Ⅲ. 研究成果の刊行に関する一覧表

1）書籍

班員	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	出版年	ページ
北風政史	朝倉正紀 北風政史	慢性心不全のエビデンス	堀正二 永井良三	循環器疾患最新の治療2012-2013	南江堂	2012	532-535
	浅沼博司 北風政史	急性心不全患者におけるアデノシンA1受容体拮抗薬rolofyllineの効果は？	小室一成 横井宏佳 山下武志 楽木宏美	EBM循環器疾患の治療2012-2013	中外医学社	2012	196-200
	高橋彩子 北風政史	病態51 糖尿病患者の左室拡張能障害の分子機構について教えてください.	山岸昌一	循環器医から寄せられる「糖尿病と血管合併症」に関する100の質問	メディカルレビュー社	2012	118-119
	高濱博幸 北風政史	高血圧性心不全－緊急時の対応	浦信行	あなたも名医！高血圧、再整理	日本医事新報社	2012	179-182
	閔庚徳 朝倉正紀 北風政史	β遮断薬・α遮断薬	池田隆徳	これで決まり！循環器治療薬ベストチョイス こんな病態・症例にこの処方	メジカルビュー社	2012	21-25
	北風政史	心不全の新しいとらえ方	北風政史	心不全診療Q＆A	中外医学社	2012	76-80
	北風政史	<納豆>健康食品の元祖【納豆】の実力は本物だった。コレステロールと中性脂肪が減り、便秘も改善した	主婦の友社	最新版コレステロール・中性脂肪がみるみる下がる大百科	主婦の友社	2012	40-41
	朝倉正紀 北風政史	カテコールアミンおよびその類似薬	井上博 許俊鋭 檜垣實男 代田浩之 筒井裕之	今日の循環器疾患治療指針第3版	医学書院	2013	145-147
	朝倉正紀 北風政史	心筋疾患	井上博 許俊鋭 檜垣實男 代田浩之 筒井裕之	今日の循環器疾患治療指針第3版	医学書院	2013	595-598

筒井裕之	筒井裕之 絹川真太郎	急性心不全	堀正二 永井良三	循環器疾患最新の治療2012-2013	南江堂	2012	271-277
	筒井裕之	慢性心不全の診断と治療	門脇孝 永井良三	カラー版、内科学	西村書店	2012	597-602
	絹川真太郎筒井裕之	心不全重症度の評価法	井上博 許俊鋭 檜垣實男 代田浩之 筒井裕之	今日の循環器疾患第3版	医学書院	2013	294-298
久保田功	宮本卓也 久保田功	不整脈	日本心臓病学会	循環器内科医のための災害時医療ハンドブック	日本医事新報社	2012	113-116
	有本貴範 久保田功	Q3.交感神経活性はどのようなマーカーでみるのがよいですか？ Q4.RAA系活性化はどのようなマーカーでみるのがよいですか？	北風政史	心不全診療Q&A エキスパート106人からの回答	中外医学社	2012	111-112
下川宏明	柴信行 下川宏明	心不全の実態（疫学）を知る	服部隆一	心不全をマスターする一病態を理解して治療できる医師になろう一	文光堂	2013	12-24
	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	Annual Review 循環器	中外医学社	2013	88-93
	Sakata Y, Shimokawa H	Cardiovascular Events: Ischemic Heart Disease	Wakabayashi I, Groschner K	Interdisciplinary Concepts of Cardiovascular Health	Springer, Wien, Austria	2013	In press
永井良三	門脇孝 永井良三	序文	門脇孝 永井良三	カラー版、内科学	西村書店	2012	iii
	森田啓行 永井良三	治療法の発展	門脇孝 永井良三	カラー版、内科学	西村書店	2012	16-18
	原田賢治 永井良三	安全・安心の医療の実践	門脇孝 永井良三	カラー版、内科学	西村書店	2012	38-40

磯部光章	加藤陽子 磯部光章	心膜炎、心筋炎.	宮脇龍太郎 石川康朗	救急・ER ノート. 胸背部痛を極める. あらゆる原因を知り、対処する	羊土社	2012	88-98
	瀬戸口雅彦 磯部光章	心筋炎	堀正二 永井良三	循環器疾患最新の治療2012-2013	南江堂	2012	195-200
	磯部光章	移植免疫とは	宮坂信之他	新版臨床免疫学第2版	講談社サイエンティフィック	2012	62-70
後藤雄一	後藤雄一	ミトコンドリア病	㈱技術情報協会	希少疾患/難病の診断・治療と製品開発	(株)技術情報協会	2012	999-1005
	後藤雄一	ミトコンドリア脳筋症	永井良三 大田健	疾患・症状別　今日の治療と看護	南江堂	2012	771-773
山岸正和	今野哲雄 山岸正和	解明されてきた遺伝性心疾患	伊藤浩	変貌する心不全診療	南江堂	2013	35-38
	山岸正和	心筋梗塞	山口徹 北原光夫 福井次矢	今日の治療指針2012:私はこう治療している	医学書院	2012	340-341
	川尻剛照 今野哲雄 林研至 山岸正和	心筋梗塞の2次予防に関するガイドライン2011年版	門脇孝 小室一成 宮地良樹	診療ガイドラインup to date 2012-2013	メディカルレビュー	2012	236-244
中谷武嗣	中谷武嗣	心臓移植の適応について教えてください	北風政史	心不全診療 Q&A エキスパート106人からの回答	中外医学社	2012	358-360
	中谷武嗣	心臓移植の手続きについて教えてください	北風政史	心不全診療 Q&A エキスパート106人からの回答	中外医学社	2012	361-363
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矢野雅文	小林茂樹 矢野雅文	心不全「バイオマーカー」	廣井秀雄	診断と治療	診断と治療社	2012	1461-1469

