02$). The net re-classification improvement afforded by addition of nutritional assessment by the CONUT score was 21% for all-cause death, 27% for survival and 49% overall ($P < 0.001$); i.e. the CONUT score on admission appropriately increased or decreased the model-predicted probability of death in a net of 21% of the patients who died later and 27% of the patients who eventually survived.

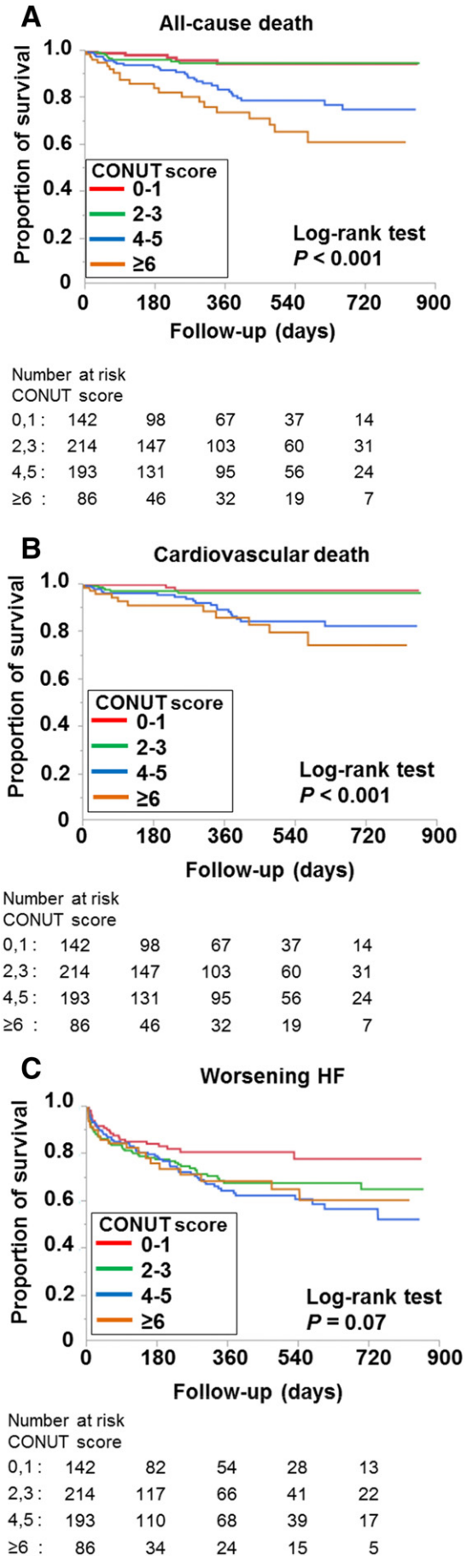
4. Discussion

In the present study, we demonstrated that malnutrition expressed as a high CONUT score on admission was independently associated with increased risk of death in patients with AHF. Furthermore, CONUT score was shown to be more useful for the assessment of nutritional status among other markers and indices, from the perspective of

Table 3
Laboratory data and initial treatment of total population.

