Table 3. Impact of Nutritional Status on All-Cause Death and First Hospitalization for HF

	No. of events/at risk (%)	No. of events/1,000 py	Model 1: unadjusted			Model 2: age- and sex-adjusted			Model 3: fully adjusted		
			HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
All-cause death											
CONUT score as continuous variable	224/3,421 (6.5)	22.7	1.38	1.29–1.48	<0.001	1.35	1.25–1.45	<0.001	1.27	1.16–1.39	<0.001
CONUT score as categorical variable											
CONUT score 0–1	105/2,121 (5.0)	17.1	1.00 (reference)			1.00 (reference)			1.00 (reference)		
CONUT score 2	38/693 (5.5)	19.0	1.15	0.79–1.67	0.46	1.05	0.72–1.52	0.80	1.04	0.69–1.58	0.85
CONUT score ≥3	81/607 (13.3)	46.2	2.98	2.23–3.98	<0.001	2.61	1.94–3.49	<0.001	1.99	1.39–2.85	<0.001
First hospitalization for HF											
CONUT score as continuous variable	127/3,421 (3.7)	13.1	1.22	1.10–1.36	<0.001	1.20	1.07–1.33	0.001	1.02	0.88–1.18	0.77
CONUT score as categorical variable											
CONUT score 0–1	62/2,121 (2.9)	10.3	1.00 (reference)			1.00 (reference)			1.00 (reference)		
CONUT score 2	29/693 (4.2)	14.8	1.49	0.96–2.31	0.08	1.40	0.90–2.18	0.14	1.13	0.69–1.86	0.62
CONUT score ≥3	36/607 (5.9)	20.5	2.22	1.48–3.36	<0.001	2.05	1.35–3.10	0.001	1.19	0.71–2.00	0.50

In model 3, we adjusted the model by age, sex, heart rate, diabetes mellitus, dyslipidemia, history of cancer, current or former smoking, LVEF, BNP levels, anemia, CKD, and treatment (ACEI, ARB, and β-blocker). AD, all-cause death; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HR, hazard ratio; py, person-years. Other abbreviations as in Tables 1,2.

all patients, a single mode of death was stated. First hospitalization for HF was defined as the first hospitalization necessitated by HF and primarily for its treatment. A patient admitted for HF hospitalization had to show signs and symptoms of HF and to require treatment with intravenous diuretics. All events were reviewed and assigned by consensus of 2 independent physicians, the members of the Tohoku Heart Failure Association.[4,5] They reviewed case reports, death certificates, medical records, and summaries provided by the investigators.

Statistical Analysis

All continuous variables are shown as mean±standard deviation. Comparisons of data among the 3 groups were performed by ANOVA test for continuous variables and by chi-square test or Fisher's exact test for dichotomous variables. Kaplan-Meier curves were plotted to evaluate the association between the CONUT score and all-cause death or first hospitalization for HF. We performed Cox proportional hazard analysis to compare the death rate for each mode of death and the rate of first hospitalization for HF. For evaluating the influence of the CONUT score on all-cause death, we constructed the following 3 Cox proportional hazard regression models: model 1, unadjusted; model 2, age- and sex-adjusted; and model 3, fully adjusted. In model 3, using step-wise selection, we excluded the following covariates: systolic blood pressure, hypertension, obesity (BMI ≥30), history of myocardial infarction, and history of valvular heart disease, and we included the following covariates: age, sex, heart rate, smoking status (never vs. current or former smoker), diabetes mellitus, dyslipidemia, history of cancer, LVEF, brain natriuretic peptide (BNP) levels, anemia (defined as hemoglobin 12 g/dl in females, and 13 g/dl in males),[13] chronic kidney disease [CKD, defined as estimated glomerular filtration rate $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$],[14] and treatment [angiotensin-converting enzyme (ACEI), angiotensin-receptor blocker (ARB), and β-blocker].

