ORIGINAL RESEARCH ARTICLE

Persistent high blood urea nitrogen level is associated with increased risk of cardiovascular events in patients with acute heart failure

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Abstract

Aims The association between kinetics of blood urea nitrogen (BUN) levels in hospital and cardiovascular outcomes in patients with acutely decompensated congestive heart failure (HF) is unclear. We aimed to estimate the impact of changes in BUN level during hospitalization on clinical prognosis in patients with acute HF.

Methods and results A total of 353 consecutive patients that were urgently hospitalized due to acutely decompensated HF and discharged alive were divided into four subgroups depending on their BUN level at admission and discharge, using a cut-off level of 21.0 mg/dL. Among 206 patients with high baseline BUN level, 46 (22%) and 160 (78%) had normal and persistent high BUN levels at discharge, respectively. In contrast, of the 147 patients with normal baseline BUN level, 55 (37%) and 92 (63%) had high and normal BUN levels at discharge, respectively. During the observational period after discharge, Kaplan–Meier analysis showed the highest rate of combined outcome of cardiovascular death and HF readmission in patients with persistent high BUN (log-rank test: $P < 0.001$). After adjustment for comorbidities, the hazard ratio for a combined outcome was significantly lower in patients with normalized BUN level compared with those with persistent high BUN (hazard ratio 0.48, 95% confidence interval 0.23–0.99, $P = 0.049$).

Conclusions Persistent high BUN levels in hospital are associated with an increased risk of cardiovascular death and HF readmission. Normalization of BUN levels during hospitalization may be associated with long-term clinical outcomes.

Introduction

A recent multicentre cohort study demonstrated that high blood urea nitrogen (BUN) levels were associated with poor cardiovascular (CV) outcomes in patients with compensated heart failure (HF) and reduced left ventricular ejection fraction (LVEF).[1] BUN clearance is regulated by the glomerular filtration rate (GFR) and by the reabsorption of urea in the collecting duct.[2,3] These processes lead to the activation of neurohumoral factors such as vasopressin, which acts to decrease the GFR and increase tubular urea reabsorption.[2,4–6]

Previous reports have observed that BUN levels correlate with the neurohumoral response of the kidneys.[1,7,8] Given that the tubular reabsorption of urea is predominantly dependent on neurohumoral activation,[4,9] an elevated BUN level may be a surrogate marker for renin–angiotensin–aldosterone system (RAAS) activity, as well as a marker related to reduction of glomerular filtration.[1,4,7,8] Vasopressin regulates vascular tone and free-water reabsorption through the vasopressin V1a and V2 receptors in the collecting duct. Thus, high baseline BUN levels in patients with acute HF represent activated free-water reuptake in the collecting duct.[10]

Although BUN and BUN/creatinine (Cr) ratio on admission have been reported to be associated with CV mortality in HF patients,[11] the impact of BUN levels at discharge on long-term prognosis among acutely decompensated HF patients has not been fully evaluated. Accordingly, this study aimed to assess the prognostic impact of baseline values and changes in BUN levels during hospitalization on clinical outcomes in acute HF patients.

Methods

Study population and endpoints

The present study initially included 444 consecutive patients who were urgently hospitalized for acute decompensation of chronic HF or acute HF in a single CV centre between July 2013 and February 2016. Patients were diagnosed with HF using the Framingham HF diagnostic criteria.[12] After the exclusion of 41 patients who were receiving regular haemodialysis, 403 consecutive patients were divided into two groups according to their admission BUN level, with a cut-off set at 21.0 mg/dL, as per previous studies.[1] A total of 353 patients were recruited into the final study, after the exclusion of 43 patients who died in hospital and 7 patients with unavailable BUN data at discharge. This final group was further divided into four subgroups according to patients' BUN levels at admission and discharge, using the cut-off value stated previously (*Figure 1*). We compared clinical profiles, medications, and in-hospital and long-term prognosis among groups. The primary endpoint of this study

was a composite of CV death post-discharge and readmission due to decompensation of HF. CV death included death resulting from an acute myocardial infarction, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV haemorrhage, and death due to other CV causes.

