Table 3 Split point of HR for outcomes in overall patients, HFrEF and HFpEF

		First split point of HR	Hazard ratio of higher HR group[a]	95% CI	*P*-value
CV death	All	63.5 bpm	1.85 (≥ 64 bpm)	1.26–2.73	0.002
	HFrEF	69.5 bpm	1.60 (≥ 67 bpm)	1.00–2.55	0.051
	HFpEF	63.5 bpm	2.04 (≥ 64 bpm)	1.17–3.53	0.012
Non-CV death	All	71.5 bpm	1.68 (≥ 72 bpm)	1.19–2.38	0.004
	HFrEF	71.5 bpm	1.34 (≥ 72 bpm)	1.22–4.50	0.011
	HFpEF	71.5 bpm	1.45 (≥ 72 bpm)	0.95–2.22	0.082

[a]Unadjusted hazard ratios of patients with HR more than optimal split point indicated by CART analysis (higher HR group) over those with HR not more than indicated (lower HR group). The minimum HRs of the higher HR group are shown in parentheses next to the hazard ratios.

Different impact of baseline HR between HFrEF and HFpEF

Bui *et al.* demonstrated that HFpEF was associated with a higher risk of in-hospital mortality with increasing admission HR compared with HFrEF among patients hospitalized for HF, suggesting that higher HR might have imparted increased in-hospital mortality in HFpEF patients.[20] As for the impacts of elevated baseline HR on long-term CV mortality, the present study may provide the first evidence that such impacts on CV death, particularly on HF death, are rather significant in HFpEF compared with HFrEF (*Figure 2*). The relationship between elevated HR and increased CV mortality in HFpEF appears reasonable, since HFpEF is generally complicated by diastolic dysfunction and thus could be further worsened by shortening of the diastolic period according to an increase in HR.[21] In the present study, there was no association between HR and hospitalization for HF in HFrEF or HFpEF (*Figure 2*). In addition, the present study may provide the first evidence for the association between baseline HR and non-CV death in HFrEF patients, following an association between HR and non-CV mortality being observed in the general population.[22–24] Although the precise mechanisms remain to be elucidated, low physical activity, elevated adrenergic activity and smoking might be possible explanations for the association between elevated HR and increased non-CV mortality.[22–24]

Cut-off value of HR for CV death in HFrEF and HFpEF

In order to determine the cut-off point for HR to partition Stage C/D patients according to the mortality rates, we performed CART analysis, demonstrating that 63.5, 69.5, and 63.5 bpm could be the primary splitting points for CV death among the overall, HFrEF, and HFpEF patients, respectively (*Table 3*). The univariate Cox regression analysis revealed that HFpEF patients with HR ≥ 63.5 bpm had an increased risk for CV death with a statistical significance (hazard ratio 2.04, $P = 0.012$ for patients with HR ≥ 64 bpm), and HFrEF patients with HR ≥ 69.5 bpm with a tendency (hazard ratio 1.60, $P = 0.051$ for patients with HR ≥ 67 bpm). These results may suggest that the therapeutic range of HR to reduce CV mortality could be lower in HFpEF compared with HFrEF patients (63.5 vs. 69.5 bpm). This was likely because a longer duration of the diastolic period is necessary to reduce CV mortality in patients with diastolic dysfunction compared with systolic dysfunction. In this context, HR reduction therapy could be an option to reduce CV mortality in HFpEF patients. Indeed, it has been reported that selective HR reduction by ivabradin improves vascular stiffness and left ventricular systolic and diastolic function in mice.[25] A subanalysis of the SHIFT trial, which enrolled patients with HF and EF < 35%, revealed that the prognostic impact of HR reduction by ivabradine was greater in patients who had baseline HR ≥ 75 and had achieved < 60 bpm or heart rate reductions > 10 bpm.[26] Although the cut-off point of HR to discern CV mortality may vary according to the baseline ejection fraction, further reduction of HR with ivabradine could be effective in patients with HFpEF. However, further investigations are required to elucidate whether HR reduction is effective in the management of HFpEF patients in real-world practice.

