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 the model 3, using step-wise selection, we excluded the following covariates; systolic blood pressure, hypertension, obesity (BMI $\geq$30 kg/m^2), history of myocardial infarction, and history of valvular heart disease, and we included the following covariates; age, sex, heart rate, smoking status (never vs. current or former smoker), diabetes mellitus, dyslipidemia, history of cancer, LVEF, brain natriuretic peptide (BNP) levels, anemia (defined as hemoglobin 12 g/dl in females, and 13 g/dl in males),[13] chronic kidney disease [CKD, defined as estimated GFR (eGFR) <60 mL/min/1.73 m^2],[14] and treatment [angiotensin-converting enzyme (ACEI), angiotensin receptor blocker (ARB), and β-blocker]. Subgroup analysis was conducted according to age ($\geq$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 the 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). Two-sided probability values of <0.05 were considered to be statistically significant. The authors had a full access to the data and take fully agreement to the manuscript as written.

Results

Baseline Characteristics

Figure 1 shows the distribution of the CONUT score and the mean (median) value was 1.4±1.4 (1.0) in the present population. The 3,421 patients were categorized as follow; 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 the 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≥55mm was noted in 610 (17.8%), echocardiographic left ventricular 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, the patients with the 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, Ca channel blocker and lipid lowering agent among the 3 groups (**Table 2**). **Supplemental Table 1** 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 due to insufficient information for the 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 the 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 per point increase in the CONUT score was associated with the increased risk of all-cause death (HR: 1.38, 95%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 the patients with the 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 and Figure 3**).

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

Nutritional Status and First Hospitalization for HF

First hospitalization for HF was noted in 139 patients (3.4%) during the study period. The patients with the 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 unadjusted (model 1) and age- and sex-adjusted model (model 2), but not in 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 evaluating associations between baseline characteristics

and impacts of CONUT score on all-cause death and hospitalization for HF. The relationships between the CONUT score and the outcomes remained unaltered by gender, use of lipid lowering agent, history of cancer, CKD, or anemia. However, the results showed that the relationships could be different according to the aging 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 the 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) (**Supplemental Figure 1A**). In addition, Kaplan-Meier curves for all-cause death and HF hospitalization showed that low NRI (indicating undernutritional status) was associated with higher events (**Supplemental Figure 1B**).

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 undernutritional status was associated with increased risk for all-cause death, HF death and non-cardiovascular death with being common in stage B patients. Also, undernutritional status 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 patients with stage B.

Nutritional Status and Deaths in Stage B Patients

We assessed the relationship between nutritional status and prognosis in stage B patients by using the CONUT score that is the sum of the scores of serum albumin levels, total cholesterol levels, and total lymphocyte count.[11] In the present study, higher CONUT score was associated with increased events of all-cause death, HF death, and non-cardiovascular death. The relation between the CONUT score and the risk of all-cause death remained unchanged even after adjustment by age, use of lipid lowering agent, history of cancer, CKD or anemia, suggesting that the score is useful for overall stage B patients. In the present study, the overall survival at 3 years was 93.8 %, a comparable survival with stage B patients in the US.[3] Notably, however, the survival at 3 years of the stage B patients with CONUT score≥3 was 73.2%, which is equal to those of patients with stage C in the US.[3] Higher CONUT score reflects undernutritional status and impaired inflammatory response, supporting the notion that metabolic disorder and immune system may 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 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 one of the major determinants for mortality after the onset of HF.[7-9]

Several studies have previously attempted to identify subjects at high risk for transition to symptomatic HF by using non-cardiac parameters. Velagaleti et al. reported that 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, lower functional residual volume/forced vital capacity (FRV1/FVC) ratios, and lower hemoglobin levels were associated with increased HF risks in the Framingham Heart Study original cohort.[16] In all the study population, no significant association was noted between the CONUT score and risk of first hospitalization for HF, although the patients with higher CONUT had higher BNP levels as compared with those with the lower score. 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 suggested that CONUT score is a useful predictor for conversion to stage C in elderly patients.

Although it is reasonable to note that undernutritional status, 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 younger generation. Accordingly, increased prevalence of overweight subjects in the younger population could be additional influencing factor as obesity, especially abdominal obesity, is also an independent risk of HF

and other cardiovascular diseases.[15-19] The differences of the medication use between younger and elderly populations should also be taken into consideration. [20,21] (**Supplemental Table 2**)

Comparison with Other Established Nutrition Assessments

Since the CONUT score is a relatively new index, it needs to be validated with the established scores. Indeed, it was shown that the CONUT score is in good agreement with other 2 classical methods, the Subjective Global Assessment (SGA) and the Full Nutritional Assessment (FNA).[11] In the present study, we also examined the prognostic impacts 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 (**Supplemental Figure 1**A and **1B**).

