III. 研究成果の刊行に関する一覧表

1) 書籍

研究者	著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
柴信行	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	文光堂	東京	2013	12～24
下川宏明	Yasuda S, Shimokawa H	The pathogenesis of vasospastic angina.	Kaski JC	Chest Pain with Normal Coronary Arteries	Springer-Verlag	London	2013	in press
	Sakata Y, Shimokawa H	Cardiovascular events: Ischemic heart disease	Wakabayashi I	Interdisciplinary Concepts of Cardiovascular Health	Springer	Wien	2013	in press
福本義弘	太田有香，奥山節子，福本義弘	慢性心不全の薬物療法 TOPICS肺高血圧症患者の治療とケア	眞茅みゆき，池亀俊美，加藤尚子	心不全ケア教本	メディカルサイエンスインターナショナル	日本	2012	171-175
	福本義弘、下川宏明	VTEの病態	中村真潮、山下武志	循環器内科医のためのXa阻害薬のすべて		日本	2012	43-50

2)雑誌

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
柴 信行	Sakata Y, Nochioka K, Miura M, Takada T, Tadaki S, Miyata S, Shiba N, Shimokawa H	Supplemental benefit of angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial: rationale and design.	J Cardiol.		in press	2013
	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.		in press	2013
	宮下光令, 柴 信行, 下川宏明	末期心不全の緩和ケアを考える	Heart	2	501-511	2012
	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―	日本内科学会雑誌	101	1715-1719	2012
下川宏明	Eba S, Hoshikawa Y, Moriguchi T, Mitsuishi Y, Satoh H, Ishida K, Watanabe T, Shimizu T, Shimokawa H, Okada Y, Yamamoto M, Kondo T.	The Nrf2 activator oltipraz attenuates chronic hypoxia-induced cardiopulmonary alterations in mice.	AJRCCM		in press	2013
	Sakata Y, Nochioka K, Miura M, Takada T, Tadaki S, Miyata S, Shiba N, Shimokawa H, for the SUPPORT Trial Investigators	Supplemental benefit of angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial: rationale and design.	J Cardiol.		in press	2013
	Obukuro K, Nobunaga M, Takigawa M, Morioka H, Hisatsune A, Isohama Y, Shimokawa H, Tsutsui M, Hiroshi Katsuki H.	Nitric oxide mediates selective degeneration of hypothalamic orexin neurons through dysfunction of protein disulfide isomerase.	J Neurosci.		in press	2013

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
下川宏明	Satoh K, Fukumoto Y, Sugimura K, Miura Y, Aoki T, Nochioka K, Tatebe S, Miyamichi-Yamamoto S, Shimizu T, Osaki S, Takagi Y, Tsuburaya R, Ito Y, Matsumoto Y, Nakayama M, Takeda M, Takahashi J, Ito K, Yasuda S, Shimokawa H.	Plasma cyclophilin A is a novel biomarker for coronary artery disease.	Curc J	77	447-455	2013
	Suzuki H, Sumiyoshi A, Kawashima R, Shimokawa H.	Diffrenet brain activation under left and right ventricular stimulation: An fMRI study in anesthetized rats.	PLOS ONE		in press	2013
	Aoki T, Takahashi J, Fukumoto Y, Yasuda S, Ito K, Miyata S, Shinozaki T, Inoue K, Yagi T, Komaru T, Katahira Y, Obata A, Hiramoto T, Sukegawa H, Ogata K, Shimokawa H	Effect of the Great East Japan Earthquake Disaster on cardiovascular diseases -A report from the 10 hospitals in the Disaster area-	Circ J	77	490-493	2013
	Tatebe S, Fukumoto Y, Sugimura K, Miura Y, Nochioka K, Aoki T, Miura M, Yamamoto S, Yaoita N, Satoh K, Shimokawa H.	Optical coherence tomography is superior to intravascular ultrasound for diagnosis of distal-type chronic thromboembolic pulmonary hypertension.	Circ J	77	1081-1083	2013
	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		in press	2013
	Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H.	Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications and prognostic impact -Multicenter registry study of the Japanese Coronary Spasm Association-	Eur Heart J.	34	258-267	2013