β-Blocker therapy in HFpEF

It is widely accepted that β-blocker therapy improves LVEF and reduces mortality in HFrEF patients through inhibition of sympathetic nervous activity and reduction in HR and oxygen consumption.[27,28] The present study suggested different prognostic impacts of β-blockers between HFrEF and HFpEF, as β-blocker therapy was associated with decreased HF mortality in patients with HFrEF but not in those with HFpEF. β-Blockers could theoretically be beneficial in patients with HFpEF because shortening of the diastolic period could exacerbate diastolic dysfunction, a common feature of the disorder.[21] However, it was previously reported that β-blockers may not be so useful in HFpEF patients,[29] a consistent finding of the present study. However, there remains a possibility that standard doses of β-blockers (for Japanese patients) in the present study was not sufficient to reduce CV mortality for HFpEF patients. In fact, Yamamoto *et al.* recently reported that a higher dose of carvedilol was associated with lower incidence of a composite of cardiovascular death and unplanned hospitalization for any cardiovascular cause in patients with HFpEF in the Japanese population.[30] Thus, further studies are warranted to examine whether higher doses of β-blockers could improve the mortality of HFpEF patients.

Study limitations

Several limitations should be mentioned for the present study. First, the number of HFrEF patients was smaller than that of HFpEF patients, and therefore the power might not be enough to detect a statistical significance in HFrEF patients; thus, interpretation should be made with caution. Second, the CHART-2 Study is a prospective, observational study that reflects the real-world practice of HF, as consecutive HF patients were enrolled with a minimal selection bias; however, we have to consider influences on the results by unknown confounders. Third, in the present study, we only used the data at the entry and did not take into consideration the possible changes in LVEF, HR, episodes of arrhythmia, particularly those of atrial fibrillation, medication, and other covariates during the follow-up period. In addition, no data were available for β-blocker therapy, such as timing of initiation, daily doses, adherence, discontinuation, and reasons for the presence or absence of prescription. Thus, it was difficult to elucidate the prognostic impact of β-blocker therapy in the present study. Fourth, in the present study, according to European Society of Cardiology guidelines,[15] we chose the cut-off value of LVEF 50% to define HFpEF. However, caution is needed in interpreting the present results when comparing other cohorts with different cut-off values to discriminate between HFrEF and HFpEF, such as 35% or 40%.[8,10] Finally, all subjects in the CHART-2 Study were Japanese people, which may limit generalization of the present results to patients in other countries.

Conclusions

We demonstrated the different impacts of elevated baseline HR on CV and non-CV mortality between HFrEF and HFpEF in the CHART-2 Study. Although the influence of elevated baseline HR on all-cause mortality was comparable, elevated HR was significantly associated with CV death in HFpEF, but insignificantly in HFrEF, particularly for HF death. Further studies are needed to elucidate the relationship between elevated baseline HR and mortality in order to improve the survival of HF patients.

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of tertiles defined by baseline heart rate of the two groups

Table S2. Actual number of event for tertiles in HFrEF and HFpEF

Table S3. Baseline characteristics across four groups defined by LVEF and β-blocker

Appendix S1. Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 study

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ORIGINAL ARTICLE
Epidemiology

Prognostic Impact of Nutritional Status in Asymptomatic Patients With Cardiac Diseases

– A Report From the CHART-2 Study –

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Background: The prognostic impact of nutritional status is poorly understood in asymptomatic patients with structural and/or functional heart diseases, classified as stage B in the ESC/AHA/ACC chronic heart failure (HF) guidelines.

Methods and Results: We evaluated the impact of nutrition, using the controlling nutritional status (CONUT) score, calculated by the serum albumin and total cholesterol levels,and lymphocyte number, in 3,421 stage B patients from the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study (mean age: 66.9±12.7 years, male: 71.6%). During a median follow-up of 2.89 years, 224 patients died from cardiovascular (45%, n=102) and noncardiovascular (55%, n=123) causes and 139 experienced hospitalization for HF. Survival at 3 years in patients with CONUT 0–1 (reference, n=2,121), 2 (n=693) and ≥3 (n=607) was 95.5, 92.3, and 73.2%, respectively (P<0.001). The adjusted Cox hazard analyses revealed that the CONUT score was significantly associated with increased incidence of all-cause death (hazard ratio 1.27 per point increase; 95% confidence interval, 1.16–1.39, P<0.001). Subgroup analysis showed that per point increase in the CONUT score was significantly associated with a 17% increase in HF hospitalization in patients ≥70 years old (P=0.049), but not in those aged <70 years.