Clinical Implications

The present study demonstrates that assessment of nutritional status with the 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 the previous study[11] and did not assess the optimal cut-off levels of the 3 parameters (serum albumin levels, total cholesterol levels, 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 undernutritional status and the prognosis, we did not evaluate the relationship between the overnutrition and the prognosis in stage B patients. Forth, 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 deaths, indicating that the status is a key prognostic factor and thus should be assessed for risk stratification in stage B patients. The nutritional intervention trial in stage B patients is needed to confirm our findings.

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Conflict of Interest

None declared.

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Figure Legends

Figure 1. Distribution of CONUT score in the present study (n=3,421).

Figure 2. Cumulative incidence curves for all-cause death (a) and first hospitalization for HF (b) according to category of CONUT score at the baseline. Vertical bars indicate SEs of the incidence estimates at 3 years of follow-up. Data shown are truncated at 3.5 years.

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

Supplemental Materials

I. **Supplemental Figure 1A. Correlation between the CONUTS Score and the Nutritional Risk Index (NRI).**

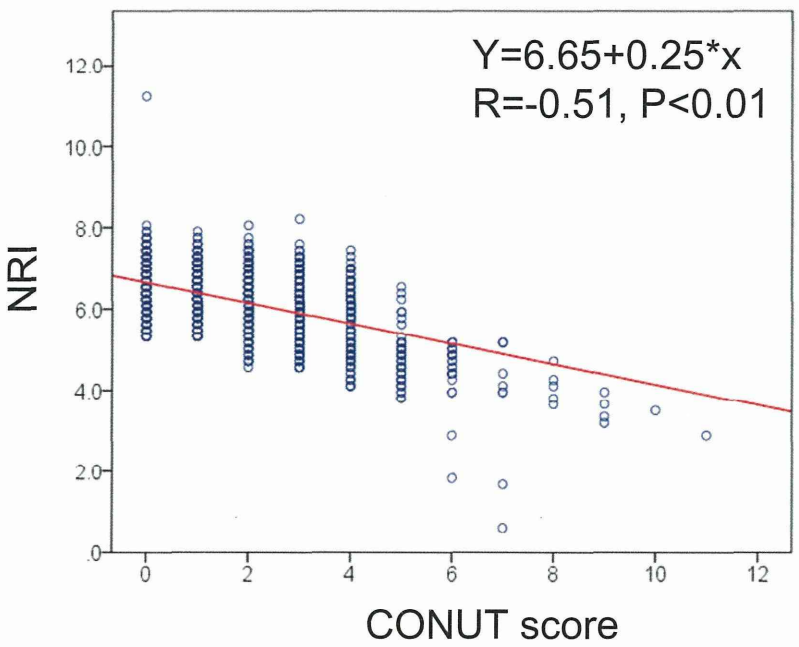
Supplemental Figure 1B. Kaplan-Meier Curves for All-cause Death and Hospitalization for HF Stratifying by the NRI.

II. **Supplemental Table 1. Baseline Characteristics of the Patients without Information of CONUT Score.**

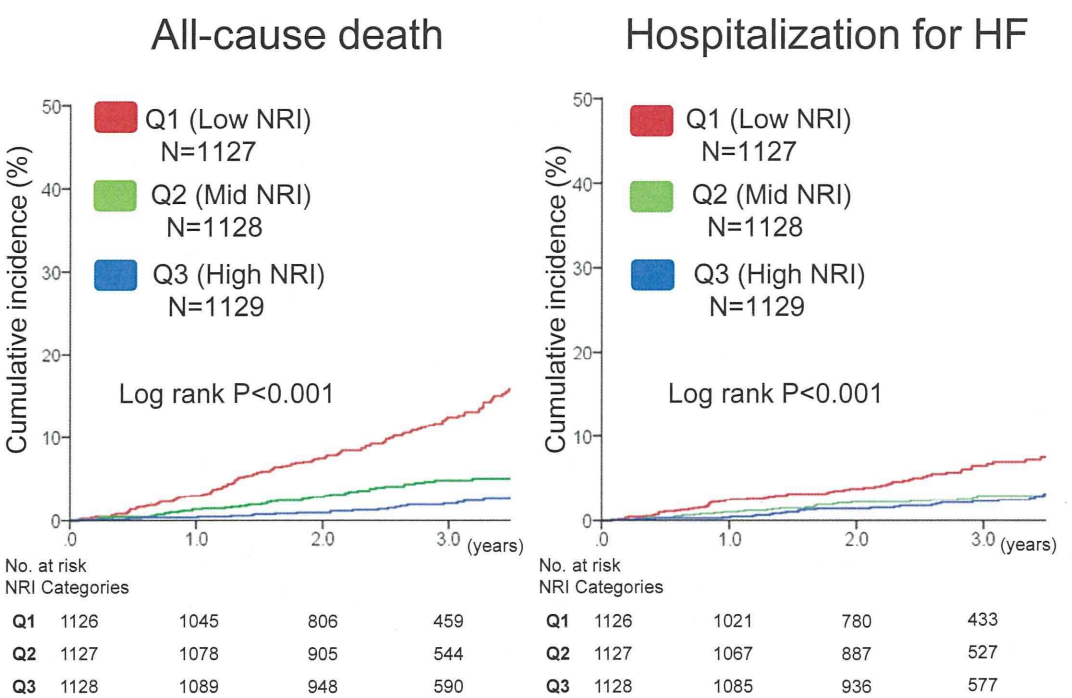
III. **Supplemental Table 2. Baseline Characteristics of the Patients According to Age.**

IV. **Supplemental Appendix. The CHART-2 Investigators.**

Supplemental Figure 1A. Correlation between the CONUTS Score and the Nutritional Risk Index (NRI).