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
下川宏明	Kawana A, Takahashi J, Takagi Y, Yasuda S, Sakata Y, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Kubo N, Momomura S, Ogawa H, Shimokawa H.	Gender differences in clinical characteristics and outcomes of patients with vasospastic angina -A report from the Japanese Coronary Spasm Association-	Circ J.		in press	2012
	Nihei T, Takahashi J, Kikuchi Y, Takagi Y, Hao K, Tsuburaya R, Shiroto T, Ito Y, Matsumoto Y, Nakayama M, Ito K, Yasuda S, Shimokawa H.	Enhanced Rho-kinase activity in patients with vasospastic angina after the Great East Japan Earthquake	Circ J	76	2892-2894	2012
	Noda K, Hosoya M, Nakajima S, Ohashi J, Fukumoto Y, Shimokawa H.	Anti-atherogenic effects of the combination therapy with olmesartan and azelnidipine in diabetic apolipoprotein e-deficient mice.	Tohoku J Exp Med.	228	305-315	2012
	Aoki T, Fukumoto Y, Yasuda S, Sakata Y, Ito K, Takahashi J, Miyata S, Tsuji I, Shimokawa H.	The Great East Japan Earthquake Disaster and cardiovascular diseases.	Eur Heart J.	2012	2804-2812	2012
	Shafee MA, Fukuda K, Wakayama Y, Nakano M, Kondo M, Hasebe Y, Kawana A, Shimokawa H.	Delayed enhancement on cardiac magnetic resonance imaging is a poor prognostic factor in patients with cardiac sarcoidosis.	J Cardiol.	2012	448-453	2012
	Hayashi D, Kawakami K, Ito K, Ishii K, Tanno H, Imai Y, Kanno E, Maruyama R, Shimokawa H, Tachi M	Usefulness of the non-contact mapping system to elucidate the conduction property for the treatment of common atrial flutter.	PACE	35	1464-1471	2012
	Sumiyoshi A, Suzuki H, Shimokawa H, Kawashima R.	Neurovascular uncoupling under mild hypoxic hypoxia: an EEG-fMRI study in rats.	J Cereb Blood Flow Metab	32	1853-1858	2012
	Dai Z, Aoki T, Fukumoto Y, Shimokawa H.	Coronary perivascular fibrosis is associated with impairment of coronary blood flow in patients with non-ischemic heart failure.	J Cardiol.	60	416-42	2012
	Serizawa F, Ito K, Kawamura K, Tsuchida K, Hamada Y, Zukeran T, Shimizu T, Akamatsu D, Hashimoto M, Goto H, Watanabe T, Sato A, Shimokawa H, Satomi S.	Extracorporeal shock wave therapy ameliorates walking ability of patients with peripheral artery disease and intermittent claudication.	Circ J	76	1486-1496	2012