Subgroup analysis was conducted according to age (≥70 years), sex, lipid-lowering agents, history of cancer, CKD and anemia, all of which may influence the CONUT score. The cut-off age of 70 years or older was based on the median and mode age (69 years). In the subgroup analysis, we adjusted the covariates in model 3. The assumption of proportional hazards was tested for the model, and no significant departure was found. We performed all analyses using IBM SPSS Statistics 18.0 (IBM, Somers, NY, USA). Two-sided probability values of <0.05 were considered to be statistically significant. The authors had full access to the data and give full agreement to the manuscript as written.

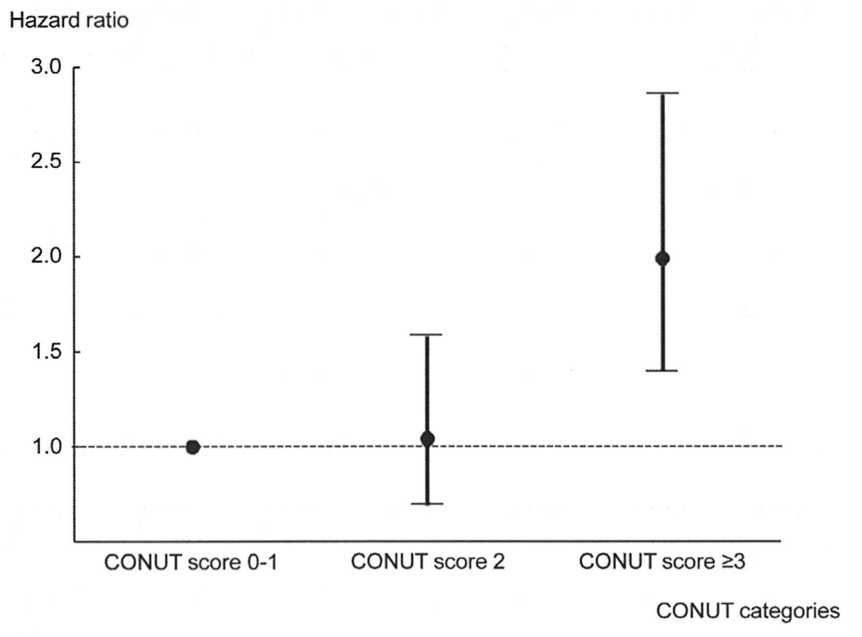

Figure 3. Relationship between the controlling nutritional status (CONUT) category and hazard ratios for the all-cause death in fully adjusted Cox regression analyses. Vertical bars represent 95% confidence intervals.

Table 4. Impact of Nutritional Status on Mortality Rate

	No. of events (% of AD)	No. of events/1,000 py	CONUT score every 1 point increase		
			HR	95% CI	P value
Cardiovascular	80 (35.7)	8.1	1.13	0.96–1.32	0.14
Heart failure	21 (9.4)	2.1	1.38	1.04–1.82	0.03
Stroke	26 (11.6)	2.6	1.22	0.92–1.61	0.17
Sudden death	26 (11.6)	2.6	0.68	0.35–1.33	0.26
MI	2 (0.9)	0.2	–		
Other cardiovascular	5 (2.2)	0.5	1.18	0.98–1.42	0.73
Noncardiovascular	123 (54.9)	12.4	1.37	1.22–1.54	<0.001
Cancer	56 (25.0)	5.7	1.23	0.99–1.51	0.051
Other noncardiovascular	67 (29.9)	6.8	1.43	1.23–1.66	<0.001
Unknown	21 (9.4)	2.1	1.14	0.78–1.67	0.50

In the multivariable Cox proportional hazard models, we adjusted the models by age, sex, heart rate, diabetes mellitus, dyslipidemia, history of cancer, current or former smoking, LVEF, BNP levels, anemia, CKD, and treatment (ACEI, ARB, and β-blocker). Abbreviations as in Tables 1–3. Mortality rate is expressed as number of events per 1,000 py.