今泉勉	武宮清子 今泉勉	弁膜症術後の外来管理	堀正二 永井良三	循環器疾患最新の治療2012-2013	南江堂	2012	192-194
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竹石恭和	中里和彦 竹石恭知 長谷川有史	放射線障害の基礎知識など	日本心臓病学会	循環器内科医のための災害時医療ハンドブック	日本医事新報社	2012	25-32
志賀剛	志賀剛	心不全を伴う心房細動をどのように薬物・非薬物的に治療するか？	小室一成 横井宏佳 山下武志 楽木宏実	EBM循環器疾患の治療2012-2013.	中外医学社	2012	325-329
	志賀剛	心不全	樋口輝彦 桑原和江 伊藤弘人	内科患者のメンタルケアアプローチ　循環器疾患編	新興医学出版社	2012	58-67
	鈴木豪 志賀剛 萩原誠久	心臓再同期治療・植込み型除細動器	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	2012	177-184
木村彰方	木村彰方	性差医学の夜明けをもたらす－難治疾患と性差	学研メディカル秀潤社	細胞工学	学研メディカル秀潤社	2013	203-209
	木村彰方	先天性心疾患の成因（遺伝子異常、解析）	東京医学社	周産期医学	東京医学社	2012	1229-1236
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吉村道博	吉村道博	冠攣縮性狭心症	山口徹 北原光夫 福井次矢	今日の治療指針2013年度版【ポケット版】	医学書院	2013	347-348
	川井真 吉村道博	アルコール性心筋症	井上博 許俊鋭 檜垣實男 代田浩之 筒井裕之	今日の循環器疾患治療指針第3版	医学書院	2013	630-632
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今中恭子	今中恭子	心筋リモデリングと細胞外マトリックス調節因子	永井良三 許俊鋭 鄭忠和 澤芳樹	循環器疾患の最新医療	先端医療技術研究所	2012	45-48
石坂信和	寺﨑文生 石坂信和	拘束型心筋症	井上博 許俊鋭 檜垣實男 代田浩之 筒井裕之	今日の循環器疾患治療指針第3版	医学書院	2013	613-618
植田初江	松山高明 植田初江	心筋症・弁膜症で使用するモダリティ -心筋生検-	北風政史	Circulation up-to-date 8 巻 増刊	メディカ出版	2013	158-163
野出孝一	佐久間理吏 野出孝一	診る　不安定プラークをバイオマーカーからとらえる	吉田富生	Heart View	メジカルビュー社	2013	42-48

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班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Ⅳ. 附録

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ORIGINAL ARTICLE
Heart Failure

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

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Background: Patients with heart failure (HF) have a high risk of cardiovascular (CV) death and re-hospitalization. The purpose of the present study was therefore to investigate predictors of CV death and re-hospitalization for acute decompensated HF (ADHF).

Methods and Results: A total of 225 patients aged 67.2±15.2 years, including 134 men (59.6%), who were hospitalized for ADHF between 2008 and 2009, were followed up. After discharge, the relationship between clinical parameters and CV events (ie, CV death or re-hospitalization for HF) was examined. Follow-up was continued until 30 April 2011. The most important predictors of re-hospitalization were serum blood urea nitrogen (BUN; adjusted hazard ratio [HR], 1.02; 95% confidence interval [CI]: 1.00–1.03, P=0.01), plasma brain natriuretic peptide (BNP; adjusted HR, 1.85; 95% CI: 1.12–3.04, P=0.02), and diastolic blood pressure (DBP; adjusted HR, 0.97; 95% CI: 0.94–1.00, P=0.049). The only predictor of CV mortality was a high BUN (adjusted HR, 1.05; 95% CI: 1.01–1.09, P=0.01).

Conclusions: High serum BUN (≥22.5 mg/dl), high plasma BNP (≥250 pg/ml), and low DBP (<60 mmHg) predict CV events in patients hospitalized for ADHF. These factors may identify high-risk patients for CV events and provide therapeutic targets for managing HF. (*Circ J* 2012; **76:** 2372–2379)

Key Words: Blood pressure; Blood urea nitrogen; Brain natriuretic peptide; Heart failure

Over the past 2 decades, various therapeutic strategies for the treatment of chronic heart failure (CHF) have been developed, and have led to improvement of the survival rate for patients with CHF. Although current interventions can slow the progression of CHF, most patients are eventually hospitalized with acute decompensated HF (ADHF). It has been reported that patients hospitalized for CHF have a high risk of cardiovascular (CV) death and readmission, with a 6-month readmission rate as high as 50%.[1] Among 2,445 residents with confirmed ADHF, the 1-year mortality after discharge from hospital was 37.3%.[2] The Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) and the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) determined a death rate of 8.9–10.3% within 60 days of discharge and 19% within 6 months, respectively.[3,4] The results of such clinical trials, however, may not be representative of current practice or applicable to general CHF patients because these clinical trials conducted in Europe and/or the USA were based on selected patients enrolled in clinical trials. Interestingly, the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 Study (CHART-2) done in Japan also found that the prevalence of ischemic etiology and risk factors (hypertension (HTN) and diabetes) have increased, and that mortality is the same as in Western studies.[5]

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Editorial p2329

To identify the patients at high risk for re-hospitalization or CV death, stratification of risk for mortality or morbidity among all of the available clinical parameters is necessary in a clinical cohort study of CHF patients, but such trials have not been performed. Therefore, it is necessary to identify useful markers to help CV physicians identify HF patients that have a high long-term risk of events at the time of discharge.