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
下川宏明	Tatebe S, Fukumoto Y, Sugimura K, Miyamichi-Yamamoto S, Aoki T, Miura Y, Nochioka K, Satoh K, Shimokawa H.	Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease.	Circ J	76	1235-1244	2012
	Tsuburaya R, Yasuda S, Shiroto T, Ito Y, Gao JY, Aizawa K, Kikuchi Y, Ito K, Takahashi J, Ishibashi-Ueda H, Shimokawa H.	Long-term treatment with nifedipine suppresses coronary hyperconstricting responses and inflammatory changes induced by paclitaxel-eluting stent in pigs in vivo: possible involvement of Rho-kinase pathway	Eur Heart J.	33	791-799	2012
福本義弘	Satoh K, Fukumoto Y, Sugimura K, Miura Y, Aoki T, Nochioka K, Tatebe S, Miyamichi-Yamamoto S, Shimizu T, Osaki S, Takagi Y, Tsuburaya R, Ito Y, Matsumoto Y, Nakayama M, Takeda M, Takahashi J, Ito K, Yasuda S, Shimokawa H.	Plasma cyclophilin A is a novel biomarker for coronary artery disease.	Curc J	77	447-455	2013
	Aoki T, Takahashi J, Fukumoto Y, Yasuda S, Ito K, Miyata S, Shinozaki T, Inoue K, Yagi T, Komaru T, Katahira Y, Obata A, Hiramoto T, Sukegawa H, Ogata K, Shimokawa H	Effect of the Great East Japan Earthquake Disaster on cardiovascular diseases -A report from the 10 hospitals in the Disaster area-	Circ J	77	490-493	2013
	Tatebe S, Fukumoto Y, Sugimura K, Miura Y, Nochioka K, Aoki T, Miura M, Yamamoto S, Yaoita N, Satoh K, Shimokawa H.	Optical coherence tomography is superior to intravascular ultrasound for diagnosis of distal-type chronic thromboembolic pulmonary hypertension.	Circ J	77	1081-1083	2013
	Tatebe S, Fukumoto Y, Sugimura K, Miyamichi-Yamamoto S, Aoki T, Miura Y, Nochioka K, Satoh K, Shimokawa H.	Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease.	Circ J	76	1235-1244	2012
	Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, Tatebe S, Miyamichi-Yamamoto S, Shimokawa H.	Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension.	Circ J.	76	485-488	2012

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
高橋潤	Aoki T, Takahashi J, Fukumoto Y, Yasuda S, Ito K, Miyata S, Shinozaki T, Inoue K, Yagi T, Komaru T, Katahira Y, Obata A, Hiramoto T, Sukegawa H, Ogata K, Shimokawa H	Effect of the Great East Japan Earthquake Disaster on cardiovascular diseases -A report from the 10 hospitals in the Disaster area-	Circ J	77	490-493	2013
	Satoh K, Fukumoto Y, Sugimura K, Miura Y, Aoki T, Nochioka K, Tatebe S, Miyamichi-Yamamoto S, Shimizu T, Osaki S, Takagi Y, Tsuburaya R, Ito Y, Matsumoto Y, Nakayama M, Takeda M, Takahashi J, Ito K, Yasuda S, Shimokawa H.	Plasma cyclophilin A is a novel biomarker for coronary artery disease.	Curc J	77	447-455	2013
	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.		in press	2013
	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		in press	2013
	Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H.	Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications and prognostic impact -Multicenter registry study of the Japanese Coronary Spasm Association-	Eur Heart J.	34	258-267	2013
	Kawana A, Takahashi J, Takagi Y, Yasuda S, Sakata Y, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Kubo N, Momomura S, Ogawa H, Shimokawa H.	Gender differences in clinical characteristics and outcomes of patients with vasospastic angina -A report from the Japanese Coronary Spasm Association-	Circ J.		in press	2012

研究者	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
高橋潤	Aoki T, Fukumoto Y, Yasuda S, Sakata Y, Ito K, Takahashi J, Miyata S, Tsuji I, Shimokawa H.	The Great East Japan Earthquake Disaster and cardiovascular diseases.	Eur Heart J.	2012	2804-2812	2012
	Miura M, Shiba N, Nochioka K, Takada T, Takahashi J, Kohno H, Shimokawa H	Urinary albumin excretion in heart failure with preserved ejection fraction: an interim analysis of the CHART 2 study.	Eur J Heart Fail.		in press	2012
	Hao K, Yasuda S, Takii T, Ito Y, Takahashi J, Ito K, Nakayama M, Shiba N, Fukumoto Y, Shimokawa H.	Urbanization, life-style changes and incidence and in-hospital mortality from acute myocardial infarction in Japan -Report from the MIYAGI-AMI Registry-	Circ J.		in press	2012

Ⅳ．研究成果の刊行物・別刷

Advance Publication by-J-STAGE

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

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.