Additionally, to evaluate the relationship between in-hospital changes in BUN levels and clinical outcomes after discharge, we divided the study population into two groups according to percent changes in BUN levels during hospitalization, with a cut-off set at 0% (*Figure S1B*). The study protocol was approved by the hospital's ethics committee, and patient enrolment was carried out according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data collection and follow-up

For each patient, we recorded admission and discharge data for the following parameters: (i) vital signs, including physical findings; (ii) New York Heart Association classification; (iii) blood pressure (BP); (iv) oral medications; and (v) laboratory values, including haemoglobin, albumin, total bilirubin, renal function [BUN, Cr, and estimated GFR (eGFR)], serum sodium concentration, C-reactive protein, lipid profiles, and haemoglobin A1c. Echocardiographic parameters including left atrial diameter (LAD), left ventricular end-diastolic diameter, LVEF, the ratio of mitral inflow E velocity to early diastolic velocity of lateral mitral annulus (E/e' ratio), and right ventricular systolic pressure were evaluated during hospitalization.

Figure 1 Patient flow chart. BUN, blood urea nitrogen; HF, heart failure.
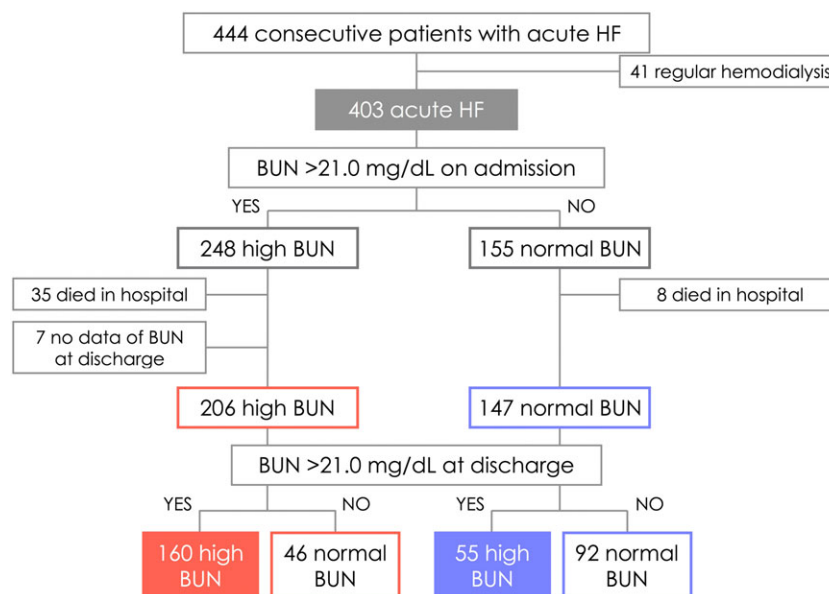
A patient was defined as hypertensive if they had a systolic BP >140 mmHg or were on antihypertensive therapy. Diabetes mellitus was diagnosed if a patient had a fasting plasma blood glucose level ≥126 mg/dL on two separate occasions, or ≥200 mg/dL at any time, or if they were receiving anti-hyperglycaemic agents including insulin. Dyslipidemia was diagnosed by a low density lipoprotein cholesterol level ≥140 mg/dL, high density lipoprotein cholesterol level <40 mg/dL, triglyceride level ≥150 mg/dL, or if the patient was receiving lipid-lowering therapy. Chronic kidney disease was defined as an eGFR <45 mL/min/1.73m^2 (calculated by the Cockcroft–Gault formula). The parameters listed previously were compared among subgroups.

After hospital discharge, outpatient office visits were scheduled bimonthly, and patients were contacted by telephone if they missed a scheduled clinic visit.

Statistical analysis

Values are expressed as mean ± standard deviation, percentiles, median with interquartile range in tables, and mean ± standard error in figures. The independent Student's *t*-test or the non-parametric equivalent Mann–Whitney U-test was used to compare continuous parameters between two groups. The Kruskal–Wallis test was used to compare continuous parameters among ≥3 groups. Fisher's exact test was used to evaluate categorical variables. Significant parameters in univariate logistic analysis were analysed using a forward stepwise logistic regression test to exclude confounding factors and to identify the independent predictors for raised BUN. Kaplan–Meier analysis was performed in order to evaluate the differences between the groups. Univariate and multivariable Cox regression analyses were performed in order to evaluate the association between in-hospital BUN kinetics and prognosis. In multivariable analysis, age, sex, sodium levels at admission, haemoglobin levels at admission, eGFR at admission, and brain natriuretic peptide (BNP) at admission were used for adjustment. To evaluate whether a change in BUN during the hospitalization is associated with prognosis independent of changes in preexisting renal markers, the absolute change in Cr was also adjusted for in multivariable models. Further, additive discriminative ability of BUN changes group was evaluated by comparing the area under the curves (AUC) of receiver operating characteristic curves analysis using binary techniques of two prediction models for combined endpoint according to the method of DeLong *et al.*[13]: basic risk model constructed with aforementioned known risk factors (age, sex, sodium levels at admission, haemoglobin levels at admission, eGFR at admission, and BNP at admission) plus absolute changes in Cr and BUN kinetic model (basic risk model plus BUN group). A two-sided *P*-value <0.05 was considered statistically significant.

