Ⅲ．研究成果の刊行に関する一覧表

文献番号	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
①	Miura M, Sakata Y, Nochioka K, Takahashi J, Takada T, Miyata S, Hiramoto T, Inoue K, Tamaki K, Shiba N, Shimokawa H.	Prognostic impact of blood urea nitrogen changes during hospitalization in patients with acute heart failure syndrome.	Circ J	77	1221-1228	2013
②	Nochioka K, Sakata Y, Takahashi J, Miyata S, Miura M, Takada T, Fukumoto Y, Shiba N, Shimokawa H, for the CHART-2 Investigators.	Prognostic Impact of Nutritional Status in Asymptomatic Patients with Cardiac Diseases -A Report from the CHART-2 Study-	Circ J		in press	2013
③	Miura M, Shiba N, Nochioka K, Takada T, Takahashi J, Kohno H, Shimokawa H, on behalf of the CHART-2 Investigators.	Urinary albumin excretion in heart failure with preserved ejection fraction -An interim analysis of the CHART-2 Study-	Eur J Heart Fail.	14	367-376	2012
④	Hao K, Yasuda S, Takii T, Ito Y, Takahashi J, Ito K, Nakayama M, Shiba N, Fukumoto Y, Shimokawa H; MIYAGI-AMI	Urbanization, life style changes and the incidence/in-hospital mortality of acute myocardial infarction in Japan: report from the MIYAGI-AMI Registry Study.	Circ J	76	1136-1144	2012

	Study Investigators.					
⑤	Yoshida M, Kadokami T, Momii H, Hayashi A, Urashi T, Narita S, Kawamura N, Ando S.	Enhancement of Cardiac Performance by Bilevel Positive Airway Pressure Ventilation in Heart Failure.	J Cardiac Fail	18	912-918	2012
⑥	Nishitani M, Shimada K, Sunayama S, Masaki Y, Kume A, Fukao K, Sai E, Yamashita H, Ohmura H, Onishi T, Shioya M, Sato H, Shimada A, Yamamoto T, Amano A, Daida H.	Effect of cardiac rehabilitation on muscle mass, muscle strength, and exercise tolerance in diabetic patients after coronary artery bypass grafting.	J Cardiol.	61	216-221	2013
⑦	Kasai T, Miyauchi K, Yanagisawa N, Kajimoto K, Kubota N, Ogita M, Tsuboi S, Amano A, Daida H.	Mortality risk of triglyceride levels in patients with coronary artery disease.	Heart.	99	22-29	2013
＊：文献番号に○の付いた文献は別刷を添付						

文献番号	著者氏名	タイトル名	書籍全体の編集者名	書籍名	出版社名	出版年	ページ
①	坂田泰彦、後岡広太郎、下川宏明	慢性心不全登録研究（CHART-2 研究）から学ぶ	朝倉正紀(編)	医学のあゆみ	医歯薬出版	2013	1271-1276
②	後岡広太郎、三浦正暢、柴　信行、高田剛史、宮田　敏、高橋　潤、福本義弘、坂田泰彦、下川宏明	CHART-2 研究―日本人の心血管病診療エビデンス構築のための10219例の前向き登録観察研究―	日本内科学会	日本内科学会誌	日本内科学会	2012	1715-1719
③	柴　信行、下川宏明	脳・心・腎連関を断つ降圧薬療法：心不全	伊藤 貞嘉	MEDICINAL	医学出版	2012	44-53
④	後岡広太郎、柴　信行、下川宏明	心不全：疾患の理解編	―	Clinical Study	メヂカルフレンド社	2012	33-40
5	柴　信行、下川宏明	心不全の実態(疫学)を知る	服部隆一（編）	心不全をマスターする－病態を理解して治療できる医師になろう－	文光堂	2013	12-24.
6	青木竜男、下川宏明	東日本大震災と心不全	小室一成、佐地　勉、佐田隆造、赤阪隆史（編）	Annual Review 循環器	中外医学社	2013	88-93
⑦	青木竜男、福本義弘、下川宏明	震災はどのようなストレスをもたらすか	下川宏明	Heart View	メジカルビュー社	2012	8-13.
8	Sakata Y, Shimokawa H	Cardiovascular Events: Ischemic Heart Disease.	Wakabayashi I, Groschner K (eds)	Inter--disciplinary Concepts of Cardiovascular Health.	Springer, Wien, Austria.	2013	in press

9	正木克由規、島田和典、代田浩之	虚血性心疾患の栄養管理 心臓リハビリテーションとは	伊東春樹	臨床栄養 虚血性心疾患の栄養管理	医歯薬出版	2012	38-43
10	代田浩之	動脈硬化性疾患予防ガイドライン改訂 新しい動脈硬化性疾患予防ガイドラインを踏まえた脂質低下療法の実際	石川友章、野津原崇	東京都医師会雑誌	東京都医師会	2012	728-736
11	大村寛敏、代田浩之	動脈硬化性疾患予防ガイドライン 2012 二次予防の層別化	柏木厚典	The Lipid	メディカルレビュー	2013	60-66
＊：文献番号に○の付いた文献は別刷を添付							

Ⅳ. 研究成果の刊行物・別刷

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Prognostic Impact of Blood Urea Nitrogen Changes During Hospitalization in Patients With Acute Heart Failure Syndrome

Masanobu Miura, MD, PhD; Yasuhiko Sakata, MD, PhD; Kotaro Nochioka, MD, PhD; Jun Takahashi, MD, PhD; Tsuyoshi Takada, MD; Satoshi Miyata, PhD; Tetsuya Hiramoto, MD, PhD; Kan-ichi Inoue, MD, PhD; Kenji Tamaki, MD, PhD; Nobuyuki Shiba, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: Elevated blood urea nitrogen (BUN) observed in patients hospitalized for acute heart failure syndrome (AHFS) may represent increased neurohumoral activation. The purpose of this study was to examine the prognostic impact of BUN changes during hospitalization on the long-term prognosis of AHFS patients.