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 ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	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 24–72 h 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

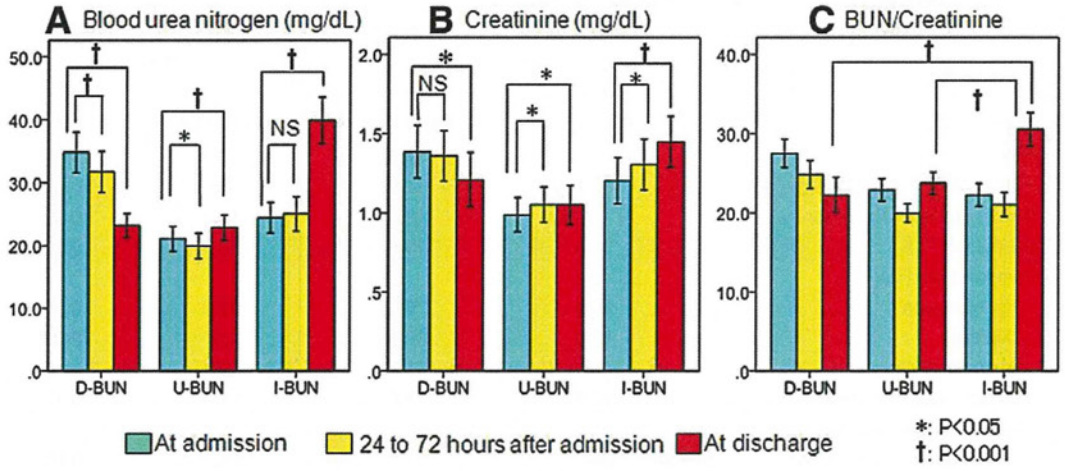

Figure 1. (**A**) Changes in BUN levels during hospitalization for AHFS. (**B**) Changes in creatinine level during hospitalization. (**C**) Changes in BUN/creatinine ratio during hospitalization. AHFS, acute heart failure syndrome; BUN, blood urea nitrogen.

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 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.

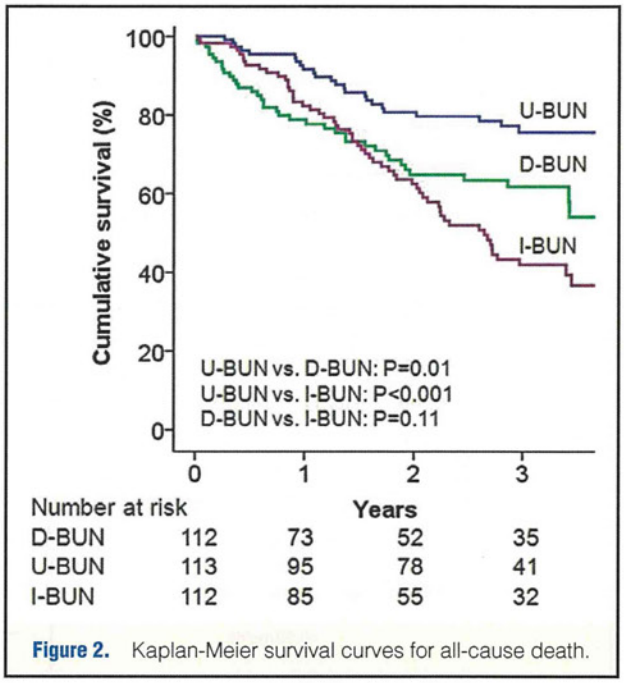

Figure 2. Kaplan-Meier survival curves for all-cause death.

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.