Results

Of 403 patients enrolled in this study, 248 patients (62%) had a BUN level >21.0 mg/dL on admission, and 155 patients (38%) had normal BUN levels (*Figure 1*). There were 35 in-hospital deaths in the high-BUN group and 8 in-hospital deaths in the normal BUN group (14.1% and 5.2%, respectively, *P* = 0.005). These patients, along with an additional seven in the high baseline BUN group for whom discharge BUN data were unavailable, were excluded from the final study. The data from 353 patients who were alive at discharge were included in the final analysis. Of the 206 surviving patients with a high baseline BUN level, 160 (78%) had high BUN levels (persistent high-BUN group), and 46 (22%) patients had normal BUN levels (normalized BUN group) at discharge. In contrast, of the 147 patients with normal baseline BUN levels, 55 patients (37%) had high BUN levels (increased BUN group) and 92 (63%) had normal BUN levels (preserved BUN group) at discharge.

Clinical profiles

(i) High vs. normal baseline BUN patients

Table 1 shows the baseline characteristics of the study participants. Firstly, the high baseline BUN population included significantly older patients with higher rates of hypertension, diabetes, atrial fibrillation, and prior revascularization; higher levels of Cr, BUN/Cr ratio, C-reactive protein, and BNP; as well as a lower diastolic BP, haemoglobin level, and sodium concentration. The New York Heart Association functional class did not differ significantly between the two groups. Echocardiographic findings showed a significantly larger LAD, a higher E/e' ratio, and a higher prevalence of reduced LVEF in the high baseline BUN population (*Table 1*). At discharge, the high baseline BUN group was observed to have a significantly higher systolic BP, C-reactive protein, and BNP; lower haemoglobin and albumin; and worse renal function (*Table S1*).

In terms of medications on admission, the high baseline BUN population received furosemide, thiazide, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and inotropes more frequently than the normal baseline BUN population (*Table 2*). The prevalence of all medications at discharge except beta-blockers and calcium channel blockers differed significantly between groups. Among them, only aldosterone antagonists were administered more frequently in the normal baseline BUN population.

(ii) Four subgroups stratified by BUN at admission and discharge

Of those patients admitted with a high baseline BUN level, the persistent high-BUN group was older, had lower levels of