Methods and Results: The Tohoku Acute Heart Failure Registry (n=497) is a multicenter retrospective cohort study enrolling AHFS patients who were admitted in 2007. The 337 survivors (mean age, 76 years; 52% male) were divided into 3 groups according to tertiles of BUN change during hospitalization: Decreased (D-BUN, ΔBUN (BUN level at discharge–BUN level at hospitalization) ≤–1.63 mg/dl, n=112); Unchanged (U-BUN, ΔBUN –1.64 to 5.73 mg/dl, n=113); Increased (I-BUN, ΔBUN >5.73 mg/dl, n=112). The D-BUN group had higher prevalence of lowest glomerular filtration rate during hospitalization, whereas the I-BUN group had higher systolic blood pressure. During a median follow-up period of 2.3 years after discharge, the Kaplan-Meier curve showed that D-BUN and I-BUN had worse prognosis compared with U-BUN. Multivariable logistic model showed that all-cause death was more frequent in I-BUN (hazard ratio, 2.94; 95% confidence interval, 1.51–5.73; P<0.001). Subgroup analysis revealed that BUN increase during hospitalization was associated with all-cause death, regardless of renal function.

Conclusions: AHFS patients with a BUN increase during hospitalization have worse long-term prognosis, independent of renal function. (*Circ J* 2013; **77:** 1221–1228)

Key Words: Acute heart failure syndrome; Blood urea nitrogen; Neurohumoral activation; Renal dysfunction

The activation of neurohumoral factors, including the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAS) and arginine vasopressin (AVP), is considered as the central pathophysiology of heart failure (HF).[1] The elevated SNS and RAS activities in the kidney enhance urea absorption in the proximal tubules and flow-dependent urea absorption in the distal tubules.[1] Furthermore, increased AVP upregulates urea transporters in the inner medullary collecting duct.[1] Thus, an elevated blood urea nitrogen (BUN) level could be regarded as a surrogate marker for neurohumoral activation in HF patients.

Several studies have reported that elevated BUN levels are associated with adverse outcomes in HF patients, especially in those hospitalized because of acute HF syndrome (AHFS).[2–8] Using recursive partitioning of 33,046 AHFS patients with 39 variables, Fonarow et al revealed that the best single predictor for in-hospital death of AHFS patients at admission was high BUN level (≥43 mg/dl), followed by low systolic blood pressure (SBP, <115 mmHg) and high serum creatinine level (≥2.75 mg/dl).[2] In addition, it has been shown that elevated BUN level at admission can predict poor in-hospital and long-term outcomes after the onset of AHFS.[4–8] Accordingly, the BUN level at admission appears to be a useful predictor of survival of AHFS patients.

However, it is unclear whether BUN levels can predict the long-term outcomes of AHFS patients, especially after dis-

Received November 16, 2012; revised manuscript received December 26, 2012; accepted January 7, 2013; released online February 7, 2013 Time for primary review: 18 days

Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai (M.M., Y.S., K.N., J.T., T.T., S.M., H.S.); Division of Cardiology, Osaki Citizen Hospital, Osaki (T.H.); Division of Cardiology, South Miyagi Medical Center, Ogawara (K.I.); Division of Cardiology, Iwate Prefectural Central Hospital, Morioka (K.T.); and Department of Cardiovascular Medicine, International University of Health and Welfare, Nasushiobara (N.S.), Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-1390

charge. In the present study, we thus examined the prognostic implication of BUN level on long-term outcome after discharge in AHFS patients. We particularly focused on the effect of BUN changes during AHFS hospitalization, because evaluation of dynamic changes in the BUN level during hospitalization could be more informative as compared with one-point assessment at admission or discharge.

Methods

The present study was approved by the Ethical Committees of Tohoku University (No. 2009-366) and the other 3 collaborating hospitals. The Ethical Committees judged that informed consent from each patient was not required for the present study.

AHFS Patients and Inclusion Criteria

The Tohoku Acute Heart Failure Registry (n=497) is a multicenter retrospective cohort study, enrolling AHFS patients who were admitted to the 4 participating hospitals. We included consecutive AHFS patients aged ≥20 years who were admitted to the hospitals in 2007. We excluded AHFS patients with acute coronary syndrome, primary pulmonary arterial hypertension or pericardial disease. AHFS was defined as a gradual or rapid change in the signs and symptoms of HF that necessitated urgent hospitalization, diagnosed by experienced cardiologists, based on the criteria of the Framingham Heart Study.[9] Medical records were reviewed by trained clinical research coordinators and the patients' data were collected for the present registry using a pre-fixed registration form. The baseline data included demographic information, medical history, clinical signs and symptoms of HF, and initial treatment at admission. Clinical signs and treatments were surveyed at 24–72 h after hospitalization and at discharge. The primary outcome of the present study was all-cause mortality after discharge. Data acquisition was performed from November 2009 to February 2011. Finally, 497 AHFS patients from the 4 participating hospitals were registered.

In the present analysis, we excluded some patients for the following reasons: hospitalization for myocarditis (n=1) or takotsubo cardiomyopathy (n=3); requiring hemodialysis (n=5); insufficient data (n=58). Furthermore, we excluded the patients who did not receive intravenous diuretics (n=43), because intravenous diuretics strongly influence fluid volume status, which may be associated with BUN change during AHFS hospitalization. Additionally, we excluded patients who died during hospitalization (n=50). In total, 337 AHFS survivors were included in the present study. The outcome of the present study was all-cause death. To evaluate the prognostic impact of BUN changes during hospitalization in AHFS patients, we divided the subjects into 3 groups based on the tertile of BUN change during hospitalization: 112 patients whose BUN levels decreased (ΔBUN ≤–1.63, D-BUN group); 113 whose BUN levels were unchanged (ΔBUN, –1.64 to 5.73, U-BUN group); 112 whose BUN levels increased during hospitalization (ΔBUN >5.73, I-BUN group). ΔBUN was defined as BUN level at discharge–BUN level at admission.

BUN Level

BUN level was measured in each participating hospital on admission, at 24–72 h after hospitalization and at discharge.

Renal Function

Estimated glomerular filtration rate (eGFR, $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was calculated at the time of hospitalization using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient.[10] Worsening renal function (WRF) was defined as an increase in serum creatinine at discharge of >0.3 mg/dl compared with that at admission, based on previous reports.[11–14]

Statistical Analysis

Comparisons among the 3 groups were performed by ANOVA test. Continuous data are described as mean±standard deviation (SD). Kaplan-Meier curves were plotted to evaluate the association between the BUN changes during hospitalization and all-cause death.