To identify such useful predictors, we conducted an analysis of clinical data in a hospital-based registry of ADHF patients to identify factors related to either long-term CV death or re-hospitalization for HF in CHF patients who mainly suffered from dilated cardiomyopathy (DCM) and who were admitted with ADHF.

Methods

Subjects

This study was conducted in accordance with the Declaration of Helsinki and received approval from the ethics committee of the National Cerebral and Cardiovascular Center. Consecutive patients who had a discharge diagnosis of ADHF were eligible for entry into the hospital registry. Data were analyzed for 251 consecutive patients admitted to the National Cerebral and Cardiovascular Center (Suita, Japan) between December 2008 and December 2009 because of ADHF (New York Heart Association class III–IV). Patients who died in hospital or who did not have complete clinical data at discharge were excluded. If HF was not the reason for hospitalization, the patients were also excluded. Patients with CHF caused by chronic kidney disease or acute renal failure and with hemodialysis were excluded. We discontinued follow-up in April 2011. The demographic profile, medical history, medications at discharge, laboratory test results, echocardiography findings, and clinical outcomes were obtained from the hospital registry. We recorded blood pressure (BP) 3 times and averaged them on the day of discharge. A fasting blood sample was obtained before discharge after an overnight fast (10–12 h) for measurement of plasma brain natriuretic peptide (BNP) and serum blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase, alanine aminotransferase, total bilirubin, uric acid, sodium, potassium, and fasting blood glucose (FBG). Estimated glomerular filtration rate (eGFR) was calculated as: $194\times age^{-0.287}\times$ serum $Cr^{-1.094}$ ($\times 0.739$ if female). HTN was defined as present in patients with (1) a history of hypertension or (2) a systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg. Patients with a history of diabetes mellitus (DM) or an FBG ≥126 mg/dl were defined as having DM. Hyperlipidemia was defined as total cholesterol ≥200 mg/dl or triglycerides ≥150 mg/dl.

Endpoints

The primary endpoint was either CV death or re-hospitalization for HF, and these endpoints were analyzed on a time-to-event basis. All outcomes were decided by 3 cardiologists. Re-hospitalization was defined as a new admission for HF after discharge from hospital following admission for ADHF. CV death was defined as death from CV disease. If re-hospitalization or death did not occur, the date of censoring was the date of final follow-up. Follow-up was continued until 30 April 2011.

Statistical Analysis

Results are expressed as the mean±SD or as percentages. Students' t-test was used to compare differences between groups for continuous variables and the chi-square test was used for categorical data. If data had a skewed distribution, including BNP, logarithmic transformation was done before statistical analysis. Cox proportional hazards regression analysis was used to evaluate the association of variables with re-hospitalization or CV mortality. Re-hospitalization due to HF and CV mortality event-free curves were drawn using the Kaplan-Meier method and were compared using the log-rank test. Analysis was performed with SPSS version 12.0 (SPSS, Chicago, IL, USA) and STATA version 11.0 (College Station, TX, USA). $P<0.05$ was considered statistically significant.

Results

Of the 251 patients enrolled, 21 were excluded due to incomplete data and 5 were excluded because of death in hospital, leaving 225 patients for analysis. Table 1 lists the baseline characteristics of these patients. Clinically relevant features of the re-hospitalized group included a high prevalence of DM, high BUN, low serum sodium, low eGFR, high percentage of use of diuretics (except spironolactone), and low DBP. The difference in plasma BNP according to re-hospitalization was borderline significant. Patients who succumbed to CV death were older, had low DBP, high plasma BNP and BUN, and low serum sodium. There was no difference in prevalence of etiologies according to re-hospitalization or CV death. There was no difference in the prevalence of aortic regurgitation according to re-hospitalization (6.3% vs. 8.0% P=0.80). The BUN/Cr ratio and the prevalence of BUN/Cr >10 did not differ according to re-hospitalization. The patients who succumbed to CV death had a higher BUN/Cr. The prevalence of BUN/Cr >10 did not differ according to CV death. The dose of furosemide was higher in patients with re-hospitalization and CV death.