Supplemental Figure 1B. Kaplan-Meier Curves for All-cause Death and Hospitalization for HF Stratifying by the NRI.



Supplemental Table 1. Baseline Characteristics of the Patients without Information of CONUT Score.

	Patients without CONUT score (N=1,042)	Patients with CONUT score (N=3,421)	P
Age – years	68.7 ± 11.8	66.9 ± 12.7	<0.001
Male - no. (%)	874 (70.4)	2448 (71.6)	0.44
Body-mass index - kg/m^2	23.9 ± 4.7	24.1 ± 4.3	0.29
BMI ≥ 30	59 (4.8)	187 (5.5)	0.19
Blood pressure – mmHg			
Systolic	130 ± 17	130 ± 18	0.87
Diastolic	74 ± 11	75 ± 12	0.03
Heart rates - beats/min	70 ± 13	70 ± 13	0.87
Current or past smoker - no. (%)	498 (42)	1638 (51)	<0.001
Medical history - no. (%)			
Previous myocardial infarction	397 (32)	1059 (31)	0.52
Hypertension	974 (78)	2653 (78)	0.55
Dyslipidemia	851 (69)	2551 (75)	<0.001
Diabetes Mellitus	272 (22)	845 (25)	0.05
Atrial Fibrillation	328 (27)	689 (20)	<0.001
Stroke	195 (16)	542 (16)	0.93
Cancer	138 (11)	405 (12)	0.54
Laboratory measurement			
Hemoglobin - g/dl	13.6 ± 1.7	13.6 ± 1.8	0.29
Anemia -no. (%)	118 (10)	403 (12)	0.07
Estimated GFR			
Mean	64 ± 22	68 ± 23	<0.001
< 60 ml/min/1.73m^2 - no. (%)	465 (37)	1112 (33)	0.002
BNP - pg/dl	120 ± 310	102 ± 159	0.02
Echocardiographic abnormalities - no. (%)			
LVDd ≥55mm	233 (22)	610 (19)	0.09
LVEF≤50%	134 (12)	413 (13)	0.56
IVS >12 mm and/or LVPW >12 mm	437 (41)	1277 (40)	0.77
Valvular heart disease	265 (21)	627 (18)	0.02

Wall-motion abnormalities	288 (26)	933 (29)	0.05
History of cardiac surgery	120 (10)	297 (9)	0.30
Congenital abnormalities	30 (2)	78 (2)	0.83
Current medication -no. (%)			
ACE-I or ARB	613 (49)	2191 (64)	<0.001
β-blocker	446 (36)	1151 (34)	0.15
Ca blocker	594 (48)	1649 (48)	0.84
Lipid lowering agent	525 (42)	1527 (44)	0.15

Results are expressed as mean±standard deviation (SD). GFR, glomerular filtration ratio; BNP, brain natriuretic peptide; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; IVS, interventricular septum; LVPW, LV posterior wall; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Supplemental Table 2. Baseline Characteristics of the Patients According to Age.

	Age <70 years					Age ≥ 70 years					
	All (N=,1773)	CONUT score 0-1 (N= 1181)	CONUT score 2 (N= 333)	CONUT score≥ 3 (N= 259)	P	All (N= 1,648)	CONUT score 0-1 (N= 940)	CONUT score 2 (N= 360)	CONUT score≥ 3 (N= 348)	P	P*
Medical history - no. (%)											
Previous myocardial infarction	562 (32)	345 (29)	118 (35)	99 (38)	0.005	497 (30)	255 (27)	123 (34)	119 (34)	0.008	0.34
Current medication -no. (%)											
ACE-I or ARB	1145 (65)	750 (64)	215 (65)	180 (70)	0.19	1046 (65)	600 (64)	230 (64)	216 (62)	0.83	0.52
Beta-blocker	649 (37)	415 (35)	135 (41)	99 (38)	0.17	502 (31)	278 (30)	109 (30)	115 (33)	0.48	<0.001
Lipid lowering agent	799 (45)	506 (43)	162 (49)	131 (51)	0.03	728 (44)	413 (44)	152 (42)	163 (47)	0.45	0.61

Results are expressed as mean±standard deviation (SD). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker. P is expressed ad the statistically difference among three groups. P* is expressed as the statistically difference between patients with age<70 years and ≥70 years.