Variable	Overall ($N = 635$)	CONUT score				*P* value
		0–1 ($N = 142$)	2–3 ($N = 214$)	4–5 ($N = 193$)	≥6 ($N = 86$)	
Laboratory data						
Albumin, g/dL	3.7 ± 0.4	4.0 ± 0.3	3.9 ± 0.3	3.7 ± 0.4	3.1 ± 0.4	<0.001
Total cholesterol, mg/dL	157 ± 40	189 ± 39	165 ± 34	143 ± 29	119 ± 28	<0.001
Lymphocyte count, count/mL	1316 ± 894	2109 ± 872	1380 ± 779	939 ± 758	692 ± 323	<0.001
Hemoglobin, g/dL	11.9 ± 2.1	12.9 ± 2.0	12.3 ± 2.0	11.2 ± 1.9	10.9 ± 2.2	<0.001
Sodium, mEq/L	140 ± 4	140 ± 3	140 ± 4	139 ± 5	139 ± 4	0.049
eGFR, mL/min/1.73 m^2	46 ± 22	53 ± 21	46 ± 21	41 ± 19	45 ± 27	<0.001
BNP, pg/mL	605 (320, 1159)	542 (227, 983)	627 (366, 1156)	629 (305, 1187)	600 (337, 1412)	0.15
Thyroid stimulating hormone, mIU/L	3.1 (1.7, 5.2)	2.4 (1.4, 4.3)	3.3 (1.9, 5.8)	3.3 (1.9, 5.5)	2.9 (1.8, 4.7)	0.20
Free T3, pg/mL	2.3 ± 1.0	2.5 ± 0.6	2.4 ± 0.5	2.1 ± 0.5	2.1 ± 2.4	0.002
Free T4, ng/dL	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.81
Cortisol, μg/dL	19.5 ± 10.0	19.5 ± 9.8	19.1 ± 12.1	19.2 ± 8.3	21.1 ± 7.5	0.44
Epinephrine, pg/mL	26 (14, 47)	25 (13, 43)	24 (12, 44)	26 (16, 49)	36 (21, 66)	0.97
Norepinephrine, pg/mL	620 (393, 890)	679 (406, 913)	603 (398, 877)	567 (388, 880)	633 (350, 896)	0.32
Intravenous treatment, n (%)						
Diuretic	461(73)	98 (69)	161 (77)	135 (71)	67 (78)	0.30
Dose of loop diuretic, mg/day	20 (10, 30)	20 (13, 40)	20 (10, 20)	20 (20, 40)	20 (16, 38)	0.14
Vasodilator	377 (59)	94 (66)	123 (59)	116 (61)	44 (51)	0.25
Inotropic agent and/or vasopressor	100 (16)	17 (12)	37 (18)	26 (14)	20 (23)	0.08

BNP = brain natriuretic peptide; CONUT = Controlling Nutritional Status; eGFR = estimated glomerular filtration rate; T3 = triiodothyronine; T4 = thyroxine.
Continuous variables are presented as mean ± SD if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).



outcome prediction. We further highlighted that the addition of nutritional assessment by CONUT score to the existing prediction model significantly increased the predictive ability for death in AHF, which was shown not only by comparison of C-statistics but also by the net reclassification improvement. Our findings indicate that nutritional assessment using the CONUT score should be taken into consideration in the decompensated phase of HF. Indeed, current guidelines and a consensus report of recommendations on prehospital and early hospital management of AHF emphasize addition of multidisciplinary care management including nutritional care to the existing hemodynamic management, in order to further reduce the risk of adverse outcomes in HF [4,6,26]. The present study results provide evidence to support these statements.

Despite the fact that the prognostic value of nutritional assessment has been studied mainly in chronic HF [7] emerging evidence has elucidated the consistent usefulness of several indices, including BMI [27] hypoalbuminemia [28] and NRI [15] as predictors of clinical outcomes in AHF. In the present study, our findings indicated the superiority of CONUT score for predicting long-term death over existing nutritional indices in AHF patients. This superiority could be explained by the underlying pathophysiological mechanisms of malnutrition in HF, especially in advanced-stage HF. First, advanced HF is characterized by reduced cardiac output and subsequent hypoperfusion in peripheral tissue, with enhanced neurohormonal and inflammatory activity including the renin-angiotensin-aldosterone system, adrenergic nervous system, cytokine production, and tissue necrosis factor/nuclear factor-kappa B pathway, as systemic compensatory reactions [29–36]. These adverse reactions affect immunity, insulin resistance [37,38] and anabolic-catabolic balance [39] leading to impaired protein and lipid metabolism, which finally results in malnutrition and cachexia. Second, advanced HF also causes malabsorption due to gut edema, increased energy expenditure due to dyspnea and increased work of breathing, and anorexia due to gut and hepatic congestion [30,31]. Based on this pathophysiological background, nutritional status is better assessed pleiotropically in HF patients. The CONUT score is thus appropriate for evaluating diverse aspects of the complex mechanism of malnutrition in HF, because each of the three components (albumin, total cholesterol, and lymphocyte count) reflects different aspects of malnutrition (impaired protein metabolism, lipid metabolism, and immunity, respectively) in advanced HF. Previous studies have already reported the usefulness of the CONUT score to detect those patients with malnutrition and worse prognosis in chronic HF [8,9]. Our study showed that the CONUT score was still as useful for nutritional assessment in the decompensated phase of HF when baseline information could not always be obtained.

