ORIGINAL RESEARCH ARTICLE

Blood urea nitrogen variation upon admission and at discharge in patients with heart failure

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Abstract

Aims   Heart failure (HF) is one of the leading causes for hospitalization and mortality. After first admission with acute decompensated HF, some patients are in high risk for short-term and long-term mortality. These patients should be identified, closely followed up, and treated. It has been observed that blood urea nitrogen (BUN) on admission is a predictive marker for short-term mortality. Recently, it has been shown that higher BUN levels on discharge are also a bad prognostic predictor. However, the prognostic value of BUN alteration during hospital stay was not investigated; therefore, we aimed to investigate the effect of BUN variation during hospitalization on mortality.

Methods and results   A retrospective study included patients with first hospitalization with the primary diagnosis of HF. The patients were divided into four groups on the basis of the values of BUN on admission and discharge, respectively: normal-normal, elevated-normal, normal-elevated, and elevated-elevated. Four thousand seven hundred sixty-eight patients were included; 2567 were male (53.8%); the mean age was 74.7 ± 12.7 years. The 90 day mortality rate in the normal-normal group was 7% lower than that in the elevated-normal (14.6%) and normal-elevated (19.3%) groups; P value < 0.01. The 90 day mortality in the elevated-elevated group (28.8%) was significantly higher than that in the other groups; $P < 0.001$. During the 36 month follow-up, these results are maintained. While sub-dividing BUN levels into <30, 30–39, and >40 mg/dL, higher BUN levels correlated with higher 90 day mortality rate regardless of creatinine levels, brain natriuretic peptide, or age. Moreover, BUN on admission and on discharge correlated better with mortality than did creatinine and glomerular filtration rate at the same points.

Conclusions   The BUN both on admission and on discharge is a prognostic predictor in patients with HF; however, patients with elevated levels both on admission and on discharge have the worst prognosis. Moreover, worsening or lack of improvement in BUN during hospitalization is a worse prognostic predictor. To the best of our knowledge, this is the first trial to discuss the BUN change during hospitalization in HF.

Introduction

Heart failure (HF) is the most common diagnosis on discharge in patients older than 65 years, leading to high rate of readmission and excess of short-term and long-term mortality.[1]

Acute decompensated HF (ADHF) is defined as 'a rapid onset or change in the signs and symptoms of HF, resulting in the need for urgent therapy' and may present as acute pulmonary oedema/congestion, cardiogenic shock, increased jugular venous pressure, hepatomegaly, and/or peripheral oedema.[1]

Cardio-renal syndrome, a bidirectional interaction between the cardiovascular and renal systems, may influence these two systems simultaneously, leading to more complicated conditions.[2]

It is recommended to monitor kidney function tests during hospitalization of ADHF, including creatinine, calculated glomerular filtration rate (GFR), and blood urea nitrogen (BUN), or urea.[3] Creatinine and GFR are independent prognostic factors in HF. More recently, it has been observed that elevated BUN levels on admission, even with normal or slightly elevated creatinine, are correlated with mortality in patients with critical illness[4–7]; a similar correlation between elevated BUN on admission and mortality has been shown also in ADHF.[8,9] Recently, elevated BUN on discharge has been correlated with worse prognosis independently from GFR.[10]

The GFR is a more reliable marker of kidney function than is BUN because urea levels are affected by protein intake, catabolism, and tubular reabsorption.[8,11,12] However, BUN seems to be a better prognostic indicator than is GFR in patients with HF.[10] The exact mechanism behind this is not fully understood.[10]

Although the correlation between BUN on admission of patients with ADHF has been studied, and more recently Kajimoto *et al.*[10] showed a prognostic value of BUN on discharge, the BUN dynamics during hospital stay have not been studied. Therefore, we aimed to investigate the prognostic value of BUN variation and the BUN level on discharge as compared with BUN on admission.

Methods

We conducted a retrospective overview study of patients who were admitted to Rambam Health Care Campus, Haifa, Israel, between 1 December 2008 and 1 February 2018. Adult patients with first-time admission with the primary diagnosis of ADHF, who were admitted to the cardiac intensive care unit, cardiology department, or internal medicine department, were included. Patients with any other primary diagnosis (such as pulmonary embolism, cardiogenic shock, and acute coronary syndrome) were excluded. The study was approved by the local institutional review committee on human research. Demographic data, concomitant diseases, regular medications, laboratory results including BUN and creatinine on admission and on discharge, and recommended treatments on discharge, as well as mortality data, were collected by MDClone© software for data gathering.