We constructed unadjusted (model a) and adjusted (models b and c) logistic regression models to evaluate the association between BUN changes and outcome. In model (b), we included the following covariates at admission that could influence both the outcome and the BUN changes during hospitalization: age, sex, history of HF hospitalization, SBP, heart rate (HR), hemoglobin level, serum sodium (Na), serum potassium (K), eGFR, comorbidities (diabetes mellitus, history of coronary artery disease (CAD), malignant tumor and cerebrovascular disease), left ventricular ejection fraction (LVEF) and use of inotropes. In model (c), we included the following covariates that could influence BUN changes and prognosis during hospitalization: age, sex, diabetes mellitus, histories of CAD, cerebrovascular disease, and malignant tumor, LVEF, changes in SBP (ΔSBP), HR (ΔHR), serum sodium (ΔNa), serum potassium (ΔK), serum creatinine (ΔCre) and hemoglobin (ΔHb), medical treatment (β-blockers, RAS inhibitors, loop diuretics and aldosterone antagonists) and number of days spent fasting after hospitalization.

We also performed multivariable logistic analysis to compare the prognostic effect of one-point BUN or creatinine level at admission or at discharge, and the change in BUN levels during hospitalization (ΔBUN) and WRF. We adjusted the baseline characteristics that included in model (b). Furthermore, we performed the multivariable logistic regression analysis to determine the predictors of BUN increase during hospitalization in the I-BUN group. We included the following covariates at admission that potentially influence BUN increases during hospitalization: age, sex, New York Heart Association class, history of HF hospitalization, clinical scenario (CS) status, HR, eGFR, diabetes mellitus, histories of CAD, malignant tumor and cerebrovascular disease, LVEF and previous treatment (β-blockers, RAS inhibitors, diuretics, and spironolactone). To examine whether renal function influences the prognostic impact of BUN changes during hospitalization, we examined the influence of BUN and creatinine levels at admission and WRF during hospitalization on BUN changes during hospitalization.

Numerical data are expressed as mean±SD. All statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc, Chicago, IL, USA) and statistical significance was defined as a 2-sided P-value <0.05.

Results

Baseline Characteristics of AHFS Patients

Mean age was 76.0±12.0 years and male patients accounted for 51.9%. The prevalence of de novo AHFS and Nohria profile C were 70.6% and 19.6%, respectively. CAD was observed in 27.9% and mean LVEF and eGFR at admission were 45.5±16.2% and 46.2±25.8 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$, respectively. The mean period of hospitalization was 30.4±19.4 days. Carperitide was given to 89% of the study patients after admis-

Table 1. Baseline Characteristics of the Study Patients

Groups	D-BUN	U-BUN	I-BUN	P value
ΔBUN (mg/dl) (median, 95% CI)	−7.8 (−13.8 to −9.5)	1.8 (1.4 to 2.2)	15.5 (13.4 to 17.6)	
n	112	113	112	
Age (years)	76.7±11.9	73.7±13	77.6±10.6	0.04
Male (%)	58	51.3	46.4	0.22
History of HF hospitalization (%)	30.4	24.8	33	0.38
History of malignant tumor (%)	17	13.3	14.3	0.72
Ischemic HF (%)	28.3	28.6	26.8	0.28
Comorbidities (%)				
Hypertension	69.6	70.8	67.9	0.89
Diabetes	43.8	36.3	33	0.24
Atrial fibrillation	50	61.9	50	0.19
Cerebrovascular disease	22.3	18.6	21.4	0.77
Clinical status at admission				
NYHA class III and IV (%)	99.1	93.8	98.3	0.09
Nohria profile C (%)	33.9	12.4	12.5	<0.001
Clinical scenario 1 (%)	52.7	49.6	62.5	0.13
SBP (mmHg)	142.4±36.4	146.2±33.9	153.3±37	0.07
DBP (mmHg)	81.3±26.1	84.3±21.8	86.1±22	0.3
HR (beats/min)	94.2±27.9	101.2±15.8	70.7±13.8	0.17
Clinical variables at admission				
LVEF (%)	45.6±16	45.2±16.5	45.9±16.2	0.96
Hemoglobin (g/dl)	11.6±2.5	12.4±2.2	11.4±2.2	0.006
BUN (mg/dl)	34.8±17.4	21.1±10.6	24.4±12.9	<0.001
Serum Cre (mg/dl)	1.4±0.9	1±0.6	1.2±0.8	0.001
Serum sodium (mEq/L)	139.5±4.4	141±3.9	140.8±4	0.02
Serum potassium (mEq/L)	4.4±0.4	4.2±0.5	4.1±0.7	<0.001
eGFR ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	38.8±18.9	53.6±27.1	46.3±28.4	<0.001
BNP (pg/ml)	1,360±1,662	939±709	1,177±1,167	0.06
Treatment at admission (%)				
Diuretics	58	50.4	54.5	0.52
Carperitide	88	90.9	90.8	0.81
Nitrates	18.8	17.7	17.9	0.98
Dopamine	8.9	8	1.8	0.06
Dobutamine	14.3	8	3.6	0.02
PDE III inhibitor	10.7	5.3	12.5	0.16
Calcium-channel blocker	9.8	9.7	9.8	1
Fasting period (days)	1.9±1.9	1.4±0.7	1.6±0.9	0.02
Length of hospital stay (days)	32.5±20.3	29±20.6	29.6±17.5	0.36

Numerical data are expressed as mean±SD.
D, decreased; BUN, blood urea nitrogen; U, unchanged; I, increased; CI, confidence interval; HF, heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; Cre, creatinine; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; PDE, phosphodiesterase.

sion. Furthermore, intravenous furosemide and intensive respiratory management were given to 54.3% and 10.1% of the study patients, respectively.