To obtain the cut-offs for these parameters, receiver operating characteristic (ROC) curve analysis was used, and 22.5 mg/dl, 2.4 pg/ml (250 pg/ml), 60 mmHg and 137.5 mmol/dl appeared to be optimal cut-offs to create dichotomous variables for valves of BUN, log BNP (plasma BNP), DBP and serum sodium, respectively. The selection of cut-offs was challenging due to the large decreases in specificity as sensitivity increased. Although the furosemide dose in patients with BUN ≥22.5 mg/dl was higher than in those with BUN <22.5 mg/dl (45.8±35.9 mg vs. 30.3±19.9 mg, P=0.001), there were no differences in the doses of spironolactone, torasemide and trichlormethiazide (spironolactone: 28.9±12.1 mg vs. 28.3±11.6 mg, P=0.77; torasemide: 8.9±8.6 mg vs. 5.1±2.0 mg, P=0.16; trichlormethiazide: 1.6±0.7 mg vs. 1.6±0.5 mg, P=0.79).

The Cox proportional hazards model showed that BUN, DBP, and plasma BNP were independent predictors of re-hospitalization (Table 2). Hazard ratios (HR) for the endpoint of re-hospitalization indicated that BUN, DBP, and BNP were significantly associated with readmission for HF (unadjusted HR, 1.02; 95% confidence interval [CI]: 1.01–1.03; unadjusted HR, 0.96; 95% CI: 0.94–0.98; unadjusted HR, 1.62; 95% CI: 1.08–2.43, respectively). Also, these 3 variables remained significant (adjusted HR, 1.02; 95% CI: 1.00–1.03; adjusted HR, 1.85; 95% CI: 1.12–3.04; and adjusted HR, 0.97; 95% CI: 0.94–1.00, respectively) even after adjusting for age, gender, SBP, serum Cr, serum sodium, DM, HTN, hyperlipidemia, and use of β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), spironolactone, and other diuretics. When BUN, BNP, and DBP were incorporated as continuous variables, we found that there was a 2% increase in the risk of re-hospitalization for every 1-mg/dl increase in

Table 1. ADHF Patient Baseline Characteristics vs. HF Re-Hospitalization and CV Mortality

	Re-hospitalization (n=225)			CV mortality (n=225)		
	Yes (n=112)	No (n=113)	P value	Yes (n=23)	No (n=202)	P value
Demographics						
Age (years)	68.3±14.7	66.2±15.6	0.30	73.5±13.9	66.5±15.2	0.04
Male	70 (62.5)	64 (56.6)	0.42	14 (60.9)	120 (59.4)	1.00
Medical history						
HTN	53 (47.3)	64 (56.6)	0.18	13 (56.5)	104 (51.5)	0.67
DM	43 (38.4)	27 (28.9)	0.02	9 (39.1)	61 (29.4)	0.48
Hyperlipidemia	35 (31.3)	35 (31.0)	1.00	9 (39.1)	61 (30.2)	0.48
Clinical characteristics						
SBP (mmHg)	110.1±16.2	114.2±16.1	0.07	110.4±17.8	112.4±16.1	0.58
DBP (mmHg)	58.8±8.9	63.1±10.0	0.001	56.9±7.6	61.5±9.8	0.03
HR (beats/min)	75.0±68.9	68.6±11.7	0.34	71.3±13.0	71.8±51.5	0.97
LVDd (mm)	59.4±14.0	58.0±11.3	0.45	59.3±13.8	58.6±12.6	0.82
LVDs (mm)	47.9±16.0	46.4071±14.0	0.45	49.7±15.7	46.9±14.9	0.41
FS (%)	21.1±11.9	21.4±13.4	0.84	18.1±9.8	21.6±12.9	0.21
Laboratory values						
Log BNP (pg/ml)	2.4±0.5	2.3±0.5	0.06	2.5±0.5	2.3±0.5	0.05
Uric acid (mg/dl)	7.5±2.1	7.1±2.1	0.19	8.2±2.0	7.2±2.1	0.04
Total bilirubin (mg/dl)	0.7±0.4	0.7±0.3	0.44	0.6±0.3	0.7±0.4	0.53
AST (U/L)	28.9±12.7	25.9±12.6	0.08	27.9±12.3	27.4±12.8	0.84
ALT (U/L)	23.9±17.8	23.5±23.1	0.87	18.9±13.3	24.3±21.2	0.24
BUN (mg/dl)	31.3±21.5	24.0±13.0	0.002	42.4±34.3	26.0±14.4	0.03
BUN/Cr	24.8±8.3	23.9±13.8	0.57	29.1±8.0	23.8±11.6	0.04
BUN/Cr >10	110 (98.2)	109 (96.5)	0.68	23 (100)	196 (97.0)	1.00
Serum Cr (mg/dl)	1.3±0.7	1.2±1.4	0.76	1.4±1.0	1.2±1.1	0.35
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	50.0±21.8	61.0±44.6	0.02	47.9±26.0	56.4±36.4	0.28
Serum sodium (mmol/L)	136.9±4.2	137.9±3.7	0.05	135.7±4.2	137.6±3.9	0.03
Serum potassium (mmol/L)	4.3±0.5	4.4±0.5	0.25	4.3±0.5	4.3±0.5	0.41
Etiology of HF						
DCM	85 (75.9)	88 (77.9)	0.15	18 (78.3)	155 (76.7)	0.38
ICM	3 (2.7)	0 (0)		1 (4.3)	2 (1.0)	
VHD	18 (16.1)	19 (16.8)		4 (17.3)	33 (16.3)	
HCM	6 (5.4)	12 (10.6)		0 (0)	18 (8.9)	
Others	7 (6.3)	3 (2.7)		1 (4.3)	9 (4.5)	
Medication at discharge						
β-blocker	72 (64.3)	69 (61.1)	0.68	13 (56.5)	128 (63.4)	0.51
ACEI	47 (42.0)	46 (40.7)	0.89	10 (43.5)	83 (41.1)	0.83
ARB	26 (23.2)	23 (20.4)	0.63	3 (13.0)	46 (22.8)	0.42
Spironolactone	65 (58.0)	57 (50.4)	0.29	12 (52.2)	110 (54.5)	0.83
Spironolactone (mg)	27.9±11.4	29.5±12.4	0.44	28.5±12.5	28.6±11.8	0.98
Diuretics except spironolactone	94 (83.9)	81 (71.7)	0.04	20 (87.0)	155 (76.7)	0.30
Furosemide (mg)	44.6±35.9	32.9±21.7	0.006	63.5±52.2	35.2±24.7	0.03
Torasemide (mg)	8.4±8.2	5.3±2.6	0.29	6.0±5.3	7.6±7.3	0.72
Trichlormethiazide (mg)	1.6±0.8	1.6±0.5	0.99	1.0±0.0	1.7±0.7	0.04