Conclusions: In the current stage B patients, poor nutritional status was associated with increased incidence of death for the overall population and of HF hospitalization for the elderly proportion. (*Circ J* 2013; **77:** 2318–2326)

Key Words: Epidemiology; Heart failure; Nutrition; Risk factors

Heart failure (HF) is a progressive disorder with severe mortality and morbidity.[1] The European Society of Cardiology (ESC), American Heart Association (AHA) and the American College of Cardiology (ACC) guideline underscores the importance of early detection and prevention in subjects at high risk for progression to symptomatic HF.[1,2] The ESC/ACC/AHA guideline classifies asymptomatic subjects with structural and/or functional heart disease as stage B, a category that is strongly associated with future development of HF.[2] It has been reported that in the US the prevalence of stage B is highest among stages A–D patients and that 34.1% of individuals older than 45 years are classified as stage B.[3] Thus, the management of stage B HF is quite important in real-world practice. In Japan also, we recently reported that the number of stage B patients was almost comparable to that of stage C/D in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study, a prospective multicenter observational study for HF in which 10,219 patients in the Tohoku district were enrolled (www.clinicaltrials.gov. Identifier: NCT00418041).[4,5] Therefore, risk stratification and management of stage B patients are warranted in the clinical setting. The progression of HF syndrome involves extracardiac disorders, including metabolic disorder and inflammation.[6,7] Undernutrition, which could be

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Table 1. Assessment by CONUT Score

Parameter	Score			
Serum albumin (g/ml)	≥3.5	3.0–3.49	2.50–2.99	<2.50
Albumin score	0	2	4	6
TC (mg/dl)	≥180	140–179	100–139	<100
Cholesterol score	0	1	2	3
Lymphocytes (count/ml)	≥1,600	1,200–1,599	800–1,199	<800
Lymphocytes score	0	1	2	3

The CONUT score is the sum of albumin, cholesterol, and lymphocytes scores. CONUT, controlling nutritional status; TC, total cholesterol.

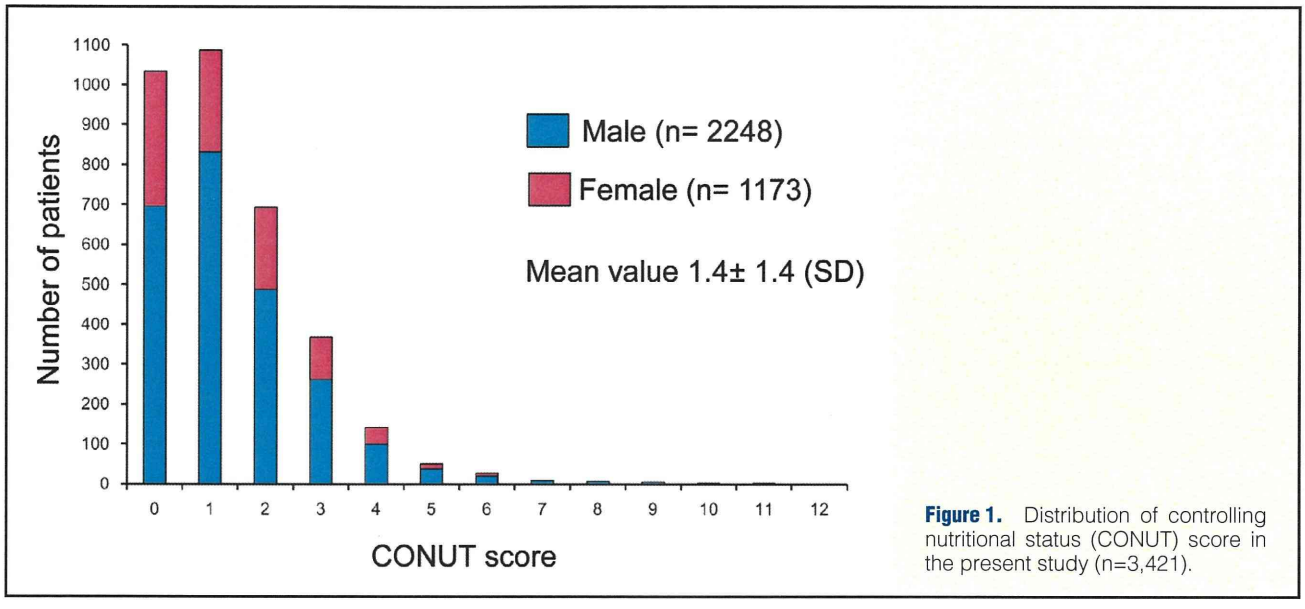

Figure 1. Distribution of controlling nutritional status (CONUT) score in the present study (n=3,421).