Table 1 Baseline clinical profiles of the study population

Variables	All patients n = 353	High BUN at baseline n = 206	At discharge High BUN n = 160	Normal BUN n = 46	P value	Normal BUN at baseline n = 147	At discharge High BUN n = 55	Normal BUN n = 92	P value	P value High vs. normal baseline BUN
Age, year	73 ± 15	76 ± 12	76 ± 11	73 ± 13	0.08	69 ± 17	77 ± 13	64 ± 18	<0.001	0.002
Age >75 years old	186 (53%)	119 (58%)	100 (63%)	19 (41%)	0.010	67 (46%)	36 (65%)	31 (34%)	<0.001	0.030
Sex, male	229 (65%)	142 (69%)	112 (70%)	30 (65%)	0.54	87 (59%)	32 (58%)	55 (60%)	0.85	0.07
BMI, kg/m²	24 ± 5	24 ± 5	24 ± 5	24 ± 5	0.96	24 ± 5	24 ± 5	24 ± 5	0.96	0.66
Hypertension	238 (67%)	154 (75%)	119 (74%)	35 (76%)	0.81	84 (57%)	41 (75%)	43 (47%)	0.001	<0.001
Diabetes	142 (40%)	94 (46%)	71 (44%)	23 (50%)	0.50	48 (33%)	21 (38%)	27 (29%)	0.27	0.016
Dyslipidemia	169 (48%)	108 (52%)	83 (52%)	25 (54%)	0.77	61 (41%)	28 (51%)	33 (36%)	0.07	0.052
Smoking	183 (52%)	116 (56%)	88 (55%)	28 (61%)	0.48	67 (46%)	23 (42%)	44 (48%)	0.48	0.052
Atrial fibrillation	173 (49%)	117 (57%)	93 (58%)	24 (52%)	0.47	56 (38%)	23 (42%)	33 (36%)	0.47	<0.001
Prior PCI/CABG	96 (27%)	70 (34%)	52 (33%)	18 (39%)	0.40	26 (18%)	13 (24%)	13 (14%)	0.14	<0.001
Prior myocardial infarction	58 (16%)	41 (20%)	31 (19%)	10 (22%)	0.68	17 (12%)	12 (22%)	5 (5%)	0.006	0.042
Prior stroke	60 (17%)	34 (17%)	30 (19%)	4 (9%)	0.11	26 (18%)	14 (25%)	12 (13%)	0.06	0.78
NYHA class										
III	197 (56%)	116 (56%)	91 (57%)	25 (54%)	0.87	81 (55%)	35 (64%)	46 (50%)	0.12	0.83
IV	156 (44%)	90 (44%)	69 (43%)	21 (46%)	0.87	66 (45%)	20 (36%)	46 (50%)	0.12	0.83
Systolic BP, mmHg	131 ± 29	129 ± 26	130 ± 25	128 ± 28	0.56	134 ± 32	136 ± 31	133 ± 33	0.28	0.47
Diastolic BP, mmHg	72 ± 19	70 ± 16	70 ± 17	69 ± 14	0.85	75 ± 22	77 ± 21	74 ± 23	0.26	0.042
Heart rate, b.p.m.	88 ± 24	86 ± 23	85 ± 23	90 ± 25	0.12	89 ± 25	87 ± 22	91 ± 27	0.75	0.23
Lab data										
Haemoglobin, g/dL	12.2 ± 2.7	11.7 ± 2.9	11.5 ± 3.0	12.6 ± 2.1	<0.001	12.9 ± 2.3	13.0 ± 2.2	12.8 ± 2.4	0.63	<0.001
Albumin, g/dL	3.6 ± 0.6	3.6 ± 0.5	3.6 ± 0.6	3.7 ± 0.7	0.20	3.6 ± 0.6	3.7 ± 0.7	3.7 ± 0.6	0.90	0.54
Total bilirubin, mg/dL	1.1 ± 0.7	1.1 ± 0.7	1.1 ± 0.7	1.3 ± 0.8	0.07	1.1 ± 0.7	1.2 ± 0.7	1.2 ± 0.6	0.86	0.30
BUN, mg/dL	29 ± 17	39 ± 17	41 ± 18	30 ± 11	<0.001	16 ± 3	18 ± 2	15 ± 3	<0.001	<0.001
Creatinine, mg/dL	1.45 ± 1.00	1.86 ± 1.13	1.99 ± 1.13	1.41 ± 1.02	<0.001	0.93 ± 0.30	1.02 ± 0.24	0.88 ± 0.33	0.009	<0.001
BUN/Cr ratio	22.0 ± 8.5	23.7 ± 8.9	23.4 ± 8.6	24.8 ± 10.1	0.59	19.7 ± 7.1	19.6 ± 6.1	19.8 ± 7.7	0.65	<0.001
eGFR, mL/min/1.73m²	48.1 ± 28.2	34.9 ± 18.7	31.9 ± 16.8	45.2 ± 21.2	<0.001	66.6 ± 28.8	55.3 ± 16.5	73.4 ± 32.4	<0.001	<0.001
Sodium, mEq/L	139 ± 5	138 ± 5	138 ± 5	138 ± 4	0.25	140 ± 4	141 ± 4	140 ± 4	0.15	<0.001
C-reactive protein, mg/dL	2.01 ± 4.03	2.55 ± 4.48	2.28 ± 4.30	3.44 ± 4.97	0.042	1.28 ± 3.21	1.49 ± 4.51	1.15 ± 2.14	0.27	<0.001
BNP, pg/mL	1002 ± 1165	1227 ± 1405	1299 ± 1522	971 ± 832	0.21	686 ± 565	721 ± 522	666 ± 590	0.20	<0.001
LDL-C, mg/dL	89 ± 32	88 ± 33	87 ± 33	91 ± 33	0.53	90 ± 30	87 ± 31	91 ± 30	0.53	0.64
HDL-C, mg/dL	52 ± 16	53 ± 16	53 ± 15	52 ± 16	0.68	50 ± 17	55 ± 21	49 ± 14	0.06	0.08
HbA1c, %	6.4 ± 1.2	6.4 ± 1.1	6.4 ± 0.9	6.5 ± 1.5	0.95	6.5 ± 1.3	6.5 ± 1.1	6.5 ± 1.5	0.77	0.71
Echocardiographic findings										
LAD, mm	47 ± 12	49 ± 12	49 ± 12	48 ± 14	0.43	45 ± 10	48 ± 12	43 ± 8	0.046	<0.001
LVDd, mm	55 ± 11	56 ± 11	56 ± 11	56 ± 12	0.89	55 ± 11	56 ± 12	54 ± 11	0.25	0.22
LVEF, %	40 ± 12	39 ± 12	39 ± 12	39 ± 13	0.90	41 ± 13	40 ± 12	42 ± 14	0.40	0.13
LVEF <50%	242 (69%)	150 (73%)	120 (75%)	30 (65%)	0.19	92 (63%)	36 (65%)	56 (61%)	0.58	0.048
E/e'	18.3 ± 8.9	19.6 ± 9.9	19.5 ± 9.1	20.1 ± 12.1	0.55	16.8 ± 7.3	18.0 ± 7.3	16.0 ± 7.2	0.09	0.042
RVSP, mmHg	43 ± 15	44 ± 14	44 ± 16	44 ± 11	0.62	42 ± 15	42 ± 12	42 ± 16	0.54	0.22