The mean BUN levels (mg/dl) at admission and discharge were 26.7±15.1 and 28.6±16.2, respectively. We divided the study subjects into 3 groups based on the tertile of the ΔBUN values as mentioned earlier (**Table 1**). The BUN levels at 24–72h after admission was not significantly increased as compared with those at admission in all groups (**Figure 1A**). The U-BUN group was characterized by younger age and had the highest eGFR and lowest brain natriuretic peptide (BNP) level. The D-BUN group was characterized by higher prevalence of Nohria profile C, the highest BNP level and the lowest eGFR at admission. Furthermore, patients in the D-BUN group were more frequently treated with inotropes (dopamine or dobutamine) at admission. In contrast, the I-BUN group was characterized by older age and had higher SBP at admission and lower hemoglobin level. The fasting period was longer in the I-BUN group than in the U-BUN group (**Table 1**).

Changes in Clinical Variables During Hospitalization

The changes in BUN level and other clinical variables during hospitalization in each group are shown in **Table 2** and **Figure 1**. The mean interval of BUN measurements was 25.7±23.6 days and was comparable among the 3 groups (21.9±18.8, 27.4±19.8 and 27.8±30.4 days in the U-BUN, D-BUN and

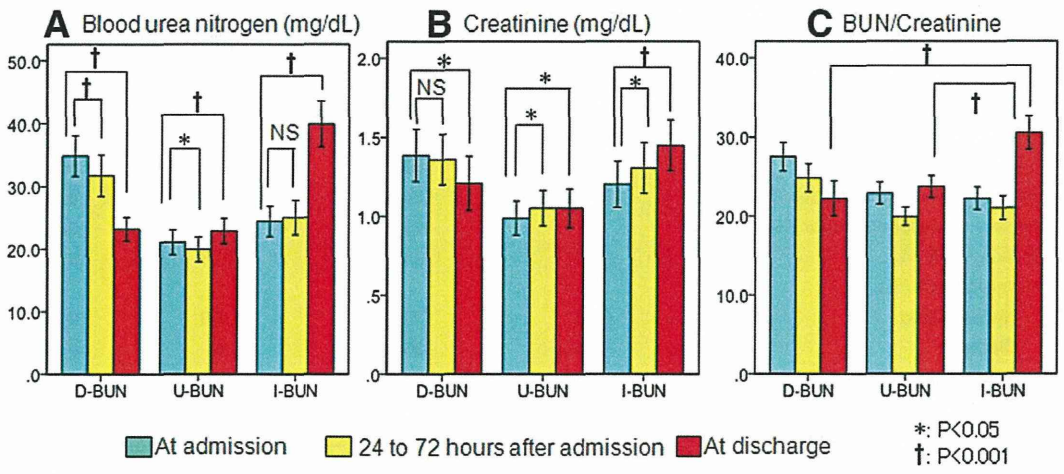

Figure 1. (**A**) Changes in BUN levels during hospitalization for AHFS. (**B**) Changes in creatinine level during hospitalization. (**C**) Changes in BUN/creatinine ratio during hospitalization. AHFS, acute heart failure syndrome; BUN, blood urea nitrogen.

Table 2. Changes in Clinical Variables During Hospitalization and Medications at Discharge

	D-BUN (n=112)	U-BUN (n=113)	I-BUN (n=112)	P value
Changes in clinical variables during hospitalization				
Interval of measurement (days)	27.4±19.7	21.9±18.8	27.8±30.3	0.11
ΔSBP (mmHg)	−26±31.7	−32.7±29.8	−36.8±31.9	0.04
ΔHR (beats/min)	−24.9±28.7	−32.5±31.6	−29.6±27.5	0.16
ΔBUN (mg/dl)	−11.7±11.5	1.8±2	15.5±11.3	<0.001
25% increase in BUN (%)	0	13.3	94.6	<0.001
ΔCre (mg/dl)	−0.2±0.7	0.1±0.2	0.3±0.4	<0.001
0.3 mg/dl increase in Cre (%)	5.4	9.7	32.1	<0.001
ΔSerum sodium (mEq/L)	0.7±5.1	−0.6±4.2	−1.2±4.9	0.01
ΔSerum potassium (mEq/L)	−0.1±0.8	0.3±0.6	0.4±0.8	<0.001
ΔHemoglobin (g/dl)	0±1.6	0±1.5	−0.3±1.5	0.27
Oral medications at admission				
Diuretics (%)	58	47.8	50	0.27
Spironolactone (%)	22.3	14.2	21.4	0.23
ACEIs (%)	24.1	22.1	29.5	0.42
ARBs (%)	25.9	25.7	26.8	0.98
β-blockers (%)	21.4	31.9	20.5	0.09
Oral medications at discharge				
Diuretics (%)	85.7	82.3	90.2	0.23
Furosemide dose (mg/day)	35.2±21.1	32.5±17.0	33.7±17.6	0.68
Spironolactone (%)	39.3	40.7	51.8	0.12
ACEIs (%)	50.9	61.1	58.9	0.27
ARBs (%)	31.3	22.1	32.1	0.18
β-blockers (%)	50.9	62.8	50.9	0.12

Numerical data are expressed as mean ± SD.
ΔSBP, SBP at discharge–SBP at hospitalization; ΔHR, HR at discharge–HR at hospitalization; ΔBUN, BUN at discharge–BUN at hospitalization; ΔCre, Cre at hospitalization–Cre at discharge; Δserum sodium (Na), Na at discharge–Na at hospitalization; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations as in Table 1.

I-BUN groups, respectively, P=0.11, Figure 1A). In the I-BUN group, ≥25% increase in BUN level was noted in 94.6% and WRF in 32.1% of the patients (Figure 1B). Furthermore, the I-BUN group had the largest BUN/creatinine ratio at discharge among the 3 groups (Figure 1C). In the U-BUN group, ≥25% increase in BUN was noted only in 13.3% and the prevalence of WRF was lower than in the I-BUN group. In the I-BUN group, the changes in SBP, serum Na level and serum K level were the largest among the 3 groups.

Medications at Discharge

Among the 3 groups, there was no significant difference in medications at either admission or discharge, although the I-BUN group tended to have more diuretics and spironolactone and the U-BUN group more angiotensin-converting enzyme inhibitors and β-blockers (Table 2). There was no difference in the furosemide dose at discharge among the 3 groups.

Prognostic Impact of BUN Changes During Hospitalization of AHFS Patients

During the median follow-up period of 2.3 years after discharge, 120 patients (35.6%) died. Figure 2 shows the Kaplan-Meier survival curves for all-cause death. The D-BUN and I-BUN groups had worse prognosis compared with the U-BUN group. Furthermore, 3-year mortality rate of the I-BUN group was approximately 150% higher compared with the D-BUN group.