caused by metabolic disorder and chronic inflammation, is an established prognostic marker when evaluated with body mass index (BMI)[8] or serum albumin level in patients with symptomatic HF.[9] However, there have been few reports investigating the prognostic impact of undernutrition in asymptomatic stage B patients. In the present study, we thus tested our hypothesis that assessment of nutritional status would be useful in risk stratification for future mortality and morbidity of stage B patients in the CHART-2 study, the largest prospective observational cohort study for HF in Japan (n=10,219).[4]

Methods

The CHART-2 Study

The study design and purpose of the CHART-2 Study have been previously described.[4,5] Briefly, the CHART-2 study is a multicenter, prospective observational study into which consecutive patients older than 20 years with significant coronary artery disease and those in stages B–D of the ESC/AHA/ACC guideline[2] were enrolled. The diagnosis of HF was based on the criteria of the Framingham study.[10] Enrollment began in October, 2006, and ended in March, 2010. All information, including medical history, laboratory data, and echocardiography data, were recorded in a computer database at the time of enrollment. Annual follow-up was made by clinical research coordinators by means of review of medical records, surveys and telephone interviews. The present study conformed to the Declaration of Helsinki and was approved by the local ethics committees in the 24 participating hospitals. Written informed consent was given by all patients. Finally, we were able to enroll 10,219 patients in the CHART-2 Study.[4,5]

Study Design

Among the 10,219 patients enrolled, there were 4,463 patients with stage B status. As mentioned later, we used the controlling nutritional status (CONUT) score to evaluate the nutritional status of each patient.[11] Because 1,042 patients (23%) had insufficient information to calculate their CONUT scores, we finally enrolled 3,421 patients with sufficient data. We examined whether nutritional status assessed by CONUT score was associated with the clinical endpoints of all-cause death and first hospitalization for HF.

Definition of Stage B

We defined HF patients at the time of registration in the CHART-2 study according to the ESC/ACC/AHA guideline:[2] stage A is high risk for HF but without structural heart disease or symptoms of HF, stage B is asymptomatic cardiac structural and/or functional disease; stage C has HF symptoms, and stage D is severe HF. Cardiac structural or functional diseases were defined by echocardiographic and clinical findings as follows: enlarged left ventricular end-diastolic dimension (LVDd, ≥55 mm), reduced left ventricular ejection fraction (LVEF, ≤50%), thickened interventricular septum (>12 mm) and/or thickened left ventricular posterior wall (>12 mm), valvular heart disease, wall motion abnormalities, congenital abnor-