BNP, brain natriuretic peptide; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; Cr, creatinine; E/e', ratio of mitral inflow E velocity to early diastolic velocity of lateral mitral annulus; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LAD, left atrial diameter; LDL-C, low density lipoprotein cholesterol; LVDd, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RVSP, right ventricular systolic pressure.

Table 2 Medications

Variables	All patients n = 353	High BUN at baseline n = 206	At discharge High BUN n = 160	At discharge Normal BUN n = 46	P value	Normal BUN at baseline n = 147	At discharge High BUN n = 55	At discharge Normal BUN n = 92	P value	P value High vs. normal baseline BUN
Furosemide										
Admission	221 (63%)	148 (72%)	118 (74%)	30 (65%)	0.26	73 (50%)	31 (56%)	42 (46%)	0.21	<0.001
Daily dose, mg	20 (0–30)	20 (0–40)	20 (0–40)	20 (0–23)	0.06	0 (0–20)	20 (0–20)	0 (0–20)	0.33	<0.001
Discharge	306 (87%)	191 (93%)	149 (93%)	42 (91%)	0.68	115 (78%)	47 (85%)	68 (74%)	0.10	<0.001
Daily dose, mg	20 (20–40)	30 (20–40)	40 (20–40)	20 (18–40)	0.003	20 (10–40)	20 (10–40)	20 (0–40)	0.64	<0.001
In-hospital furosemide use	309 (88%)	184 (89%)	144 (90%)	40 (87%)	0.59	125 (85%)	51 (93%)	74 (80%)	0.06	0.25
Oral use	191 (54%)	112 (54%)	89 (56%)	23 (50%)	0.51	79 (54%)	30 (55%)	49 (53%)	>0.99	0.91
IV use	240 (68%)	141 (68%)	109 (68%)	32 (70%)	>0.99	99 (67%)	46 (84%)	53 (58%)	0.001	0.91
Total IV dose, mg	20 (0–73)	30 (0–80)	40 (0–80)	30 (0–85)	0.95	20 (0–60)	40 (10–80)	10 (0–50)	0.002	0.07
Aldosterone antagonist										
Admission	122 (35%)	77 (37%)	60 (38%)	17 (37%)	0.95	45 (31%)	18 (33%)	27 (29%)	0.67	0.21
Discharge	204 (58%)	107 (52%)	82 (51%)	25 (54%)	0.71	97 (66%)	42 (76%)	55 (60%)	0.040	0.009
Thiazide										
Admission	58 (16%)	46 (22%)	40 (25%)	6 (13%)	0.09	12 (8%)	4 (7%)	8 (9%)	0.76	<0.001
Discharge	55 (16%)	41 (20%)	37 (23%)	4 (9%)	0.031	14 (10%)	6 (11%)	8 (9%)	0.66	0.011
Tolvaptan										
Admission	11 (3%)	9 (4%)	7 (4%)	2 (4%)	>0.99	2 (1%)	0 (0%)	2 (2%)	—	0.13
Discharge	48 (14%)	37 (18%)	33 (21%)	4 (9%)	0.06	11 (7%)	3 (5%)	8 (9%)	0.71	0.005
Beta-blocker										
Admission	165 (47%)	111 (54%)	81 (51%)	30 (65%)	0.08	54 (37%)	21 (38%)	33 (36%)	0.78	0.002
Discharge	255 (72%)	156 (76%)	115 (72%)	41 (89%)	0.016	99 (67%)	43 (78%)	56 (61%)	0.030	0.09
ACE-I/ARB										
Admission	211 (60%)	139 (67%)	113 (71%)	26 (57%)	0.07	72 (49%)	34 (62%)	38 (41%)	0.016	<0.001
Discharge	267 (76%)	166 (81%)	131 (82%)	35 (76%)	0.38	101 (69%)	43 (78%)	58 (63%)	0.06	0.012
Calcium channel blocker										
Admission	103 (29%)	61 (30%)	47 (29%)	14 (30%)	0.89	42 (29%)	19 (35%)	23 (25%)	0.22	0.91
Discharge	95 (27%)	63 (31%)	52 (33%)	11 (24%)	0.27	32 (22%)	12 (22%)	20 (22%)	0.99	0.07
Digoxin/PD-IIIi										
Admission	59 (17%)	43 (21%)	35 (22%)	8 (17%)	0.51	16 (11%)	7 (13%)	9 (10%)	0.58	0.014
Discharge	58 (16%)	43 (21%)	31 (19%)	12 (26%)	0.32	15 (10%)	5 (9%)	10 (11%)	0.73	0.009