Echocardiographic data were collected for each patient who underwent echocardiographic study during the index hospitalization or in the last 6 months prior to admission.

The BUN was divided into three groups: <30, 30–39, and ≥40 mg/dL. Creatinine was divided into <1.3, 1.3–1.5, and >1.5 mg/dL. GFR was calculated using Modification of Diet in Renal Disease equation. In-hospital and 90 day mortality was analysed according to the aforementioned categories. Furthermore, BUN in admission was compared with BUN on discharge and was divided into four groups: A, normal (<30 mg/dL) on both admission and discharge (normal-normal); B, normal on admission and elevated (≥30 mg/dL) on discharge (normal-elevated); C, elevated on admission and normal on discharge (elevated-normal); and D, elevated on both admission and discharge (elevated-elevated).

The primary outcome was 90 day mortality in the different BUN variation groups as compared with Group A. The secondary outcomes were long-term mortality (up to 36 months) in the different BUN variation groups, mortality according to BUN on admission and on discharge (separately), corrected to different age groups, creatinine levels, and brain natriuretic peptide (BNP) groups. Mortality data were retrieved both from the electronic medical records of the hospital and from the database of the Ministry of Interior, so that no patient would have been lost to follow-up.

Statistical analysis

The BUN was divided into normal and elevated groups as mentioned before. While analysing BUN in different creatinine, age, and BNP groups, BUN was divided into <30, 30–39, and >40. Creatinine was divided into normal (≤1.5 mg/dL) and elevated (>1.5 mg/dL); age was divided into <80, 80–90, and >90 years; and BNP levels were divided into <400, 400–1999, and >2000 pg/mL.

Using bi-variable logistic regression, we analysed the relationship between demographic data, BUN, other laboratory results, and overall mortality. All variables with P value < 0.05 were included in the multivariate analysis, using stepwise Cox regression.

We used a multivariate, stepwise logistic regression to identify variables with independent effect on mortality. The goodness of fit of the model was determined by Hosmer–Lemeshow test. The discrimination threshold was classified by area under a curve receiver operating characteristic (AUC ROC).

The correlation between the BUN levels and other laboratory test results was tested by the ordinal-by-ordinal Spearman correlation. The same statistical analysis was performed with creatinine and GFR as predictor of all the aforementioned outcomes.

The significance level for testing the statistical hypothesis was determined as $P < 0.05$. The data processing was done with SPSS statistical software 23, Chicago, Illinois.

Results

Between December 2008 and February 2018, 4768 patients were admitted to our hospital with first hospitalization of HF as a primary diagnosis; 2567 were male (53.8%). The mean time for follow-up was 30.7 ± 30.1 months, with median of 20.7 months. The mean age was 74.7 ± 12.7 years. The baseline characteristics of the cohort are presented in *Table 1*.

The multivariate analysis included parameters that were found statistically significant in a univariate analysis: age, atrial fibrillation, BUN, creatinine, white blood cells, BNP, and serum sodium on admission (*Table 2*).

Primary outcomes

The 90 day mortality for patients in the normal-normal BUN group was 7%, while in the elevated-normal, normal-

Table 2 Parameters that correlated with 90 day mortality in multivariate analysis

|		Odds ratio	95% confidence interval
Age	<80	1.00	
	80–90	2.03	1.71–2.41
	>90	3.56	2.72–4.67
Sodium ≤ 130 (mEq/L)		1.56	1.20–2.02
WBC (K/µL)		1.74	1.46–2.06
Bilirubin (mg/dL) > 1.2		1.53	1.18–1.97
BNP (pg/mL)	400>	1.00	
	401–1999	1.66	1.20–2.29
	>2000	2.70	1.86–3.93
BUN (mg/dL)	<30	1.00	
	30–39	1.85	1.48–2.32
	>40	3.52	2.94–4.21
Creatinine (mg/dL) > 1.5		2.49	2.09–2.96
Atrial fibrillation		1.36	1.15–1.6