Table 2. Baseline Characteristics of Patients by CONUT Score

	All (n=3,421)	CONUT score			P value
		0–1 (n=2,121)	2 (n=693)	≥3 (n=607)	
Age (years)	66.9±12.7	65.8±12.3	68.0±12.5	69.2±12.7	<0.001
Male, n (%)	2,448 (71.6)	1,528 (28.0)	488 (29.6)	432 (28.8)	0.69
Serum albumin (g/ml)	4.2±0.7	4.3±0.7	4.1±0.4	3.7±0.6	–
TC (mg/dl)	185±35	195±30	160±34	160±34	–
Lymphocytes (count/ml)	1,779±865	2,059±923	1,446±483	1,180±469	–
BMI (kg/m^2)	24.1±4.3	24.4±4.5	23.5±3.8	23.4±4.3	<0.001
BMI ≥30	187 (5.5)	138 (6.5)	24 (3.5)	25 (4.1)	0.002
Blood pressure (mmHg)					
Systolic	130±18	131±18	129±18	129±19	0.001
Diastolic	75±12	76±12	74±12	73±12	<0.001
Heart rate (beats/min)	70±13	70±13	69±13	70±14	0.28
Current or past smoker, n (%)	1,638 (47.9)	1,042 (49.1)	321 (46.2)	275 (45.3)	0.33
Medical history, n (%)					
Previous MI	1,059 (31.0)	600 (28.3)	241 (34.8)	218 (35.9)	<0.001
Hypertension	2,653 (77.6)	1,659 (78.2)	511 (77.3)	483 (79.6)	0.02
Dyslipidemia	2,551 (74.6)	1,612 (76.0)	499 (72.0)	440 (72.5)	0.05
Diabetes mellitus	845 (24.7)	507 (23.9)	157 (22.7)	181 (29.8)	0.004
Atrial fibrillation	689 (20.1)	406 (19.1)	155 (22.4)	128 (21.1)	0.4
Stroke	542 (15.8)	309 (14.6)	113 (16.3)	120 (19.8)	0.008
Cancer	405 (11.8)	207 (9.8)	105 (15.2)	93 (15.3)	<0.001
Laboratory measurement					
Hemoglobin (g/dl)	13.6±1.8	14.0±1.6	13.4±2.0	12.5±1.9	<0.001
Anemia, n (%)	403 (11.8)	133 (6.3)	90 (13.0)	180 (29.7)	<0.001
Estimated GFR					
Mean	68±23	69±22	66±20	64±26	<0.001
<60 ml·min^{-1}·1.73 m^{-2}, n (%)	1,112 (32.5)	621 (29.3)	247 (35.6)	244 (40.2)	<0.001
BNP (pg/dl)	102±159	80±110	117±167	160±252	<0.001
Echocardiographic abnormalities, n (%)					
LVDd ≥55 mm	610 (17.8)	353 (16.6)	126 (18.2)	131 (21.6)	0.02
LVEF ≤50%	413 (12.1)	240 (11.3)	87 (12.6)	86 (14.2)	0.15
IVS >12 mm and/or LVPW >12 mm	1,277 (37.3)	820 (38.7)	243 (35.1)	214 (35.3)	0.07
Valvular heart disease	627 (18.3)	380 (17.9)	131 (18.9)	116 (19.1)	0.73
Wall motion abnormalities	933 (27.3)	554 (26.1)	207 (29.9)	172 (28.3)	0.11
History of cardiac surgery	297 (8.7)	165 (7.8)	64 (9.2)	68 (11.2)	0.03
Congenital abnormalities	78 (2.3)	47 (2.2)	15 (2.2)	16 (2.6)	0.81
Current medication, n (%)					
ACEI or ARB	2,191 (64.0)	1,350 (63.6)	445 (64.2)	396 (65.2)	0.77
β-blocker	1,151 (33.6)	693 (32.7)	244 (35.2)	214 (35.3)	0.31
CCB	1,649 (48.2)	1,044 (49.2)	322 (46.5)	283 (46.6)	0.31
Lipid-lowering agent	1,527 (44.6)	919 (43.3)	314 (45.3)	294 (48.4)	0.08

Results are expressed as mean±SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium-channel blocker; IVS, interventricular septum; GFR, glomerular filtration ratio; LVDD, left ventricular (LV) end-diastolic diameter; LVEF, LV ejection fraction; LVPW, LV posterior wall; MI, myocardial infarction. Other abbreviations as in Table 1.

malities, and previous cardiac surgery (eg, coronary artery bypass grafting).[4]

Evaluation of Nutritional Status by CONUT Score

The CONUT score was developed by Ignacio de Ulíbarri et al in 2005 as a screening tool for undernutrition in a hospital population.[11] Three parameters are used to calculate the score: serum albumin level (g/dl), total cholesterol level (mg/dl), and total lymphocyte count (count/ml) (**Table 1**). Thus, the CONUT score enables assessment of protein reserves, caloric depletion, and immune defenses in each patient.[11]

To validate the relationship between the CONUT score and the nutritional risk index (NRI), an established nutrition score,[12] we calculated NRI as:

$$\text{NRI} = [1.519 \times \text{serum albumin (g/dl)}] + [41.7 \times \text{present weight (kg)/ideal body weight (kg)}].^{12}$$