Body weight and BMI have also been used as traditional indices of nutritional assessment in HF patients, and higher BMI is known to be related to better clinical outcomes, the so-called “obesity paradox” [40]. Our analyses also showed that BMI was an independent predictor of death even when adjusted by CONUT score, however, its predictive value was inferior to that of the CONUT score as shown in Fig. 3. BMI is influenced by several factors irrelevant to nutritional status, such as additional weight gain due to systemic edema, especially in the decompensated phase of HF. Therefore, BMI alone may be unsuitable for nutritional assessment in AHF patients. For the same reason, NRI, which is calculated by the combination of serum albumin and body weight, has little advantage over serum albumin in terms of nutritional assessment in AHF. On the other hand, hypoalbuminemia is generally a prominent single index of malnutrition; however, it reflects only small aspects of malnutrition in HF.

We expect that early detection of malnutrition and early effective nutritional management with continuous multidisciplinary care would improve outcomes. Education, for example, is one of the important

Fig. 2. Kaplan-Meier analyses of clinical outcomes categorized by CONUT score. A, All-cause death. B, Cardiovascular death. C, Worsening HF. CONUT, Controlling Nutritional Status, HF, heart failure.

Table 4
Cox proportional hazards model for all-cause death.

Variable	No. of events/ at risk (%)	Model 1 Crude		Model 2 Age, sex-adjusted		Model 3 Fully-adjusted by major confounders[a]		Model 4 Fully-adjusted using OPTIMIZE-HF nomogram[b]	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CONUT score as continuous variable									
	64/635 (10)	1.47 (1.27–1.60)	<0.001	1.40 (1.25–1.60)	<0.001	1.26 (1.11–1.42)	<0.001	1.23 (1.08–1.39)	0.002
CONUT score as categorical variable									
CONUT score 0–1	5/142 (4)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
CONUT score 2–3	9/214 (4)	1.20 (0.40–12.8)	<0.001	1.09 (0.37–3.50)	0.88	0.80 (0.27–2.65)	0.69	0.90 (0.31–2.96)	0.85
CONUT score 4–5	30/193 (16)	4.40 (1.85–12.8)	<0.001	3.76 (1.57–11.2)	0.002	2.15 (0.86–6.57)	0.11	2.46 (0.99–7.46)	0.05
CONUT score ≥6	20/86 (23)	7.70 (3.11–23.1)	<0.001	6.85 (2.75–20.7)	<0.001	3.67 (1.34–11.8)	0.010	3.31 (1.22–10.5)	0.017

CI = confidence interval; CONUT = Controlling Nutritional Status; HR = hazard ratio; OPTIMIZE-HF = organized program to initiate lifesaving treatment in hospitalized patients with heart failure.
[a] Model 3 was adjusted by major confounders such as age, systolic blood pressure, hemoglobin, estimated glomerular filtration rate, serum sodium, body mass index, and statin use.
[b] Model 4 was adjusted by all potential confounders, some of which were represented by the OPTIMIZE-HF nomogram to avoid overfitting; OPTIMIZE-HF nomogram, hemoglobin, history of malignancy, and statin use.

parts of management of HF, and is much more effectively provided during hospitalization than in an ambulatory setting. Recently, supplementation of macronutrients (e.g., leucine [41]) and micronutrients (e.g., thiamine [28]) has been reported to have potential therapeutic effects for HF. The effect of using CONUT as a triage tool to assess the need for intensive multidisciplinary care in patients admitted with AHF needs further investigation.