Data given as mean±SD or n (%).
ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; CV, cardiovascular; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate ($194 \times age^{-0.287} \times serum\ Cr^{-1.094}$ (×0.739 if female)); FS, fractional shortening; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; HTN, hypertension; ICM, ischemic cardiomyopathy; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; SBP, systolic blood pressure; VHD, valvular heart disease.

BUN, as well as an 8.5% increase in risk for every 1-pg/ml increase in BNP. There was also a 3% decrease in the risk of re-hospitalization for every 1-mmHg increase of DBP. We found that adjusted odds ratio (OR) of BUN ≥22.5 mg/dl vs. <22.5 mg/dl, log (BNP) ≥2.4 pg/ml vs. <2.4 pg/ml (BNP ≥250 pg/ml vs. <250 pg/ml) and DBP ≥60 mmHg vs. <60 mmHg were 1.58 (95% CI: 1.01–2.49, P=0.047), 1.57 (95% CI: 1.05–2.43, P=0.03) and 0.57 (95% CI: 0.36–0.91, P=0.02) after adjustment for the aforementioned parameters. In contrast, only BUN was associated with a significant increase of CV death (unadjusted HR, 1.03; 95% CI: 1.02–1.04), and this association remained significant (adjusted HR, 1.05; 95% CI: 1.01–

Table 2. Variables Associated With HF Re-Hospitalization or CV Mortality

	Univariate model		Multivariate model	
	Hazard ratio	P value	Hazard ratio	P value
Re-hospitalization cohort				
Age (per year)	1.01 (1.00–1.03)	0.10	1.01 (1.00–1.03)	0.13
Gender (male vs. female)	1.16 (0.79–1.70)	0.46	1.19 (0.77–1.84)	0.44
SBP (per mmHg)	0.99 (0.97–1.00)	0.03	1.01 (0.99–1.02)	0.58
DBP (per mmHg)	0.96 (0.94–0.98)	<0.001	0.97 (0.94–1.00)	0.049
LogBNP (per pg/ml)	1.62 (1.08–2.43)	0.02	1.85 (1.12–3.04)	0.02
BUN (per mg/dl)	1.02 (1.01–1.03)	<0.001	1.02 (1.00–1.03)	0.01
Serum Cr (per mg/dl)	1.00 (0.88–1.14)	0.99	0.84 (0.61–1.15)	0.28
Serum sodium (per mmol/L)	0.94 (0.90–0.99)	0.009	0.97 (0.92–1.03)	0.31
DM	1.16 (0.94–1.44)	0.16	1.07 (0.84–1.37)	0.60
HTN	0.80 (0.55–1.16)	0.24	0.72 (0.45–1.17)	0.19
Hyperlipidemia	1.04 (0.70–1.55)	0.85	1.03 (0.67–1.58)	0.91
β-blocker	1.00 (0.68–1.47)	1.00	1.09 (0.68–1.75)	0.73
ACEI	1.08 (0.74–1.58)	0.68	1.32 (0.84–2.09)	0.23
ARB	0.99 (0.64–1.54)	0.97	1.38 (0.81–2.35)	0.24
Spironolactone	1.26 (0.86–1.83)	0.23	1.11 (0.73–1.69)	0.62
Diuretics use except spironolactone	1.72 (1.04–2.84)	0.04	1.47 (0.85–2.52)	0.17
Cardiovascular mortality cohort				
Age (per year)	1.04 (1.01–1.08)	0.03	1.02 (0.98–1.07)	0.31
Gender (male vs. female)	1.00 (0.43–2.30)	0.99	1.20 (0.47–3.06)	0.70
SBP (per mmHg)	0.99 (0.97–1.02)	0.54	1.01 (0.98–1.05)	0.47
DBP (per mmHg)	0.94 (0.89–0.99)	0.02	0.94 (0.88–1.01)	0.10
LogBNP (per pg/ml)	2.58 (1.08–6.18)	0.03	2.34 (0.89–6.00)	0.09
BUN (per mg/dl)	1.03 (1.02–1.04)	<0.001	1.05 (1.01–1.09)	0.01
Serum Cr (per mg/dl)	1.10 (0.88–1.37)	0.42	0.38 (0.10–1.50)	0.17
Serum sodium (per mmol/L)	0.91 (0.83–0.99)	0.03	0.97 (0.86–1.09)	0.59
DM	1.48 (0.64–3.42)	0.36	1.15 (0.42–3.15)	0.79
HTN	1.23 (0.54–2.80)	0.63	0.83 (0.29–2.41)	0.74
Hyperlipidemia	1.38 (0.60–3.18)	0.46	1.17 (0.40–3.39)	0.77
β-blocker	0.74 (0.32–1.68)	0.46	0.90 (0.31–2.59)	0.85
ACEI	1.08 (0.47–2.47)	0.85	1.50 (0.57–3.95)	0.42
ARB	0.52 (0.16–1.76)	0.30	0.81 (0.21–3.23)	0.77
Spironolactone	0.91 (0.40–2.06)	0.82	0.67 (0.25–1.82)	0.43
Diuretics use except spironolactone	1.96 (0.58–6.58)	0.28	1.66 (0.46–5.95)	0.44