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; PDE-IIIi, phosphodiesterase III inhibitor.

haemoglobin and C-reactive protein, and poorer renal function compared with the normalized BUN group. Of those patients admitted with normal BUN levels, the group with increased BUN at discharge was older, had a larger proportion of patients with hypertension and impaired renal function, and a larger LAD compared with the preserved BUN group. At discharge, the persistent high-BUN group had a significantly lower systemic BP and persistent low haemoglobin than the normalized BUN group (*Table S1*; *Figure S2*).

The high baseline BUN population had a significantly higher BUN/Cr ratio on admission compared with the normal baseline BUN population (23.7 vs. 19.7, *P* < 0.001); however, this difference was not observed at discharge. The BUN/Cr ratio at discharge was similar between the persistent high-BUN group and the increased BUN group, as well as between the preserved BUN group and the normalized BUN group (25.4 vs. 27.3, *P* = 0.12; 18.7 vs. 20.2, *P* = 0.72, respectively). In terms of change in BUN during hospitalization, absolute change was higher in the increased BUN group than the persistent high-BUN group (12.6 vs. 1.7 mg/dL, *P* < 0.001; *Figure 1A*).

With respect to admission medications in the high baseline BUN population, patients in the increased BUN group were more likely to be on an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker compared with those in the preserved BUN group (*Table 2*). However, at discharge, there were more patients taking natriuretic drugs and fewer patients taking beta-blockers in the persistent high-BUN group compared with the normalized BUN group. In contrast, among patients with normal baseline BUN levels, the increased BUN group was more likely to be taking an aldosterone antagonist and a beta-blocker compared with the preserved BUN group.

Prognosis

During 342 days of median follow-up after discharge, there were 99 combined events, including 18 CV deaths and 81 readmissions due to HF (72 in the persistent high-BUN group, 10 in the normalized BUN group, 4 in the increased BUN group, and 13 in the preserved BUN group). Kaplan–Meier analysis of the four subgroups revealed the highest rate of composite endpoints in the persistent high-BUN group (*P* < 0.001, *Figure 2*).

In univariate Cox regression analysis, the normalized BUN, preserved BUN, and increased BUN groups showed a significantly lower hazard ratio (HR) compared with the persistent high-BUN group (*Table 3*). This finding retained significance even after adjustment for other comorbidities and absolute changes in Cr. Receiver operating characteristic curves analysis was performed for the two risk prediction models. Although both the basic risk model (AUC: 0.70, 95%

Figure 2 Combined outcome of cardiovascular death and rehospitalization due to heart failure after discharge. Comparisons of combined outcome among four subgroups categorized by blood urea nitrogen (BUN) levels at admission and discharge. Norm indicates normal.
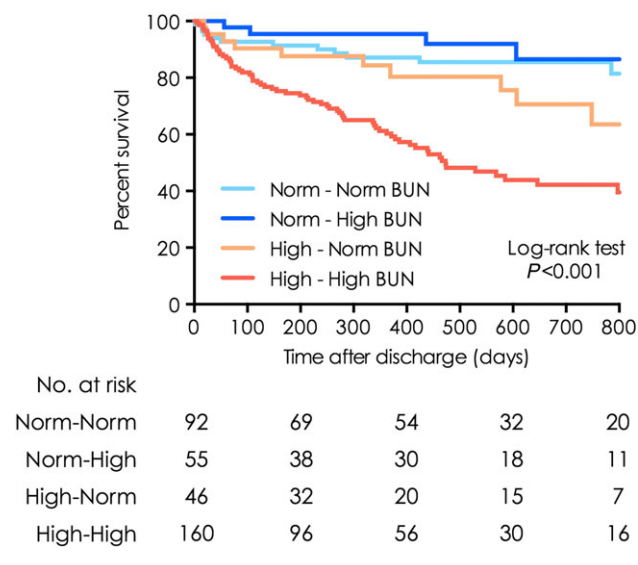
confidence interval: 0.64–0.76) and the BUN kinetic model (AUC: 0.74, 95% confidence interval: 0.69–0.80) showed significant predictive ability for the combined outcome, the BUN kinetic model showed significantly better prognostic predictive ability compared with the basic risk model in AUC (*P* = 0.023). Model calibration was checked with the Hosmer–Lemeshow test, and the results indicated good calibration of both models (*P* = 0.64 for basic risk model and *P* = 0.17 for BUN kinetic model, respectively).