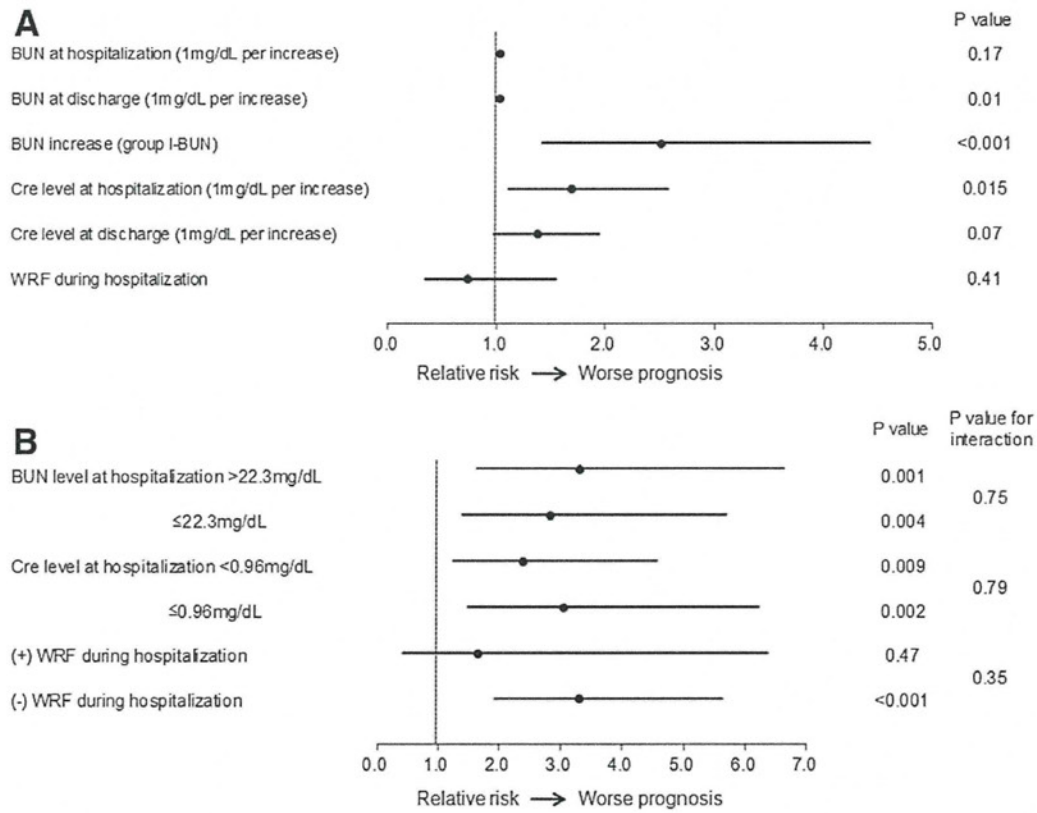

Figure 3. Multivariable logistic analysis. (**A**) Models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge and BUN increase and WRF during hospitalization for all-cause death. (**B**) Subgroup analysis of prognostic value of BUN increase 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 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ 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 24–72 h after admission was almost same level among the 3 groups. However, the change in SBP during the 24–72 h after admission was –43.9±35.8 vs. –29.4±31.2 mmHg 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* 2012 December 1 [Epub ahead of print].
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.

企画編集 眞茅みゆき
（北海道大学大学院 医学研究科 循環病態内科学）

第9回

末期心不全の緩和ケアを考える

宮下光令
東北大学大学院 医学系研究科 保健学専攻 緩和ケア看護学分野 教授

柴 信行
国際医療福祉大学病院 循環器内科 教授

下川宏明
東北大学大学院 医学系研究科 循環器病態学分野 教授

はじめに

近年の高齢化に伴い，非がん疾患の緩和ケアが注目されてきています。慢性心不全の治療目標は，生命予後だけでなく患者が良好なQOL（quality of life；生活の質）の保持することであり[1]，看護師も患者の予後を考慮し，適切な緩和ケアを行う必要があります。このような背景で2011年に『循環器疾患における末期医療に関する提言』が出版されています。