Abbreviations as in Table 1.

1.09) after adjustment for the aforementioned parameters. When BUN was incorporated as a continuous variable, we found that it was the strongest predictor of CV mortality and that there was a 5% increase in the risk of CV death for every 1-mg/dl increase in BUN. In contrast, serum Cr was not an independent predictor of either re-hospitalization or CV death. When the Cr was replaced by eGFR in the regression model, the OR of eGFR was 1.00 (95% CI: 0.99–1.00, P=0.26). eGFR was not found to be an independent predictor of re-hospitalization in the present study.

Given that BUN was found to be a shared and strong predictor of both CV death and re-hospitalization for HF, we stratified the patients according to serum BUN level to examine whether the predictive value of BUN overcame the predictive value of plasma BNP or DBP. We divided the patients according to the BUN cut-off of 22.5 mg/dl, thus obtaining low BUN (<22.5 mg/dl) and high BUN (≥22.5 mg/dl) subgroups. We also divided the patients into 2 groups according to log (BNP)= 2.4 pg/ml (BNP, 250 pg/ml) to obtain a low BNP subgroup (<250 pg/ml) and a high BNP subgroup (≥250 pg/ml). Furthermore, we divided the patients into 2 groups at the cut-off DBP of 60 mmHg to obtain a low DBP subgroup (<60 mmHg) and a high DBP subgroup (≥60 mmHg). Kaplan-Meier curves for re-hospitalization were plotted for groups with BUN above or below the mean and log BNP above or below the mean (**Figure 1**). The low BUN+low BNP subgroup had a significantly lower re-hospitalization rate compared with the high BUN+high BNP subgroup, the high BUN+low BNP subgroup, and the low BUN+high BNP subgroup (log-rank test, P=0.001, 0.001, and 0.001, respectively). Kaplan-Meier curves for re-hospitalization were also plotted for the groups with BUN above or below 22.5 mg/dl and DBP above or below 60 mmHg (**Figure 2**). As a result, the low BUN+high DBP subgroup showed a significant decrease of re-hospitalization compared with the low BUN+low DBP subgroup and the high BUN+low DBP subgroup (log-rank test, P=0.04 and <0.001, respectively).

Furthermore, Kaplan-Meier curves for re-hospitalization were plotted for groups with BNP above or below 250 pg/ml and DBP above or below 60 mmHg in the high BUN subgroup (**Figure 3A**) and in the low BUN subgroup (**Figure 3B**). In the high BUN

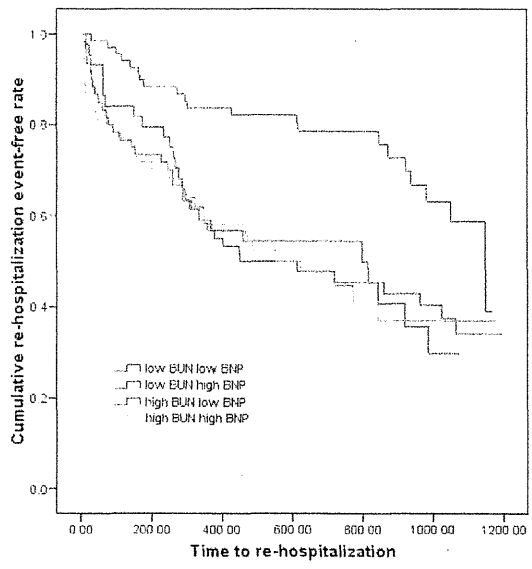

Figure 1. Kaplan-Meier plots for re-hospitalization event-free curves according to different combinations of blood urea nitrogen (BUN) and brain natriuretic peptide (BNP) levels. All participants were divided into 2 groups according to cut-offs for BUN (22.5 mg/dl) and BNP (250 pg/ml). Cumulative re-hospitalization event-free rates in the low BUN + low BNP subgroup (n=68), low BUN+high BNP subgroup (n=44), high BUN + low BNP subgroup (n=60), and high BUN + high BNP subgroup (n=53) were 39.3%, 29.8%, 34.2% and 37.1%, respectively (log-rank test, P=0.002).