Table 3 shows the results of multivariable logistic regression models for all-cause death. In the unadjusted model (a), as compared with the U-BUN group (reference), both the D-BUN and I-BUN groups showed 181% and 277% increase, respectively, in the risk for all-cause death (P=0.049 and P<0.001, respectively). In model (b), as compared with the U-BUN group (reference), the hazard ratio (95% confidence interval [CI]) for all-cause death of the D-BUN and I-BUN groups was 1.09 (0.54–2.21) and 2.94 (1.51–5.73), respectively. In model (c), the hazard ratio (95% CI) for all-cause death in groups D-BUN and I-BUN was 0.93 (0.43–2.01) and 4.27 (2.14–8.52), respectively, as compared with the U-BUN group (reference). Furthermore, the I-BUN group also had significantly higher hazard ratios for all-cause death as compared with the D-BUN group in both model (b) and (c) (hazard ratio 2.78, 95% CI 1.36–5.68, P=0.002; hazard ratio 4.19, 1.77–9.91, P=0.001, respectively).

Figure 3A shows the results of multivariable logistic models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge, and BUN increase and WRF during hospitalization for all-cause death. BUN increase during hospitalization had the highest heart rate for all-cause death compared with BUN and creatinine levels both at admission and at discharge. Figure 3B shows that BUN increase was significantly associated with

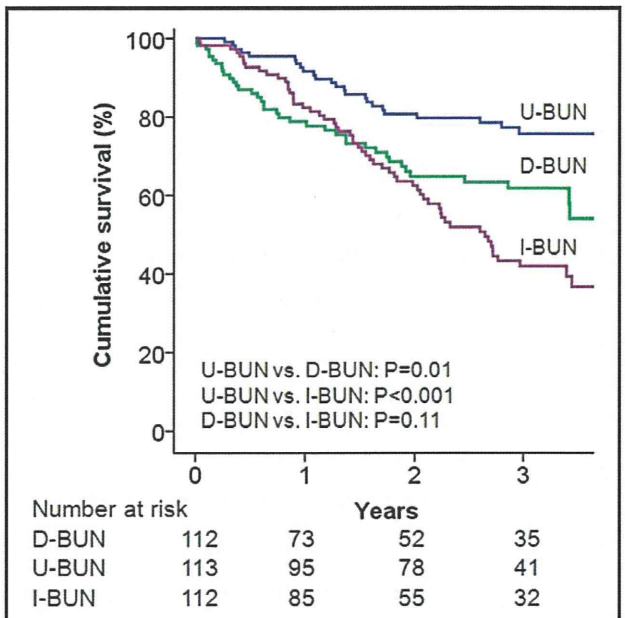

Figure 2. Kaplan-Meier survival curves for all-cause death.

all-cause death, regardless of serum BUN or creatinine level at admission. Furthermore, the prognostic impact of BUN increase during hospitalization for all-cause death was insignificant in AHFS patients with WRF, whereas it was significant in those without WRF.

Predictors of BUN Increase During Hospitalization

In the I-BUN group, the prevalence of patients with ≥25% increase in BUN level during hospitalization was 94.6%. Among the covariates, only SBP at admission was associated with the increase in BUN level during hospitalization (Table 4). The analysis also showed that CS1 (SBP >140 mmHg) was associated with 81% increase in the prevalence of the BUN increase compared with CS >1 (hazard ratio 1.81, 95% CI 1.05–3.12, P=0.03). Importantly, β-blocker use before hospi-

Table 3. Logistic Regression Models for All-Cause Death

Hazard ratio categories	All-cause death	U-BUN (reference)	D-BUN	I-BUN
No. of events (%)		25 (22.1)	38 (33.9)	57 (50.9)
No. of events/100 person-year		11.7	14.1	25.2
Unadjusted				
Hazard ratio		1.00	1.81	2.77
95% CI			1.00–3.27	1.73–4.44
P value	<0.001		0.049	<0.001
Baseline adjusted				
Hazard ratio		1.00	1.09	2.94
95% CI			0.54–2.21	1.51–5.73
P value	<0.001		0.81	0.002
Adjusted by the covariates including the change in clinical status				
Hazard ratio		1.00	0.93	4.26
95% CI			0.43–2.01	2.14–8.52
P value	<0.001		0.76	<0.001

See text for explanations of hazard ratio categories. Abbreviations as in Table 1.