今回は非がん疾患の緩和ケアの基本的な考え方とともに，循環器疾患のなかでも緩和ケアのニーズが高い心不全における緩和ケアの基本的な考え方，終末期の症状と治療，看護支援などについて解説します。

緩和ケアとは何か

2002年にWHOは緩和ケアを以下のように定義しました。

> 緩和ケアとは生命を脅かす疾患による問題に直面している患者とその家族に対して，痛みやその他の身体的問題，心理社会的問題，スピリチュアルな問題を早期に発見し，適切なアセスメントに基づく治療やケアを行うことによって，苦痛を予防または和らげることで，QOLを改善するアプローチである[2]。

この定義にみられるように，緩和ケアは「がん」に限らず，循環器疾患の終末期などを含む，生命を脅かす疾患に直面している患者すべてに適応されるものです。緩和ケアの対象とする「苦痛」は全人的苦痛という言葉で表現されています。全人的苦痛とは，痛みや呼吸困難などの身体症状だけでなく，不安や抑うつなどの精神的苦痛，仕事や経済・家庭の問題などの社会的苦痛，人生の意味への問いや死への恐怖な

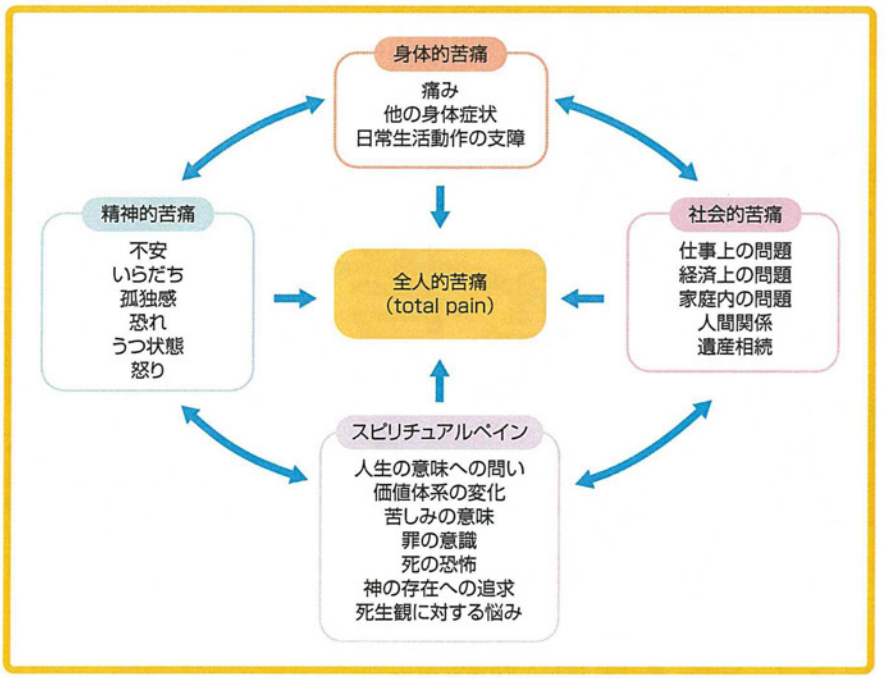

図1 全人的苦痛(文献3より引用)

どのスピリチュアルペインなど，人間をあらゆる面から包括的に捉えるという考え方です（図1）[3]。苦痛を包括的に捉え，緩和し，その人らしく生きることを支えることを目標にします。そのほかにも緩和ケアには以下のような特徴があります。

1）患者だけでなく家族もケアの対象とする
2）患者の苦痛を和らげ，死を自然な過程と捉える
3）死を早めることも，無理に引き延ばすことも目的としない
4）医師・看護師をはじめとした多職種チームによりケアがなされる
5）死別後の家族の精神的なつらさ（悲嘆）もケアの対象とする