Additionally, CV events during observational period were quite similar between patients who had increased BUN (*n* = 189) and decreased BUN (*n* = 164) during hospitalization (Log-rank *P* = 0.76, *Figure S1B*).

Predictors for elevated blood urea nitrogen

Logistic regression analysis revealed that high BUN levels (cut-off 26.5 mg/dL) and low haemoglobin levels (cut-off 11.5 g/dL) on admission were independent predictors for the persistency of high BUN levels in those patients with a high baseline BUN (HR 5.94, *P* < 0.001; HR 2.34, *P* = 0.031, respectively; *Table 4*).

Discussion

The principal findings of this retrospective analysis were that patients with persistent high-BUN had higher rates of combined events of CV death and HF readmission and that

Table 3 Multivariate analysis by Cox regression of cardiovascular death and heart failure hospitalization

Variables	Event rate (%)	Age-sex adjusted HR	95% CI	P value	Multivariate adjusted HR	95% CI	P value
Persistent high-BUN	45.0	1.0			1.0		
Normalized BUN	21.7	0.43	0.22–0.83	0.013	0.48	0.23–0.99	0.049
Preserved BUN	14.1	0.29	0.16–0.54	<0.001	0.40	0.18–0.85	0.018
Increased BUN	7.3	0.13	0.05–0.36	<0.001	0.19	0.06–0.55	0.002

BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio.

Table 4 Logistic regression analysis for persistent blood urea nitrogen

Variables	Cut-off	Univariate			Multivariate		
		OR	95% CI	P value	OR	95% CI	P value
Age	>75 years old	2.36	1.15–4.91	0.012	—	—	—
Haemoglobin	<11.5 g/dL	3.15	1.50–6.93	0.001	2.34	1.08–5.06	0.031
Creatinine	>1.5 mg/dL	3.08	1.46–6.75	0.001	—	—	—
BUN	>26.5 mg/dL	7.93	3.67–17.7	<0.001	5.94	2.64–13.4	<0.001

BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio.

normalizing patients' BUN levels before discharge may be associated with better outcome. The combined event rate in the normalized BUN group was similar to that observed in both groups with normal BUN levels on admission. These findings highlight the prognostic implications of variations in BUN levels between admission and discharge in patients with acute HF.

Blood urea nitrogen and renal function

Elevated BUN levels can predict renal hypoperfusion. This haemodynamic status of the kidney may be due to low cardiac output or renal venous congestion secondary to HF. Under conditions of reduced renal perfusion such as dehydration or low cardiac output, a complex neurohormonal mechanism is activated, which stimulates the release of vasopressin and activates the renal sympathetic nervous system and RAAS, all of which contribute to a disproportionate reabsorption of urea.[2,6,7,14] However, it is important to note that the BUN level does not fully reflect intrinsic renal function, as blood urea level is highly affected by the intake and catabolism of proteins, as well as by tubular reabsorption.[4,7,15] Instead, the BUN level reflects the neurohormonal mechanism described previously and is a more accurate marker of this mechanism than the eGFR. Therefore, baseline BUN levels represent the severity of HF and are better prognostic markers of adverse clinical events compared with Cr or eGFR.[7,16]

As we demonstrated, the presence of a reduced eGFR alone is not necessarily indicative of a poor prognosis in patients with cardiac dysfunction. Rather, the systemic conditions that lead to a reduction in glomerular filtration (i.e. those that activate neurohumoral responses in the kidneys) may be more important to long-term renal

prognosis and survival. At baseline, the persistent high-BUN group had higher Cr than the normalized BUN group; however, multivariate analysis excluded this parameter as an independent factor for high BUN persistency.