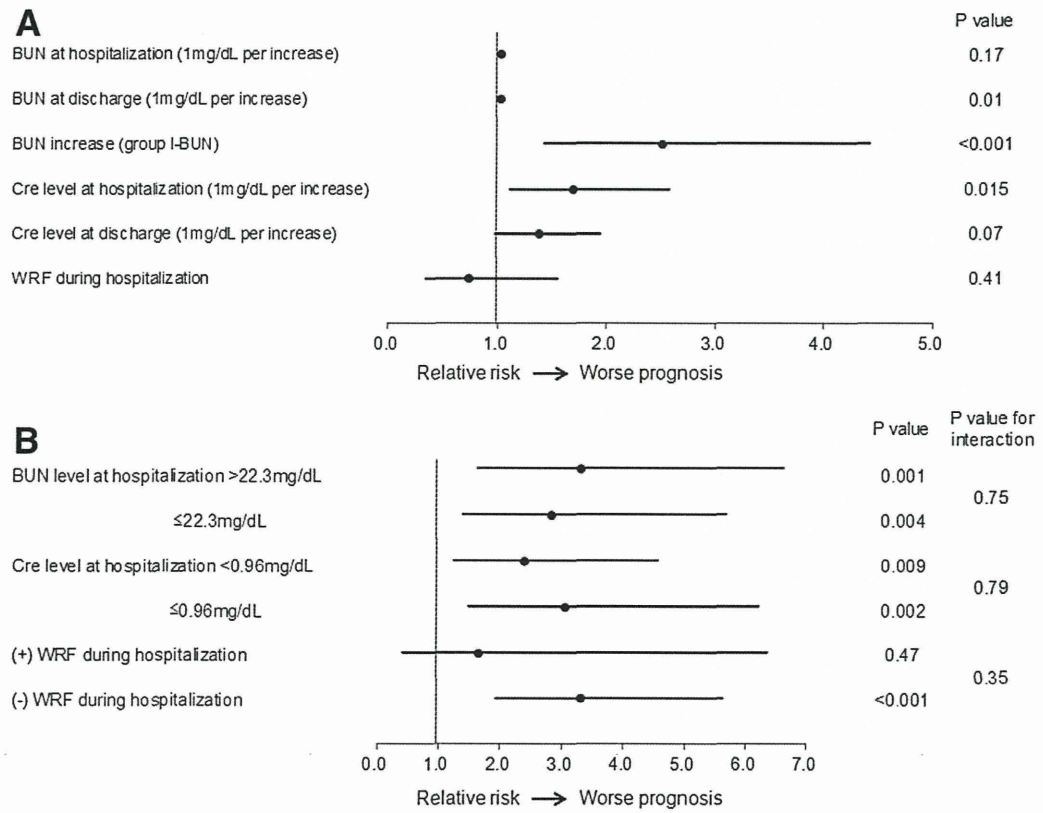

Figure 3. Multivariable logistic analysis. (**A**) Models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge and BUN increase and WRF during hospitalization for all-cause death. (**B**) Subgroup analysis of prognostic value of BUN increase according to serum BUN and creatinine levels at admission and WRF during hospitalization. BUN, blood urea nitrogen; WRF, worsening renal function.

Table 4. Predictors of BUN Increase During Hospitalization for AHFS

	Hazard ratio	95% CI	P value
Male (vs. female)	1.23	0.66–2.02	0.61
Age (per 1-year older)	1.01	0.99–1.04	0.34
Ischemic HF	1.02	0.56–1.86	0.96
Past history			
HF hospitalization	0.77	0.42–1.39	0.96
Diabetes	0.87	0.51–1.5	0.62
Malignant tumor	0.74	0.36–1.52	0.41
Cerebrovascular disease	0.87	0.45–1.67	0.67
Previous medications			
ACEIs	1.68	0.89–3.18	0.11
ARBs	0.85	0.45–1.6	0.62
Diuretics	1.19	0.66–2.15	0.56
β-blockers	0.51	0.26–0.99	0.047
Clinical condition at admission			
CS 1 (vs. CS 2 & 3)	1.81	1.05–3.12	0.03
HR (per 1 beat/min increase)	1	0.99–1.01	1
NYHA class III and IV (vs. class II)	1.81	0.19–16.9	0.6
SpO2 (per 1% decrease)	1.01	0.96–1.06	0.79
Hemoglobin (per 1 g/dl increase)	0.92	0.8–1.05	0.21
LVEF (per 1% increase)	1	0.98–1.01	0.56
eGFR (per 1 mml·min^{-1}·1.73 m^{-2} increase)	0.99	0.7–1.42	0.97

AHFS, acute heart failure syndrome. Other abbreviations as in Tables 1,3.

talization was associated with 49% decrease in the incidence of the BUN increase during hospitalization (hazard ratio 0.51, 95% CI 0.26–0.99, P=0.047) (**Table 4**).

Discussion

The novel findings of the present study were that AHFS patients with increased BUN levels during hospitalization had worse long-term prognosis after discharge, regardless of renal function, and that the BUN increase during hospitalization was a strong predictor of the long-term prognosis of post-AHFS patients. Thus, the present study suggests that more attention should be paid to BUN changes during hospitalization for risk stratification of post-AHFS patients, regardless of creatinine-based measures of renal function.

Prognostic Importance of BUN Increase During AHFS Hospitalization

Elevated BUN level at admission is well known to be associated with increased in-hospital mortality and adverse outcomes after discharge.[2,4–8] However, the BUN level during hospitalization for AHFS often fluctuates dynamically because it is widely influenced not only by neurohumoral factors but also by several biological parameters, including fluid volume balance, nutritional status, and hemodynamics.[15] Therefore, it is clinically important to evaluate BUN changes during hospitalization to predict the prognosis of AHFS patients. In the present study, we found that the patients with increased BUN levels during hospitalization (I-BUN group) had the worse prognosis compared with those with unchanged BUN levels (U-BUN group) or decreased BUN levels (D-BUN group). Singh et al reported that BUN level at admission was more important than subsequent in-hospital fluctuations of BUN in terms of predicting short-term and long-term risk.[16] However, the length of the hospital stay in their study was shorter than in ours (5.3±6.4 vs. 30.4±19.4 days), which could explain the discrepancy in the results of the 2 studies.

We did not have enough data to examine the association between BUN increase and neurohumoral factors (eg, RAS activities). However, it has been reported that a higher BUN level is associated with a greater degree of elevation of neurohumoral activation.[17] Therefore, in the present study a BUN increase during AHFS hospitalization may have reflected activated neurohumoral systems.

Our results also demonstrated that the prognosis of the D-BUN group was relatively better than that of the I-BUN group, although the D-BUN group had worse clinical profiles characterized by higher prevalence of Nohria profile C, use of inotropes and lower eGFR at admission. Thus, it is suggested that even if AHFS patients have elevated BUN levels and a more severe clinical status at admission, their long-term prognosis could be improved if their BUN levels are decreased during hospitalization with intensive medical treatment.

WRF and BUN Increase During Hospitalization

It has been reported that WRF is a complication in approximately one-third of AHFS patients and is associated with poor prognosis.[11–14,18] In the present study, the I-BUN group had a higher prevalence of WRF, suggesting a close association between WRF and BUN increase during hospitalization. However, it is noteworthy that the effect of BUN increase during hospitalization (ie, I-BUN group) was associated with the worst long-term survival, regardless of the presence or absence of WRF. Indeed, the present study showed that an increase in BUN level had a higher hazard ratio in patients without WRF than in those with WRF (**Figure 3B**). Thus, evaluation of BUN increase during hospitalization, regardless of WRF, could be important for appropriate risk stratification of AHFS patients.