非がん疾患の緩和ケアの特徴

非がん患者の終末期ケアには表1に示したような特徴があります[4]。

病態の変化

図2に，非がん疾患による終末期を迎える経過の図を示します[5]。がんは最後の1ヵ月に急速に身体機能が低下することが多いですが，循環器疾患などは時に急性増悪を繰り返しながら比較的ゆっくりと身体機能が低下します。また，認知症，神経疾患などは長い時間をかけてなだらかに身体機能が低下します。非がん疾患では急速に死が訪れるというより，それまでの療養生活の延長上に死があると考えられます。

表1　非がん疾患の緩和ケアの特徴

終末期を迎える経過ががんと異なり，比較的ゆっくり，時に急速に病態が変化する
予後の予測が難しい
DNAR（心肺蘇生指示）や延命治療の中止の判断が難しい
治療が最後まで継続されることがあり，それが苦痛の緩和につながることがある
高齢者では認知症などの合併により，患者本人による意思決定が困難である
高齢者では侵襲的治療の適応の判断が難しいことがある
高齢者では家族による長期的な介護の負担が大きい場合がある

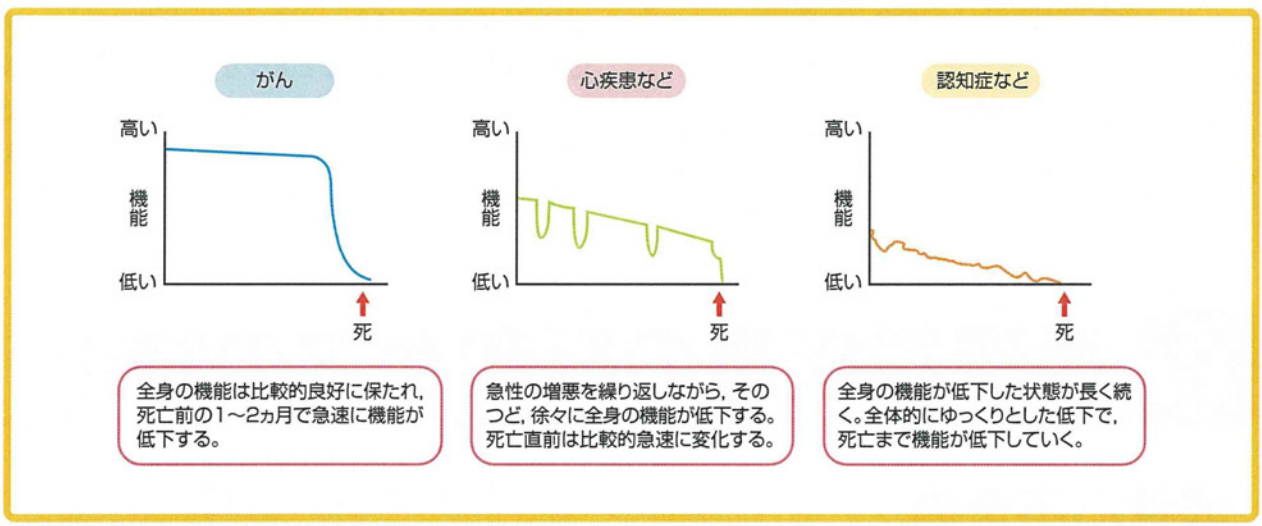

図2　がん・非がん疾患の終末期を迎える経過（文献5より引用）

予後の予測

前述のとおり，非がん疾患では終末期を迎える経過が比較的ゆるやかであり，時に病態が変化するため，予後の予測が困難なことが多いです。心不全では急激な増悪がみられても，治療によって回復することがあります。

DNAR・延命治療中止の判断

予後の予測が難しいため，非がん疾患はDNAR（do not attempt resuscitate：心肺停止時に蘇生処置〔人工呼吸器装着や心臓マッサージなど〕を行わないこと）の判断が難しくなります。人工呼吸器の装着や補助人工心臓，血液透析などの治療が奏功することもあり，延命治療をどの時点で中止するかも難しい判断になります。