We defined "ideal body weight" as height (m)×height (m)×23.0 [ideal BMI]. BMI of 23.0 was determined from the results of our previous study on the relationship between BMI and chronic HF.[8] We evaluated the CONUT score both as a continuous variable (per 1 point increase) and as a categorical variable as

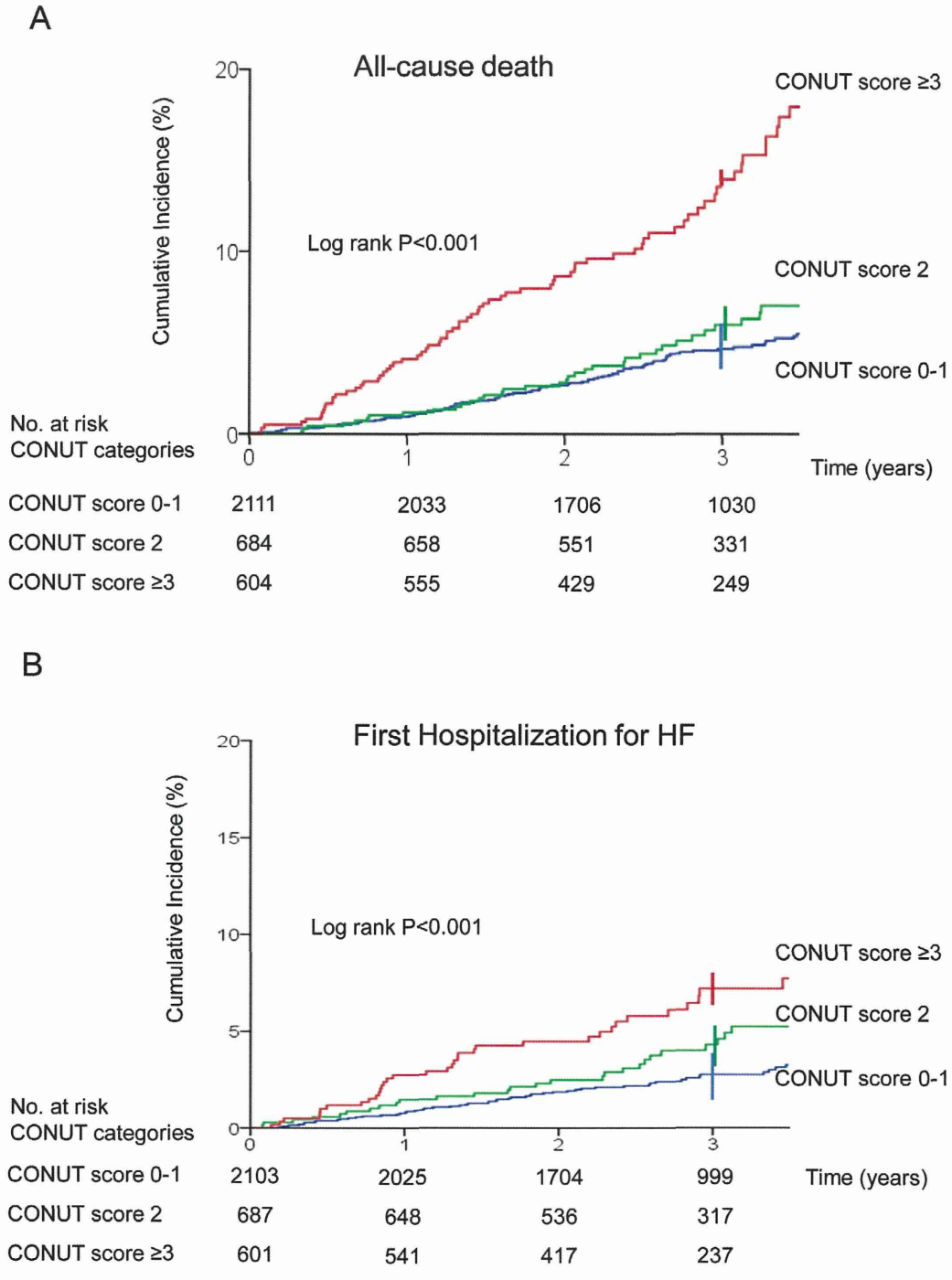

Figure 2. Cumulative incidence curves for (**A**) all-cause death and (**B**) first hospitalization for heart failure (HF) according to category of controlling nutritional status (CONUT) score at baseline. Vertical bars indicate SEs of the incidence estimates at 3 years of follow-up. Data shown are truncated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

performed in a previous study [undernutrition degree: normal, CONUT 0–1 (reference); light, CONUT 2; moderate-severe, CONUT ≥3].[11] For the CONUT score evaluation, we obtained all blood samples from the patients when they had a clinically stable status at enrollment. Clinical status was considered stable when treatment and clinical parameters were unchanged during the previous 3 months.