Results

Baseline Characteristics

Figure 1 shows the distribution of the CONUT score; the mean (median) value was 1.4±1.4 (1.0) in the present population. The 3,421 patients were categorized as follows: CONUT 0–1 (n=2,121), CONUT 2 (n=693), and CONUT ≥3 (n=607). Table 2 shows the baseline characteristics of the patients categorized by CONUT score. Mean age was 66.9±12.7 years and male patients accounted for 71.6%. Mean levels of serum albumin, total cholesterol, and lymphocytes were 4.2±0.7 (g/ml), 185±35 (mg/dl), and 1,779±865 (counts/ml), respectively. Of the 3,421 patients, LVDd ≥55 mm was noted in 610 (17.8%), echocardiographic LV hypertrophy in 413 (12.1%), valvular heart disease in 627 (18.3%), LV wall motion abnormalities in 933 (27.3%), history of cardiac surgery in 297 (8.7%), and congenital abnormalities in 78 (2.3%). As expected, patients with a CONUT score ≥3 were older and had lower BMI, lower Hb levels, and higher prevalence of cancer history. There was no difference in sex, heart rate at baseline, smoking status, hypertension, atrial fibrillation, or the use of ACEI/ARB, β-blocker, calcium-channel blocker and lipid-lowering agents among the 3 groups (Table 2). Table S1 shows the clinical characteristics of the 1,042 stage B patients who were registered in the CHART-2 study but excluded from the present study because of insufficient information for CONUT score calculation. The characteristics of these patients were comparable to those enrolled in the present study. Survival at 3 years was 93.8% in the 3,421 patients of the present study population and 94.1% in the 1,042 patients excluded from the present study (log-rank P=0.36).

Nutritional Status and Death

During the median follow-up of 2.89 years, 224 (6.5%) patients died. As shown in Figure 2A, Kaplan-Meier curves revealed that the patients with CONUT score ≥3 had the highest event rate for all-cause death among the 3 groups (log-rank P<0.001). The Cox proportional hazard analyses revealed that

Table 5. Impact of Nutritional Status on All-Cause Death and First Hospitalization for HF

	All-cause death					First hospitalization for HF				
	No. of events/at risk (%)	No. of events/ 1,000 py	HR	95% CI	P value	No. of events/at risk (%)	No. of events/ 1,000 py	HR	95% CI	P value
Age ≥70 years	121/1,648 (7.3)	26.2	1.26	1.13–1.41	<0.001	60/1,648 (3.6)	13.0	1.17	1.00–1.38	0.049
Age <70 years	53/1,773 (3.0)	10.1	1.30	1.11–1.53	0.002	35/1,773 (2.0)	6.8	0.70	0.51–0.97	0.03
Male	175/2,448 (7.1)	24.6	1.31	1.18–1.46	<0.001	85/2,448 (3.5)	12.3	1.12	0.94–1.34	0.20
Female	49/973 (5.0)	17.2	1.18	0.98–1.43	0.09	42/973 (4.3)	15.2	0.85	0.65–1.11	0.24
W/ lipid-lowering agent	81/1,527 (5.3)	18.3	1.38	1.16–1.63	<0.001	50/1,527 (3.3)	11.5	0.92	0.71–1.20	0.55
W/o lipid-lowering agent	143/1,894 (7.6)	26.4	1.24	1.11–1.39	<0.001	77/1,894 (4.1)	14.6	1.06	0.89–1.26	0.53
W/ history of cancer	64/405 (15.8)	55.8	1.51	1.21–1.88	<0.001	17/405 (4.2)	15.1	1.16	0.76–1.77	0.50
W/o history of cancer	160/3,016 (5.3)	18.3	1.23	1.11–1.37	<0.001	110/3,016 (3.6)	12.7	0.99	0.85–1.17	0.99
W/ CKD	121/1,112 (10.9)	37.6	1.24	1.09–1.40	0.001	70/1,112 (6.3)	22.4	1.11	0.93–1.33	0.25
W/o CKD	103/2,309 (4.5)	15.6	1.25	1.09–1.44	0.002	57/2,309 (2.5)	8.7	0.92	0.72–1.19	0.53
W/ anemia	69/403 (17.1)	62.0	1.41	1.23–1.61	<0.001	32/403 (7.9)	29.8	1.04	0.79–1.37	0.78
W/o anemia	155/3,018 (5.1)	17.5	1.15	1.01–1.31	0.04	95/3,018 (3.1)	10.8	1.03	0.86–1.23	0.09

