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

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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-

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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

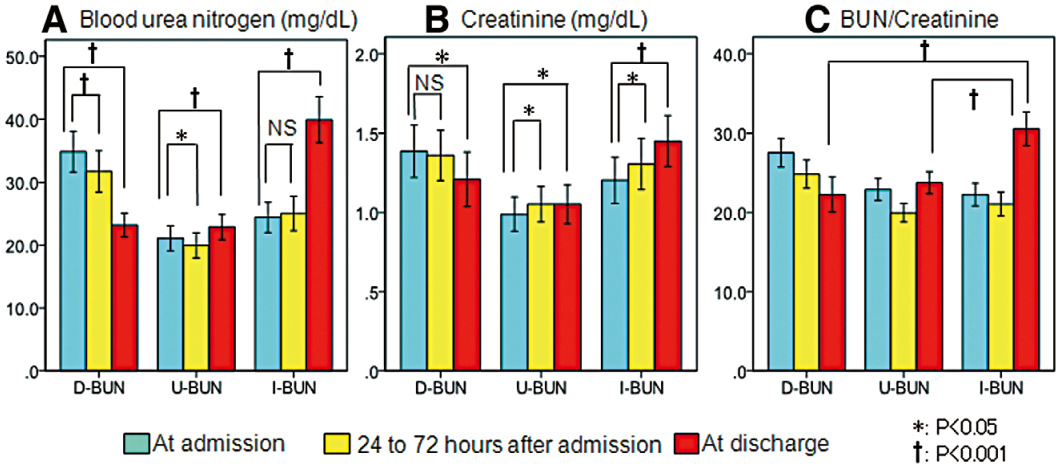

Figure 1. (**A**) Changes in BUN levels during hospitalization for AHFS. (**B**) Changes in creatinine level during hospitalization. (**C**) Changes in BUN/creatinine ratio during hospitalization. AHFS, acute heart failure syndrome; BUN, blood urea nitrogen.

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.

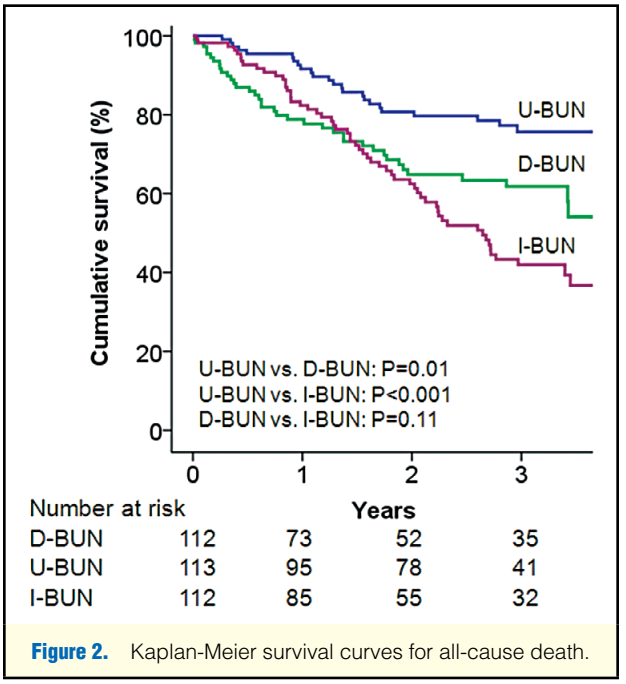

Figure 2. Kaplan-Meier survival curves for all-cause death.

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.

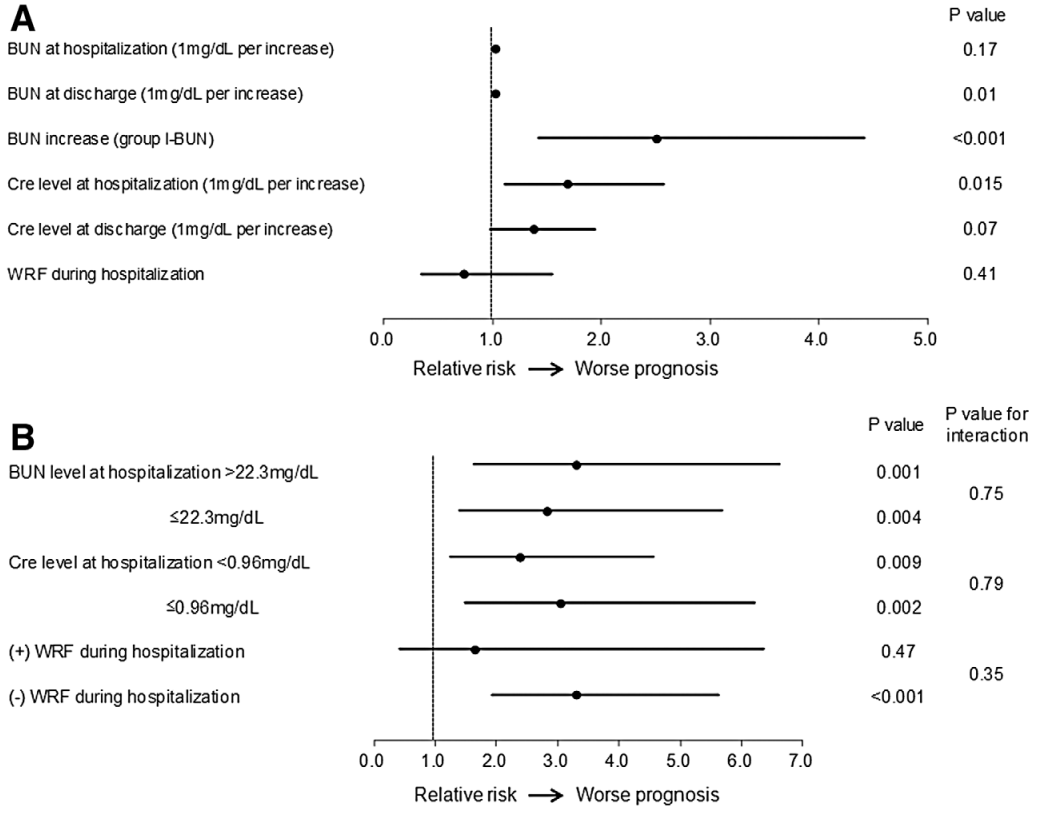

Figure 3. Multivariable logistic analysis. (**A**) Models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge and BUN increase and WRF during hospitalization for all-cause death. (**B**) Subgroup analysis of prognostic value of BUN increase 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·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 24–72 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.

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Disclosures

Conflict of Interest: None.

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