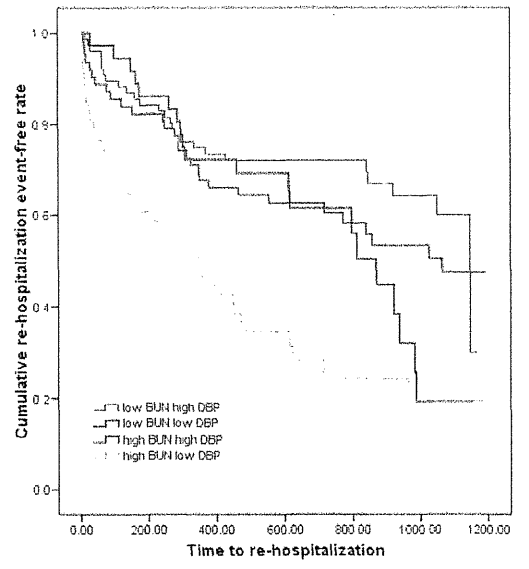

Figure 2. Kaplan-Meier plots for re-hospitalization event-free curves according to different combinations of blood urea nitrogen (BUN) and diastolic blood pressure (DBP) levels. All participants were divided into 2 groups according to mean BUN (22.5 mg/dl) and DBP (60 mmHg). Cumulative re-hospitalization event-free rates in the low BUN + low DBP subgroup (n=36), low BUN + high DBP subgroup (n=76), high BUN + low DBP subgroup (n=51), and high BUN + high DBP subgroup (n=62) were 19.2%, 30.0%, 19.4% and 47.6%, respectively (log-rank test, P<0.001).

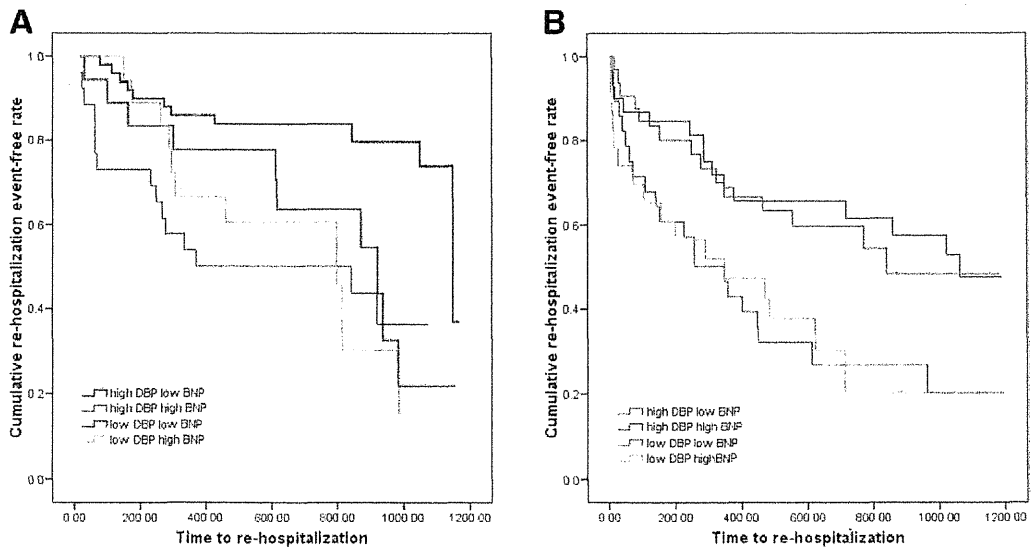

Figure 3. (**A**) Kaplan-Meier plots for re-hospitalization event-free curves according to different combinations of brain natriuretic peptide (BNP) and diastolic blood pressure (DBP) levels in the low blood urea nitrogen (BUN) subgroup (<22.5 mg/dl). All participants were divided into 2 groups according to the cut-offs for BNP (250 pg/ml) and DBP (60 mmHg). Cumulative re-hospitalization event-free rates in the low BNP + low DBP subgroup (n=18), low BNP + high DBP subgroup (n=50), high BNP + low DBP subgroup (n=18), and high BNP + high DBP subgroup (n=26) were 21.8%, 37.0%, 15.2% and 36.5%, respectively (log-rank test, P=0.001). (**B**) Kaplan-Meier plots for re-hospitalization event-free curves grouped according to different combinations of BNP and DBP levels in the high BUN subgroup (≥27.9 mg/dl). All participants were divided into 2 groups according to the mean of BNP (2.33 pg/ml) and DBP (61 mmHg). Cumulative re-hospitalization event-free rates in the low BNP + low DBP subgroup (n=28), low BNP + high DBP subgroup (n=32), high BNP + low DBP subgroup (n=23), and high BNP + high DBP subgroup (n=30) were 20.1%, 47.4%, 20.1% and 48.2%, respectively (log-rank test, P=0.005).