WBC, white blood cell.
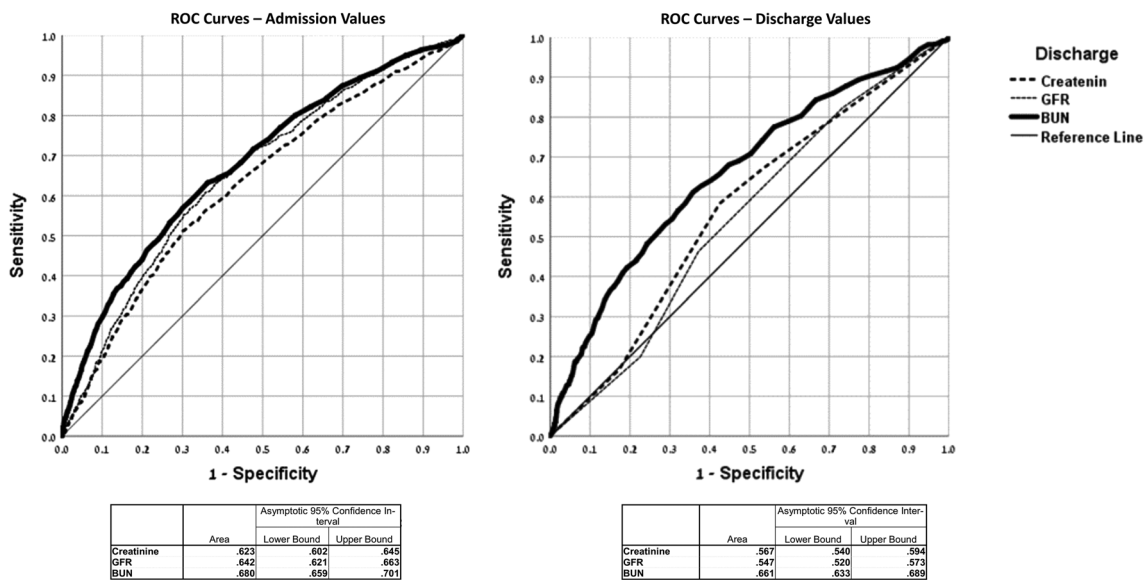
Table 1 Demographic, background, and lab data

Parameter		No. (%)	In-hospital mortality %	In-hospital mortality OR	90 day mortality %	90 day mortality OR
Female		2201 (46.2)	9	1.30 (1.05–1.60)	18.5	1.23 (1.06–1.43)
Age (years)	<60	584 (12.2)	4.3	1.0	8.7	1.0
	60–69	911 (19.1)	3.4	0.79 (0.46–1.35)	9.4	1.09 (0.76–1.57)
	70–79	1420 (29.8)	7.3	1.77 (1.13–2.77)	14.3	1.74 (1.26–2.41)
	80–89	1526 (32.0)	11.2	2.82 (1.83–4.34)	23.5	3.20 (2.35–4.37)
	>90	327 (6.9)	15.0	3.94 (2.38–6.52)	33.6	5.30 (3.67–7.65)
Diabetes		2521 (52.9)	7.2	0.81 (0.65–0.99)	15.7	0.83 (0.71–0.96)
Hypertension		3964 (83.1)	7.7	0.84 (0.64–1.10)	16.9	0.96 (0.79–1.17)
CKD		1229 (25.8)	9.4	1.28 (1.01–1.60)	21.2	1.48 (1.25–1.74)
IHD		1882 (39.5)	8.6	1.14 (0.91–1.4)	17.7	1.1 (0.94–1.28)
COPD		697 (14.6)	7.3	0.9 (0.66–1.22)	17.5	1.05 (0.85–1.29)
BUN admission, mg/dL	<20	1484 (31.1)	4.1	1.0	8.4	1.00
	20–29	1342 (28.1)	5.1	1.26 (0.89–1.80)	12.7	1.60 (1.26–2.04)
	30–39	779 (16.3)	9.1	2.34 (1.64–3.33)	19.3	2.62 (2.03–3.38)
	≥40	1163 (24.4)	15.4	4.24 (3.14–5.74)	31.2	4.98 (3.99–6.21)
BUN discharge, mg/dL	<20	863 (18.1)	1.6	1.0	6.3	1.00
	20–29	1074 (22.5)	2.5	1.56 (0.82–3.00)	9.3	1.54 (1.09–2.17)
	30–39	751 (15.8)	5.7	3.68 (2.00–6.79)	14.2	2.49 (1.77–3.51)
	≥40	1338 (28.1)	18.6	13.87 (8.03–23.93)	32.4	7.19 (5.34–9.69)
Creatinine admission, mg/dL	≤1.3	2521 (52.9)	5.1	1.0	11.7	1.00
	1.31–1.5	579 (12.1)	7.3	1.45 (1.01–2.08)	15.5	1.38 (1.07–1.79)
	>1.5	1597 (33.5)	12.6	2.69 (2.13–3.38)	25.7	2.61 (2.21–3.07)
Creatinine discharge, mg/dL	≤1.3	2036 (42.7)	3.1	1.0	10.0	1.00
	1.31–1.5	502 (10.5)	4.2	1.37 (0.83–2.26)	12.0	1.22 (0.90–1.66)
	>1.5	1418 (29.7)	16.9	6.35 (4.77–8.46)	29.5	3.75 (3.12–4.51)
GFR admission	>90	289 (6.1)	6.8	1.0	7.3	1.00
	60–90	1164 (24.4)	4.4	1.61 (0.76–3.43)	10.2	1.45 (0.90–2.36)
	30–59	2012 (42.2)	7.8	2.95 (1.44–6.07)	16.8	2.59 (1.63–4.09)
	<30	953 (19.6)	15.0	6.20 (3–12.8)	29.8	5.42 (3.40–8.63)
GFR discharge	>90	262 (5.5)	1.9	1.0	8.0	1.00
	60–90	908 (19)	3.0	1.58 (0.6–4.13)	9.7	1.23 (0.75–2.03)
	30–59	1665 (34.9)	5.2	2.83 (1.14–7.05)	14.5	1.95 (1.22–3.11)
	<30	890 (18.6)	22.2	14.71 (5.99–36.14)	34.9	6.16 (3.87–9.83)
HF type	HFpEF	1240 (26)	5.8	1.00	14.5	1.00
	HFmrEF	331 (6.9)	4.8	0.82 (0.47–1.44)	11.2	0.74 (0.51–1.08)
	HFrEF	1014 (21.2)	4.3	0.8 (0.55–1.16)	11.4	0.78 (0.61–0.98)

BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF type, heart failure type; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; OR, odds ratio.

Figure 1 Mortality rate in different BUN variation groups. 90d. mortality, 90 day mortality; Elevated(A)-Elevated(D), elevated BUN on admission, elevated on discharge; Elevated(A)-Normal(D), elevated BUN on admission, normal on discharge; Normal(A)-Elevated(D), normal BUN on admission, elevated on discharge; Normal(A)-Normal(D), normal BUN on admission, normal on discharge.
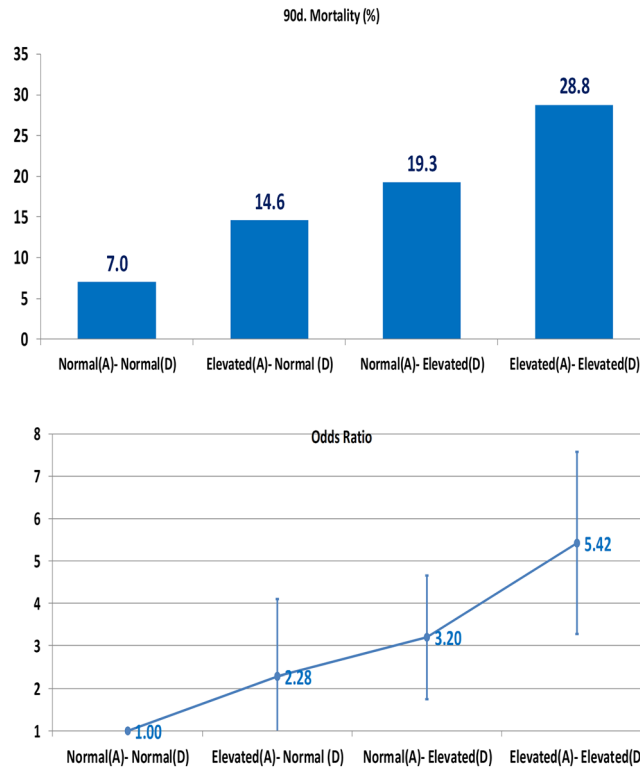
Figure 2 ROC curves for correlation between creatinine, BUN, and GFR on admission or discharge, and 90 day mortality rate. BUN, blood urea nitrogen; CR, creatinine; GFR, glomerular filtration rate.

	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Creatinine	.623	.602	.645
GFR	.642	.621	.663
BUN	.680	.659	.701

	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Creatinine	.567	.540	.594
GFR	.547	.520	.573
BUN	.661	.633	.689