4.1. Study limitations

First, this study was conducted in a single-center registry, and external validity should be examined by expanding the study sites. Second, we could not compare other widely used nutritional indices, such as Subjective Global Assessment [42] and Mini Nutritional Assessment [43] because detailed nutritional information, including dietary intake, weight change, and physical examination findings of muscle and fat, were not obtained in our registry. Third, nutritional management was conducted according to usual practice in this study, and thereby patients with a worse nutritional status might have received more intensive nutritional care. Fourth, we did not use the original stratification of CONUT score (0–1, 2–4, 5–8, and ≥9) by Ignacio de Ulíbarri et al. [10]. Instead, we classified 0–1, 2–3, 4–5, and ≥6, balancing the numbers for each group (distribution of the score was shown in Fig. 1A), taking care not to be arbitrary. The correlation between CONUT score and the outcome was robust regardless of the score stratification. However, the number of patients with a CONUT score ≥9 were too scarce to be evaluated. Fifth, the CONUT score may partly reflect the natural history of HF progression; however, our registry was not equipped with the data of HF duration. Instead, we had data of history of HF admission. At least the association of CONUT score with all-cause death was sufficiently robust and the addition of this covariate into the fully adjusted Cox model (model 3) didn't change the results as we showed in Supplemental Table 2. Lastly, the validity of adapting the OPTIMIZE-HF model in this study needs to be considered. The OPTIMIZE-HF nomogram was a risk model for death within 60 days after discharge in AHF, enabling risk prediction on admission [19]. On the other hand, the primary outcome

Table 5
Cox proportional hazards model for cardiovascular death and worsening heart failure.

Variable	No. of events/ at risk (%)	Model 1 Crude		Model 2 Age, sex-adjusted		Model 3 Fully-adjusted by major confounders[a]		Model 4 Fully-adjusted using OPTIMIZE-HF nomogram[b]	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cardiovascular death									
CONUT score as continuous variable									
	39/635 (6)	1.43 (1.25–1.64)	<0.001	1.42 (1.23–1.63)	<0.001	1.24 (1.05–1.47)	0.016	1.10 (1.05–1.15)	0.018
CONUT score as categorical variable									
CONUT score 0–1	2/142 (1)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
CONUT score 2–3	6/214 (3)	1.93 (0.44–13.1)	0.40	1.79 (0.41–12.2)	0.46	1.18 (0.26–8.23)	0.84	1.34 (0.30–9.21)	0.72
CONUT score 4–5	20/193 (10)	7.25 (2.12–45.4)	<0.001	6.13 (1.76–38.7)	0.002	3.09 (0.83–20.1)	0.10	3.61 (0.99–23.3)	0.05
CONUT score ≥6	11/86 (13)	10.5 (2.82–67.9)	<0.001	9.21 (2.45–59.8)	<0.001	3.94 (0.90–27.4)	0.07	4.17 (1.01–28.3)	0.048
Worsening heart failure									
CONUT score as continuous variable									
	160/635 (25)	1.09 (1.01–1.17)	0.021	1.08 (1.00–1.17)	0.040	1.00 (0.91–1.08)	0.93	0.99 (0.91–1.08)	0.84
CONUT score as categorical variable									
CONUT score 0–1	24/142 (17)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
CONUT score 2–3	56/214 (26)	1.61 (1.01–2.65)	0.044	1.58 (0.99–2.60)	0.06	1.12 (0.68–1.87)	0.67	1.22 (0.75–2.03)	0.43
CONUT score 4–5	59/193 (31)	1.86 (1.17–3.04)	0.008	1.78 (1.11–2.94)	0.017	1.11 (0.67–1.89)	0.68	1.14 (0.69–1.92)	0.62
CONUT score ≥6	21/86 (24)	1.77 (0.98–3.18)	0.06	1.71 (0.94–3.09)	0.08	1.00 (0.53–1.90)	0.98	1.02 (0.54–1.91)	0.95

CI = confidence interval; CONUT = Controlling Nutritional Status; HR = hazard ratio; OPTIMIZE-HF = organized program to initiate lifesaving treatment in hospitalized patients with heart failure.
[a] Model 3 was adjusted by major confounders such as age, systolic blood pressure, hemoglobin, estimated glomerular filtration rate, serum sodium, body mass index, and statin use.
[b] Model 4 was adjusted by all potential confounders, some of which were represented by the OPTIMIZE-HF nomogram to avoid overfitting; OPTIMIZE-HF nomogram, hemoglobin, history of malignancy, and statin use.