The endpoints of the present study were all-cause death and the first hospitalization for HF. Cardiovascular death was defined as death attributable to a cardiovascular origin. Noncardiovascular death was defined as death for reasons other than cardiovascular origin (eg, renal, respiratory, cancer, trauma and infection). Unknown death was defined as death for which no specific morbid event classification could be assigned. For

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		
			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
CONUT score as categorical variable					
CONUT score 0–1	105/2,121 (5.0)	17.1	1.00 (reference)		
CONUT score 2	38/693 (5.5)	19.0	1.15	0.79–1.67	0.46
CONUT score ≥3	81/607 (13.3)	46.2	2.98	2.23–3.98	<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
CONUT score as categorical variable					
CONUT score 0–1	62/2,121 (2.9)	10.3	1.00 (reference)		
CONUT score 2	29/693 (4.2)	14.8	1.49	0.96–2.31	0.08
CONUT score ≥3	36/607 (5.9)	20.5	2.22	1.48–3.36	<0.001

	Model 2: age- and sex-adjusted			Model 3: fully adjusted		
	HR	95% CI	P value	HR	95% CI	P value
All-cause death						
CONUT score as continuous variable	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	1.00 (reference)			1.00 (reference)		
CONUT score 2	1.05	0.72–1.52	0.80	1.04	0.69–1.58	0.85
CONUT score ≥3	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	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	1.00 (reference)			1.00 (reference)		
CONUT score 2	1.40	0.90–2.18	0.14	1.13	0.69–1.86	0.62
CONUT score ≥3	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.

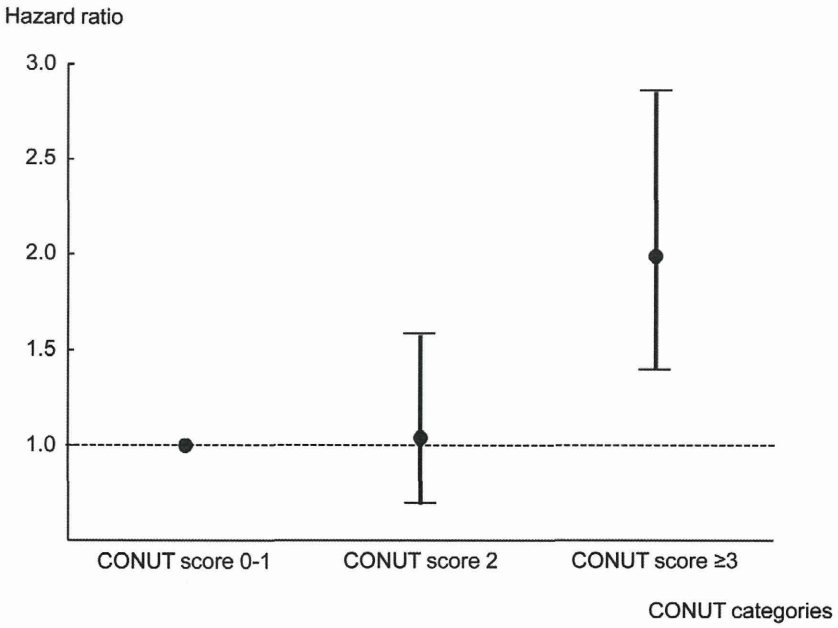

Figure 3. Relationship between the controlling nutritional status (CONUT) category and hazard ratios for the all-cause death in fully adjusted Cox regression analyses. Vertical bars represent 95% confidence intervals.

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 non-cardiovascular origins, and 21 (9.4%) of unknown cause. The CONUT score was significantly associated with HF and non-cardiovascular 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.