Anemia is defined as hemoglobin 12 g/dl in females, and 13 g/dl in males. In this analysis, we included the following covariates: age, sex, heart rate, smoking status (never vs. current or former smoker), diabetes mellitus, dyslipidemia, history of cancer, LVEF, BNP levels, anemia, CKD, and treatment. w/, with; w/o, without. Other abbreviations as in Tables 2,3.

per point increase in the CONUT score was associated with increased risk of all-cause death [hazard ratio (HR): 1.38, 95% confidence interval (CI), 1.29–1.48, 1.35, 95% CI, 1.25–1.45, and 1.27,1.16–1.39 for models 1, 2, and 3, respectively] and that patients with CONUT score ≥3 had a 99% increase in the risk for all-cause death as compared with those with the 0–1 score (P<0.001) (**Table 3**, **Figure 3**).

Table 4 shows the mortality rate and association between cause of death and CONUT score. Of the 252 deaths, 80 (35.7%) was attributed to cardiovascular origins, 123 (54.9%) to noncardiovascular origins, and 21 (9.4%) of unknown cause. The CONUT score was significantly associated with HF and noncardiovascular deaths (**Table 4**).

Nutritional Status and First Hospitalization for HF

First hospitalization for HF was noted for 139 patients (3.4%) during the study period. The patients with CONUT score ≥3 had the highest incidence of hospitalization for HF among the 3 groups (log-rank P<0.001) (**Figure 2B**). However, as shown in **Table 3**, the Cox regression analyses revealed that per point increase in the CONUT score was associated with an increase in the risk of hospitalization for HF in the unadjusted (model 1) and age- and sex-adjusted model (model 2), but not in the fully adjusted model (model 3). This trend was also observed in the models using the CONUT score as a categorical variable (**Table 3**).

Baseline Characteristics and Prognostic Impacts of CONUT Score in Stage B Patients

Table 5 shows the subgroup analysis of associations between baseline characteristics and the impact of the CONUT score on all-cause death and hospitalization for HF. The relationships between CONUT score and the outcomes remained unaltered by sex, use of lipid-lowering agents, history of cancer, CKD, or anemia. However, the results showed that the relationships could be different according to the age category. In the patients aged 70 years or older, the HR (95% CI) of the CONUT score for hospitalization for HF was 1.17 (95% CI 1.00–1.38, P=0.049), whereas it was 0.70 (95% CI 0.51–0.97, P=0.03) in those younger than 70 years (**Table 5**).

Correlation Between CONUT Score and the NRI

There was a significant inverse correlation between the CONUT score and the NRI (Pearson R=–0.51, P<0.01) (**Figure S1A**). In addition, Kaplan-Meier curves for all-cause death and HF hospitalization showed that low NRI (indicating undernutrition) was associated with higher events (**Figure S1B**).

Discussion

In the present study, we examined whether nutritional status was associated with mortality and future HF in stage B patients registered in the CHART-2 Study, a multicenter prospective observational study for HF in Japan. The results showed that undernutrition was associated with an increased risk for all-cause death, HF death and noncardiovascular death among the stage B patients. Also, undernutrition was associated with increased risk for HF hospitalization in the elderly (>70 years), suggesting that nutritional status is a predictor for conversion to stage C in elderly, stage B patients.

Nutritional Status and Death in Stage B Patients

We assessed the relationship between nutritional status and prognosis in stage B patients by using the CONUT score, which is the sum of the scores of serum albumin and total cholesterol levels, and total lymphocyte count.[11] In the present study, higher CONUT score was associated with increased numbers of all-cause death, HF death, and noncardiovascular death. The relationship between the CONUT score and the risk of all-cause death remained unchanged even after adjustment by age, use of lipid-lowering agents, history of cancer, CKD or anemia, suggesting that the score is useful for all stage B patients. In the present study, the overall survival at 3 years was 93.8%, comparable to that of stage B patients in the USA.[3] Notably, however, the survival at 3 years of the stage B patients with CONUT score ≥3 was 73.2%, which is equal to that of stage C patients in the USA.[3] Higher CONUT score reflects undernutrition and impaired inflammatory response, supporting the notion that metabolic disorder and the immune system play a crucial role in the development of cardiovascular diseases.