Predictors for BUN Increase During AHFS Hospitalization

The present results showed that higher SBP at admission was significantly associated with BUN increase during hospitalization. In previous reports, higher SBP at admission was found to be a risk factor for WRF,[14] but AHFS patients with higher SBP, who were often classified as CS1, have significantly decreased mortality compared with those with normal or lower SBP.[19] Thus, caution should be paid to AHFS patients with higher SBP at admission, because they are likely to develop BUN increase during subsequent hospitalization, which may increase the risk of death after discharge. In the present study, SBP at 24–72h after admission was almost same level among the 3 groups. However, the change in SBP during the 24–72h after admission was –43.9±35.8 vs. –29.4±31.2mmHg in the patients with WRF and those without WRF, respectively (P=0.03). Considering that early SBP drop may cause WRF in AHFS patients,[20] reduction in SBP should be achieved carefully in AHFS patients with higher SBP in order to prevent WRF and BUN increase during hospitalization.

AHFS Treatment to Prevent BUN Increase

In the present study, β-blockers use before admission was inversely associated with BUN increase during hospitalization (eg, 49% decrease in the I-BUN group). However, de novo AHFS accounted for approximately 70% of AHFS patients and only 24.6% patients had been treated with β-blocker(s) before admission. Considering the renal protective effects of β-blockers[21] their use before hospitalization for AHFS may be important to prevent BUN increase during hospitalization. Indeed, the ACC/AHA Guidelines recommend that β-blocker therapy should be started at the earlier stage of cardiovascular disease.[22] Thus, the present results may support the notion that β-blocker initiation at the earlier stage of HF could reduce the incidence of BUN increase through inhibition of SNS and RAS activation.

Study Limitations

Several limitations should be mentioned. First, this study was a retrospective observational study in Japan, so caution is needed when interpreting the present results in comparison with other cohorts. For example, the median hospital stay for AHFS in the present study (24.0 days) was much longer than in Western countries.[23,24] However, the present study suggests the importance of re-evaluating the BUN level, at a 1-month interval, for risk stratification of the patients. Second, the BUN measurement was not performed at a central laboratory. Third, the lack of assessment of pulmonary congestion or volume overload during hospitalization was a major limitation. Fourth, we did not have enough data on nutrition status (eg, serum albumin and body mass index), which may affect the BUN changes during hospitalization. However, we performed logistic analysis adjusted for fasting period, which may influence nutritional status, and found no influence of fasting. Finally, we excluded the patients who died during hospitalization, which might have influenced the present results.

Conclusions

AHFS patients with increased BUN levels during hospitalization have worse long-term prognosis after discharge, regard-

less of creatinine-based measures of renal function. Although it has been established that a higher BUN level at admission is associated with poor in-hospital prognosis, the present study provides further insights into the importance of BUN changes during hospitalization for risk stratification of AHFS patients.

Acknowledgments

We thank all the members of the Tohoku Heart Failure Society and staff of the Department of Evidence-based Cardiovascular Medicine for their kind contributions. This study was supported by a Research Grant from Pfizer Health Research Foundation (N.S.), Grants-in-Aid from a Research Grant from the Ministry of Health, Labour, and Welfare (H.S. and N.S.), and a Research Grant from the Ministry of Education, Culture, Sports, Science, and Technology (H.S. and N.S.), Japan.

Disclosures

Conflict of Interest: None.

References

1. Kazory A. Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure. *Am J Cardiol* 2010; **106:** 694–700.
2. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. *JAMA* 2005; **293:** 572–580.
3. Chen CY, Yoshida A, Asakura M, Hasegawa T, Takahama H, Amaki M, et al. Serum blood urea nitrogen and plasma brain natriuretic peptide and low diastolic blood pressure predict cardiovascular morbidity and mortality following discharge in acute decompensated heart failure patients. *Circ J* 2012; **76:** 2372–2379.
4. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004; **116:** 466–473.
5. Smith GL, Shlipak MG, Havranek EP, Foody JM, Masoudi FA, Rathore SS, et al. Serum urea nitrogen, creatinine, and estimators of renal function: Mortality in older patients with cardiovascular disease. *Arch Intern Med* 2006; **166:** 1134–1142.
6. Kinugasa Y, Kato M, Sugihara S, Hirai M, Kotani K, Ishida K, et al. A simple risk score to predict in-hospital death of elderly patients with acute decompensated heart failure: Hypoalbuminemia as an additional prognostic factor. *Circ J* 2009; **73:** 2276–2281.
7. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, et al. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: Insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail* 2007; **13:** 360–364.
8. Klein L, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF Jr, et al; OPTIME-CHF Investigators. Hospitalization or changes in renal function during hospitalization for worsening heart failure predict post discharge survival: Results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail* 2008; **1:** 25–33.
9. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446.
10. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11:** 41–50.
11. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol* 2000; **85:** 1110–1113.
12. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at hospitalization, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **43:** 61–67.
13. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B; POSH Investigators. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: Results of the prospective outcomes study in heart failure (POSH). *Eur Heart J* 2006; **27:** 1216–1222.
14. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. *J Card Fail* 2010; **16:** 541–547.
15. Gotsman I, Zwas D, Planer D, Admon D, Lotan C, Keren A. The significance of serum urea and renal function in patients with heart failure. *Medicine* (*Baltimore*) 2010; **89:** 197–203.
16. Singh G, Peterson EL, Wells K, Williams LK, Lanfear DE. Comparison of renal predictors for in-hospital and postdischarge mortality after hospitalized heart failure. *J Cardiovasc Med* 2012; **13:** 246–253.
17. Schrier RW. Blood urea nitrogen and serum creatinine: Not married in heart failure. *Circ Heart Fail* 2008; **1:** 2–5.
18. Shirakabe A, Hata N, Kobayashi N, Shinada T, Tomita K, Tsurumi M, et al. Prognostic impact of acute kidney injury in patients with acute decompensated heart failure. *Circ J* 2013; **77:** 687–696.
19. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at hospitalization, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006; **296:** 2217–2226.
20. Voors AA, Davison BA, Felker GM, Ponikowski P, Unemori E, Cotter G, et al; Pre-RELAX-AHF study group. Early drop in systolic blood pressure and worsening renal function in acute heart failure: Renal results of Pre-RELAX-AHF. *Eur J Heart Fail* 2011; **13:** 961–967.
21. Ito H, Nagatomo Y, Kohno T, Anzai T, Meguro T, Ogawa S, et al. Differential effects of carvedilol and metoprolol on renal function in patients with heart failure. *Circ J* 2010; **74:** 1578–1583.
22. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the ACC/AHA Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; **53:** e1–e90.
23. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149:** 209–216.
24. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur Heart J* 2006; **27:** 2725–2736.