Prognosis

The results in this study indicate that sustained high levels in BUN throughout the course of a patient's admission may increase the risk of adverse CV events, independent of absolute changes in Cr. Importantly, only patients with persistent high-BUN had very poor long-term CV prognosis. However, interestingly, patients with a high baseline BUN level, which normalized by discharge fared better because the risk of CV events for this group was not different from that of patients with normal baseline BUN levels. Thus, normalization of BUN levels before hospital discharge in acute HF patients with high baseline BUN levels may translate into improved long-term CV survival. Main reason for the lowest risk of CV events in the increased BUN group, rather than the preserved BUN group should be a small sample size in this study, especially in the subgroup analysis. Regardless of small sample size, another possible reason is that some patients in the preserved BUN group did not achieve enough water excretion; in contrast, sufficient decongestion may have been achieved in the increased BUN group.

Blood urea nitrogen levels may represent the status of systemic circulation in addition to an intrinsic reserve of the kidneys. Therefore, the population with persistent high BUN during hospitalization should have had impaired organic perfusion because of damaged cardiac and renal functions even after discharge. This would explain the finding that BUN kinetics during hospitalization in patients with high baseline BUN level affected the risk of CV events after

discharge. Accumulating evidence has revealed that isolated renal parenchymal damage is related to long-term CV mortality. However, we found that both renal parenchymal damage and high BUN levels at discharge were required for poor CV outcomes. The results of this study highlight the importance of paying attention not only to the baseline BUN level but also to changes in this value and in the serum Cr levels over time, in order to improve long-term survival in acute HF patients.

Overall in-hospital mortality in this study was as high as 10.7%. Among them, in-hospital CV death was observed in 29 patients out of 404 enrolled patients (7.2%). This ratio was similar to the incidence reported in the largest Japanese registry of 7.7%.[17,18] It was still higher than that in other contemporary HF registries in Western countries. One of the possible reasons was that it has been difficult to implement clinical interventions that significantly influence the hospitalization period, because of a lack of sufficient facilities to care for HF patients after hospital discharge. Such social situations may also contribute to the higher in-hospital mortality rate than that reported in Western registries.

Medications and blood urea nitrogen

Certain cardioprotective drugs are known to have prognostic benefit in HF patients, and these were similarly administered to the four subgroups in this study. This is in contrast to the daily furosemide dose and the prevalence of other diuretics at discharge, which was higher in the persistent high-BUN group compared with other three groups. The association between high doses of loop diuretics and increased mortality has been reported to be largely dependent on the presence of an elevated BUN level, suggesting that the worsened survival associated with loop diuretics may be mediated by neurohumoral activation[1,7,8,17] In the present study, patients with persistent high BUN may have received excessive dose of diuretics, which may have caused renal hypoperfusion, activation of neurohumoral factors, and subsequently resulted in poor CV survival. Regarding with comparable hospitalization period between the persistent high-BUN group and the increased BUN group, patients who were failed to decrease BUN level during hospitalization should be the refractory population for improving congestive status. However, unregulated administration of high-dose diuretics may impair the restoration of BUN to normal in acute HF patients.[18–21] Accordingly, if physicians fail to restore BUN levels in acutely decompensated HF patients, appropriate dose titration of diuretics and supplementation of sufficient doses and types of cardioprotective drugs should be considered in order to improve post-discharge prognosis.

As per the current guidelines for the management of acute HF, beta-blockers and RAAS inhibitors were administered to patients in all subgroups. However, patients with high baseline BUN levels were already receiving treatment with intensive medication compared with those with normal baseline BUN levels. Therefore, patients with normal baseline BUN levels had more room for medical optimization of therapy. For example, aldosterone antagonists are proven prognosis-improving drugs, and these were administered aggressively to the normal baseline BUN population. In contrast, the prevalence of furosemide use at admission was already higher in the high baseline BUN population, and its dose was increased further in the persistent high-BUN group. This may have contributed to the difference in CV prognosis between the two groups high baseline BUN population subgroups.

Study limitations

This is a retrospective study performed in a single centre, which evaluated the results obtained from a small number of patients over a relatively short period of observation. The association between BUN at discharge and clinical outcomes may have been influenced by factors other than those explored in this study. Furthermore, to avoid overfitting for multivariate analysis, we excluded several baseline parameters without statistical significance under univariate analysis including systolic BP, heart rate, and total dose of intravenous furosemide during hospitalization.

Conclusions

A persistent high BUN level is associated with increased CV mortality in patients with acute HF. Normalization of BUN levels during hospitalization may improve long-term clinical outcomes.

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Conflict of interest

Funding

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Clinical parameters at discharge
Figure S1. In-hospital change in BUN and prognosis after discharge.
Figure S2. Changes of diverse parameters between admission and discharge.

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