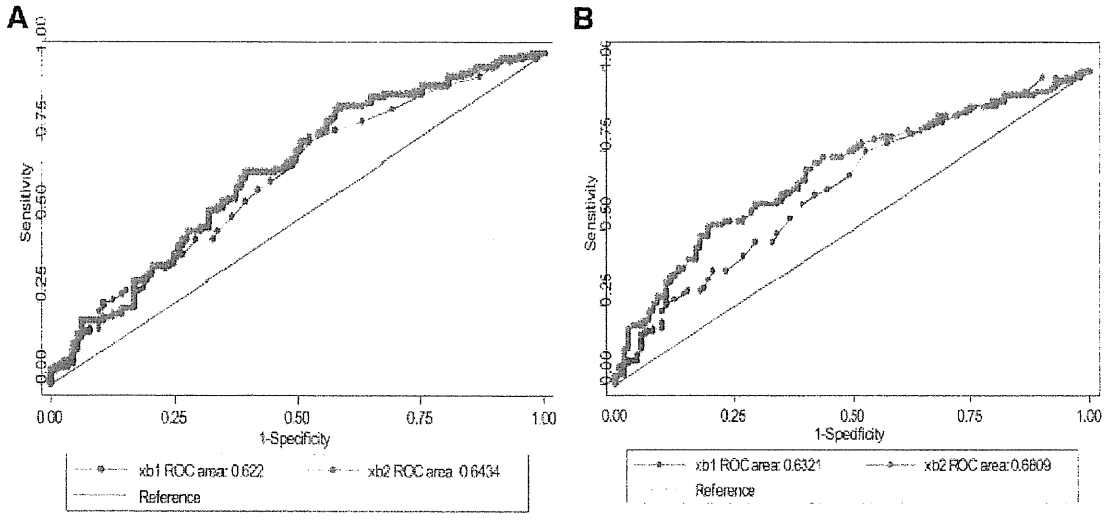

Figure 4. Receiver operating characteristic (ROC) curve for blood urea nitrogen (BUN), brain natriuretic peptide (BNP) and diastolic blood pressure (DBP) in the identification of re-hospitalization with heart failure. The composite of (**A**) BNP or (**B**) DBP was not shown to add value significantly beyond BUN alone in identifying re-hospitalization.

subgroup, the low BNP+high DBP subgroup showed a significant decrease of re-hospitalization compared with the low BNP+low DBP subgroup and the high BNP+low DBP subgroup (log-rank test, P=0.006 and <0.001, respectively). In the low BUN subgroup, the low BNP+high DBP subgroup showed a significant decrease of re-hospitalization compared with the high BNP+high DBP subgroup and the low BNP+low DBP subgroup, and the high BNP+low DBP subgroup (log-rank test, P<0.001 and 0.009 and 0.002, respectively).

The ROC curve data showed that BNP superimposed on the existing BUN level expanded the model from 0.622 to 0.6434 (P=0.38) and DBP superimposed on the existing BUN level expanded the model from 0.6321 to 0.6809 (P=0.12; **Figure 4**).

Discussion

This study has shown that high serum BUN, high plasma BNP, and low DBP are all associated with re-hospitalization for HF, while high BUN was the only predictor of CV death in patients with ADHF. These 3 clinical parameters may be useful for predicting the outcome for patients with HF, and as markers of the response to treatment. Because high BUN blunted the predictive value of plasma BNP and DBP, there was a hierarchy of predictive power for these 3 parameters and BUN was tightly associated with future CV events in patients admitted for ADHF. In fact, high BUN was associated with an increased rate of re-hospitalization for HF irrespective of either BNP or DBP.

In the present study, the majority of enrolled patients had DCM, suggesting that the present conclusion may be more applicable to patients with DCM. Indeed, the prevalence (76.9%) of DCM in the present study was greater than in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study (24.0%),[6] suggesting that the severity of HF in the present study was higher than average. Therefore, the present results may be more applicable to patients with DCM. Indeed, the Beta-blocker Evaluation of Survival Trial (BEST) study showed that low survival rate is associated with elevated BUN in patients with compensated chronic HF caused by primary or secondary DCM and a left ventricular ejection fraction (LVEF) ≤35%,[7] which is consistent with the present study. In contrast, according to the Acute Decompensated Heart Failure National Registry (ADHERE), the best single predictor of in-hospital death was high BUN (≥43 mg/dl) among 39 variables tested.[8] These results are in agreement with the present findings. An increase of BUN has been found to be a better predictor of mortality and re-hospitalization than the serum Cr level or the GFR in recent studies,[9,10] and these findings were also consistent with the present ones. We assessed CV mortality, however, while other studies investigated all-cause mortality,[7,9,10] so the present data suggest that abnormal renal function may cause deterioration of cardiac function that results in CV death. In patients with HF, low cardiac output decreases renal blood flow and GFR, leading to an increase of urea and thus BUN, so a low cardiac output is linked to high BUN. BUN may also be affected by intestinal function, nutritional status such as protein intake or systemic catabolism, and neurohumoral factors. For example, arginine vasopressin influences reabsorption of urea in the collecting tubule,[11] and norepinephrine has been reported to be increased in patients with BUN >21.0 mg/dl.[12] Therefore, the pathophysiological role of BUN may be different from that of serum Cr or GFR, and BUN may be a specific and independent biomarker of re-hospitalization and CV death in patients with ADHF because higher BUN is linked with CV death in HF patients. The BUN concentration is not only influenced by tubular re-absorption of urea in the kidneys, but also by protein intake and systemic catabolism, so high BUN may be related to multiple aspects of the pathophysiology of CHF.

The present study has indicated that high BNP and low DBP are also associated with a higher risk of re-hospitalization. Cheng et al found that BNP <430 pg/ml at the time of discharge was a strong negative predictor of re-hospitalization,[13] and the Outcomes of a Prospective Trial of Intravenous Milrinone for