Prognostic Impact of Nutritional Status in Asymptomatic Patients with Cardiac Diseases -A Report from the CHART-2 Study-

Kotaro Nochioka, MD. PhD.;[*] Yasuhiko Sakata, MD. PhD.;[*] Jun Takahashi, MD. PhD.;[*]
Satoshi Miyata, PhD.;[*] Masanobu Miura, MD. PhD.;[*] Tsuyoshi Takada, MD.;[*]
Yoshihiro Fukumoto, MD. PhD.;[*] Nobuyuki Shiba, MD, PhD.;[**]
Hiroaki Shimokawa, MD. PhD.;[*] For the CHART-2 Investigators'

[*]Department of Cardiovascular Medicine and Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine and [**] Department of Cardiovascular Medicine, International University of Health and Welfare.

Total word count: 4,147 words with 3 figures, 5 tables, 1 supplemantal figure, and 2 supplemental tables.

Short title: Nutritional Status and Prognosis in Stage B Patients

Address for correspondence:

Yasuhiko Sakata, MD, PhD.
Department of Evidence-based Cardiovascular Medicine
Tohoku University Graduate School of Medicine
1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
TEL: +81-22-717-7153
FAX: +81-22-717-7156
E-mail: sakatayk@cardio.med.tohoku.ac.jp

Abstract

Background: 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 levels, total cholesterol and lymphocyte number, in 3,421 stage B patients from our 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 due to cardiovascular (45%, n=102) and noncardiovascular (55%, n=123) origins 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 (HR) 1.27 per point increase; 95% CI, 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 (P=0.049), but not in those with <70 years.

Conclusions: In stage B patients, poor nutritional status was associated with increased incidence of death for overall population and that of HF hospitalization for elderly population.

(220/220 words)

Keywords; nutrition, epidemiology, heart failure, risk factors

Introduction

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 guidelines classify 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 the prevalence of stage B was highest among stages A to D patients and that 34.1% of individuals older than 45 years is classified as stage B in the US.[3] Thus, the management of stage B HF is quite important in the real world practice. Also in Japan, we have recently reported that the number of patients with stage B was almost comparable with that of stage C/D in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2), a prospective multicenter observational study for HF, where 10,219 patients were enrolled in the Tohoku district (www.clinicaltrials.gov. Identifier: NCT00418041).[4, 5] Therefore, risk stratification and management of stage B patients are warranted in the clinical settings. The progression of HF syndrome involves extra-cardiac disorders including metabolic disorder and inflammation.[6,7] Undernutrition, which could be 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 patients with asymptomatic stage B patients. In the present study, we thus tested our hypothesis that assessment of nutritional status is useful in the risk stratification for future mortality and morbidity in 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 multi-center, prospective observational study, where consecutive patients older than 20 years with significant coronary artery disease and those in the stages B to D of the ESC/AHA/ACC guidelines[2] were enrolled. The diagnosis of HF was based on the criteria of the Framingham study.[10] The enrollment was started in October, 2006, and was 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 was conformed to the Declaration of Helsinki and approved by the local ethics committee in the 24 participating hospitals. A written informed consent was obtained from 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 of stage B status. As mentioned below, we employed the controlling nutritional status (CONUT) score for evaluation of nutritional status of each patient.[11] Since 1,042 patients (23 %) had insufficient information to calculate CONUT score, we finally enrolled 3,421 patients with sufficient data. We examined whether nutritional status assessed with the CONUT score is associated with clinical endpoints of all-cause death and first hospitalization.

Definition of Stage B Patients

We defined HF patients at the time of registration in the CHART-2 study, according to the ESC/ACC/AHA guidelines classification;[2] stage A is at high risk for HF but without structural heart disease or symptom of HF, stage B with asymptomatic cardiac structural and/or functional diseases, stage C with HF symptoms, and stage D with 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 (IVS, >12 mm) and/or thickened left ventricular posterior wall (LVPW, >12 mm), valvular heart diseases, wall-motion abnormalities, congenital abnormalities, and previous cardiac surgery (e.g. coronary artery bypass grafting).[4]

Evaluation of Nutritional Status with the CONUT Score

The CONUT score has been developed by Ignacio et al. in 2005 as a screening tool for detection of undernutrition in a hospital population.[11] Three parameters are used for calculating the score, including serum albumin levels (g/dl), total cholesterol levels (mg/dl), and total lymphocyte count (counts/ml) (**Table 1**). Thus, the CONUT score allows the assessment of protein reserves, caloric depletion, and immune defenses in each patient.[11] To validate the relationship between CONUT score and another nutritional index,we the relationship between CONUT score and the nutritional risk index (NRI), an established nutrition score.[12] We have calculated NRI by the following formula;
NRI = [1.519 × serum albumin (g/dL)] + [41.7 × present weight (kg)/ideal body weight (kg)].[12] We defined "ideal body weight" as height (m) ×height (m) ×23.0 (ideal BMI). BMI level of 23.0 was determined by the results from our previous study on the relationship

between BMI and chronic HF.[8] We evaluated the CONUT score both as a continuous variable (per one point increase) and as a categorical variable as performed in a previous study [undernutrition degree; normal, CONUT 0-1 (reference); light, CONUT 2; and moderate to severe, CONUT ≥3].[11] For the CONUT score evaluation, we obtained all blood samples from the patients with clinically stable status at the enrollment. Clinical status was considered as stable when the treatment and clinical parameters were not changed during the last three months.

The endpoints of the present study were all-cause death and the first hospitalization for HF. Cardiovascular death was defined as death that was attributed to cardiovascular origins. Non-cardiovascular death was defined as death due to reasons other than cardiovascular origins (e.g. renal, respiratory, cancer, trauma and infection). Unknown death was defined as death for which no specific morbid event classification could be assigned. For 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 summary provided by the investigators.

Statistical Analysis

All continuous variables are shown as mean ± standard deviation (SD). Comparisons of data among the 3 groups were performed by ANOVA test in continuous variables and by chi-square test or Fisher's exact test in 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