Nutritional Status and First Hospitalization for HF in Stage B Patients

In the present study, we examined whether nutritional status could influence the transition from stage B to stage C as a possible non-cardiac factor, because undernutrition is well established not only as a prognostic risk factor in patients with HF but also as a major determinant of mortality after the onset of HF.[7–9]

Several previous studies have attempted to identify subjects at high risk for transition to symptomatic HF by using non-cardiac parameters. Velagaleti et al reported that the urinary albumin to creatinine ratio, as well as BNP, was a key factor for new-onset HF in 2,754 Framingham Heart Study participants.[15] Lam et al also reported that higher serum creatinine level, lower functional residual volume/forced vital capacity (FRV1/FVC) ratio, and lower hemoglobin level were associated with increased HF risk in the Framingham Heart Study's original cohort.[16] In all the study populations, no significant association was noted between CONUT score and risk of first hospitalization for HF, although patients with higher CONUT score had higher BNP levels as compared with those with lower scores. However, in patients aged 70 or older, higher CONUT score was associated with a 17% increase in first hospitalization for HF, whereas it was inversely associated with first hospitalization for HF in patients younger than 70 years (**Table 5**). This result suggests that the CONUT score is a useful predictor of conversion to stage C in elderly patients.

Although it is reasonable to note that undernutrition, which is more commonly observed in elderly patients, was associated with an increased incidence of HF hospitalization, caution is needed when interpreting the observation in patients younger than 70 years. One of the possible explanations is that overnutorition, rather than undernutrition, might be more influential on the development of HF in the younger generation. Accordingly, increased prevalence of overweight subjects in the younger population could be additional influencing factor, because obesity, especially abdominal obesity, is also an independent risk of HF and other cardiovascular diseases.[15–19] The differences in the medication use between younger and elderly populations should also be taken into consideration[20,21] (**Table S2**).

Comparison With Other Established Nutrition Assessments

Because the CONUT score is a relatively new index, it needs to be validated with established scores. Indeed, it has been shown that the CONUT score is in good agreement with 2 other classical methods: the Subjective Global Assessment (SGA) and the Full Nutritional Assessment (FNA).[11] In the present study, we also examined the prognostic impact of the CONUT score and the NRI and found that both scores have comparable prognostic significance. Thus, we used the CONUT score to evaluate the prognostic impact of nutritional status in stage B patients (**Figures S1A,B**).

Clinical Implications

The present study demonstrates that assessment of nutritional status by CONUT score is useful for risk stratification of stage B patients. Although patients with stage B are asymptomatic and thus their risks are less likely to be recognized and treated, the present study indicates that assessment of nutritional status with the CONUT score should be implemented in stage B patients.

Study Limitations

Several limitations should be mentioned for the present study. First, we used the classification of the CONUT score reported in a previous study[11] and did not assess the optimal cut-off levels of the 3 parameters (serum albumin level, total cholesterol level, and total lymphocyte count). Second, classification of HF staging was done by investigators at each institution and thus may have caused classification bias. However, because all the investigators were established cardiologists and data were prospectively collected, class assignment bias should be minimal. Third, although we assessed the relationship between the undernutrition and prognosis, we did not evaluate the relationship between overnutrition and prognosis in stage B patients. Fourth, we did not exclude stage B patients with liver cirrhosis, which might have influenced the serum levels of albumin and cholesterol in the present study.

Conclusions

In the present study, we were able to demonstrate that nutritional status was associated with increased incidence of death, indicating that the status is a key prognostic factor and thus should be assessed for risk stratification of stage B patients. A nutritional intervention trial in stage B patients is needed to confirm our findings.

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Supplementary Files

Supplementary File 1

Table S1. Baseline Characteristics of the Patients Without Information for a CONUT Score

Table S2. Baseline Characteristics of the Patients According to Age

Figure S1. (A) Correlation between CONUT score and the nutritional risk index (NRI).

Data S1. Appendix

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-13-0127