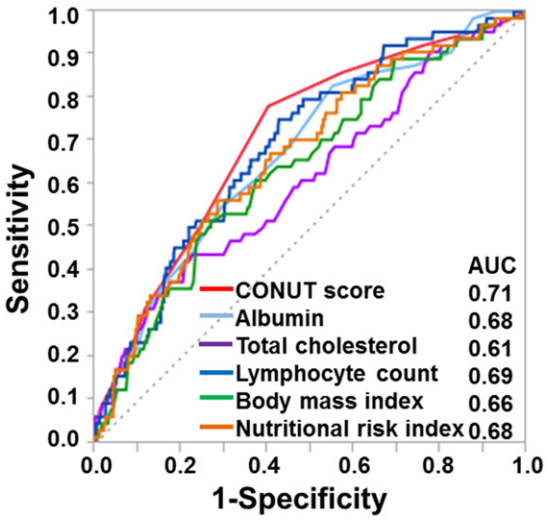


Fig. 3. Predictive performance of nutritional index and markers for all-cause death. AUC, area under the curve, CONUT, Controlling Nutritional Status.

of this study was the combination of in-hospital and post-discharge death, and the median follow-up period was 324 days. The outcome in this study could not be either in-hospital or post-discharge death. This is because our study was intended to show the importance of early detection of malnutrition in the decompensated phase of HF in order to consider early effective nutritional management during the hospital stay and continuous multidisciplinary management thereafter for long-term survival. O′Connor et al. reported that the nomogram for post-discharge death even demonstrated reasonable discrimination in validation cohorts predicting short-term mortality [19]. Indeed, the scores of the two OPTIMIZE-HF nomograms described by O′Connor et al. [19] for post-discharge death and by Abraham et al. [18] for in-hospital death were highly related ($R^2 = 0.80$, data not shown) in our AHF cohort. Furthermore, the C-statistic of the nomogram was 0.75 in this study, which was consistent with that in the original paper (0.72) [19].

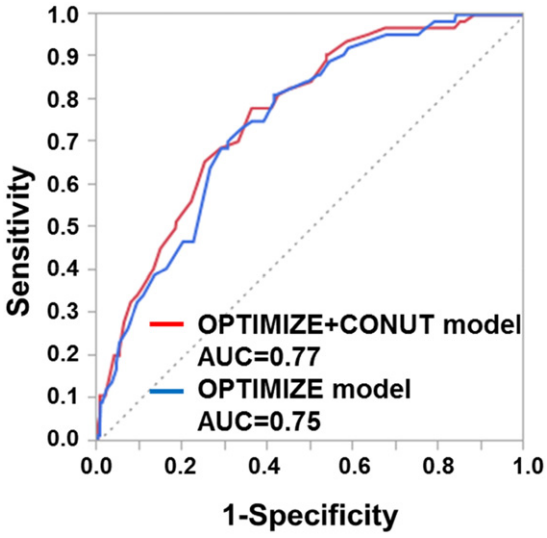


Fig. 4. Significance of adding CONUT score to existing AHF risk prediction model for all-cause death. AHF, acute heart failure, AUC, area under the curve, CONUT, Controlling Nutritional Status, OPTIMIZE-HF, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

5. Conclusion

Malnutrition assessed with the CONUT score on admission was an independent determinant of death in AHF patients. Moreover, addition of the CONUT score to the existing outcome prediction model increased the predictive ability for death with net reclassification improvement. These findings suggest that assessment of nutritional status by CONUT score should be considered in the decompensated phase of HF.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

For supplemental material including supplemental tables, and a list of investigators, clinical research coordinators and data managers, please see the online version of this article. Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.ijcard.2016.12.064.

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