治療の継続

図3に，がんと非がん疾患の緩和ケアの考え方の図を示します。がんでは終末期に近づくにつれて治癒を目的とした治療は行わなくなりますが，非がん疾患では治療による生命予後や症状の改善の可能性があるため，原疾患の治療が最後まで続けられることがあります。例えば心不全に対する強心薬の持続点滴などがそれにあたります。

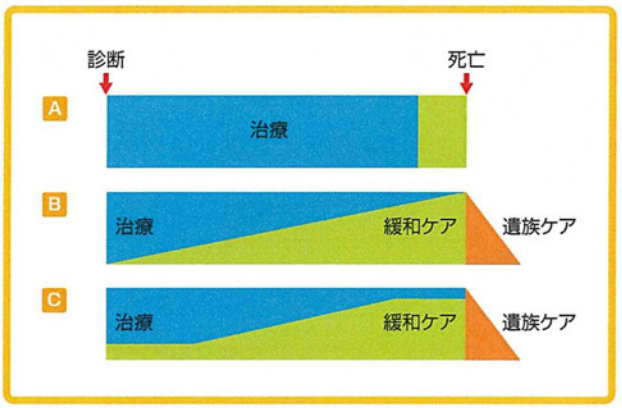

図3 がんと非がん疾患の緩和ケアの考え方
A：以前の考え方（ある時点で治療からケアへ方針が変更される）。
B：最近の緩和ケアの考え方（治療の初期段階から緩和ケアが導入され，徐々にその割合が高まる）。
C：非がん疾患の緩和ケアの考え方（徐々に緩和ケアの割合が高くなるが，死亡の直前まで原疾患への治療も並行して行われる）。

高齢者に付随する問題

心不全患者は高齢であることが多く，認知症などを合併することも少なくありません。緩和ケアでは基本的に患者の意思をできるかぎり尊重して希望に沿ったケアを提供することを目的としますが，認知機能が低下している場合にはケアの目標の設定が難しくなることがあります。また，高齢者では侵襲的治療の適応の判断が難しくなることも少なくありません。比較的ゆるやかに病状が変化するため在宅で介護が必要な状態で過ごすことも多く，家族介護者の負担が大きくなることもあります。

循環器疾患の緩和ケアの特徴

慢性心不全の終末期の軌跡

慢性心不全は，治療の経過中に何度か急性増悪を経験し，再入院率が高い疾患です。急性増悪によって心筋細胞が損傷し，心機能が急激に低下します。急性期を脱すると心機能は部分的に回復しますが，次に急性増悪を経験するとさらに心機能は低下します。このように，慢性心不全は急性期と慢性期を繰り返しながら徐々に全身状態が悪化していくという特徴があります[4]。

慢性心不全の末期の定義

2005年に米国心臓病協会（American Heart Association；AHA）から発行された慢性心不全のガイドラインに，refractory end-stage HF（難治性末期心不全）とend-of-life considerations（終末期ケアで検討すべきこと）の項が追加されました[6]。ガイドラインでは最大限の治療にも関わらず安静時にも著明な症状を有するものをstage Dの難治性末期心不全とし，考えられる治療を勧告しています（表2）[7]。

また，日本の提言では心不全の末期状態として以下を挙げています[1]。

1) 適切な治療をしていることが原則
2) 器質的な心機能障害により，適切な治療にかかわらず，慢性的にNYHA Ⅳの症状を訴え，頻回または持続的点滴薬物療法を必要とする
3) 6ヵ月以内に1回以上の入院歴，左室駆出率（EF）が20%以下であるなどの具体的な病歴や心機能を基準とすることもあり得る
4) 終末期が近いと判断されることを含むこともあり得る

これらに加えて脳性ナトリウム利尿ペプチド（BNP）の100pg/mLの増加は死亡率の35%の増加につながり，BNP値が500pg/mL以上では予後がかなり悪いため，BNP値も予後の指標として使われることがあります[8]。さらに，心不全に腎不全を合併した場合も予後が悪