Figure 3 Correlation between BUN and mortality rate in different creatinine groups. CR, creatinine.
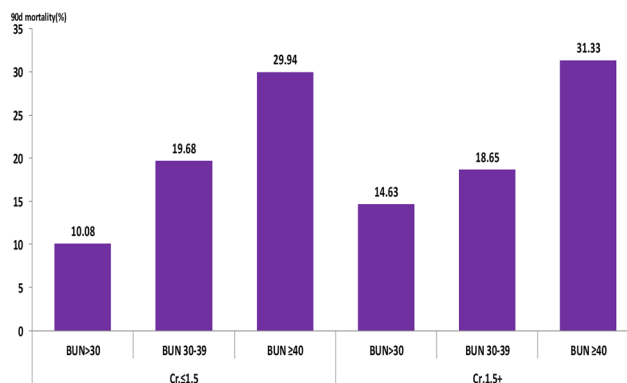
Figure 4 Correlation between BUN or creatinine and 90 day mortality in different age groups. BUN, blood urea nitrogen; CR, creatinine.
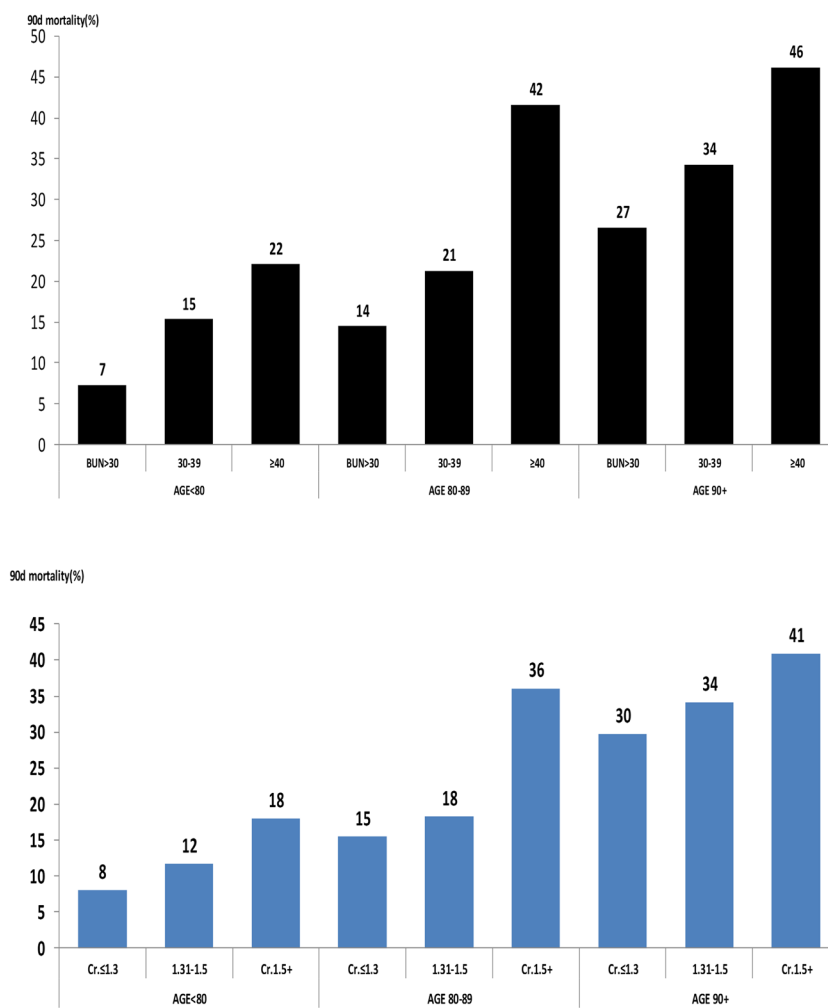
elevated, and elevated-elevated groups, it was 14.6%, 19.3%, and 28.8%, respectively. The 90 day mortality in the three latter groups were significantly higher than that of the first group; $P < 0.001$. It is noteworthy that the mortality in the last group was significantly higher than that of the first three ones; $P < 0.001$. No statistical significance was seen between elevated-normal and normal-elevated groups, 0.1 (*Figure 1*).

Secondary outcomes

The correlation between BUN, creatinine, or GFR on admission and mortality, as seen in AUC ROC, was 0.68, 0.623, and 0.642, respectively. The correlation with mortality as

seen in AUC ROC for BUN, creatinine, and GFR on discharge was 0.661, 0.567, and 0.547, respectively (*Figure 2*).

Blood urea nitrogen levels according to different creatinine, age, or brain natriuretic peptide groups

After BUN groups were divided into creatinine below and above 1.5 mg/dL, yet higher BUN levels correlated with higher mortality in both groups regardless of creatinine levels (*Figure 3*). The results were also divided into three age groups: <80 years, 80–90, and >90; similarly in these groups, higher BUN correlated with higher mortality (*Figure 4*). Notably, a correlation between creatinine and mortality was also observed in these groups, however, to a lesser extent than with BUN (*Figure 4*). A correction to BNP groups was also

Figure 5 Correlation between BUN or creatinine and 90 day mortality in different BNP groups. BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CR, creatinine.
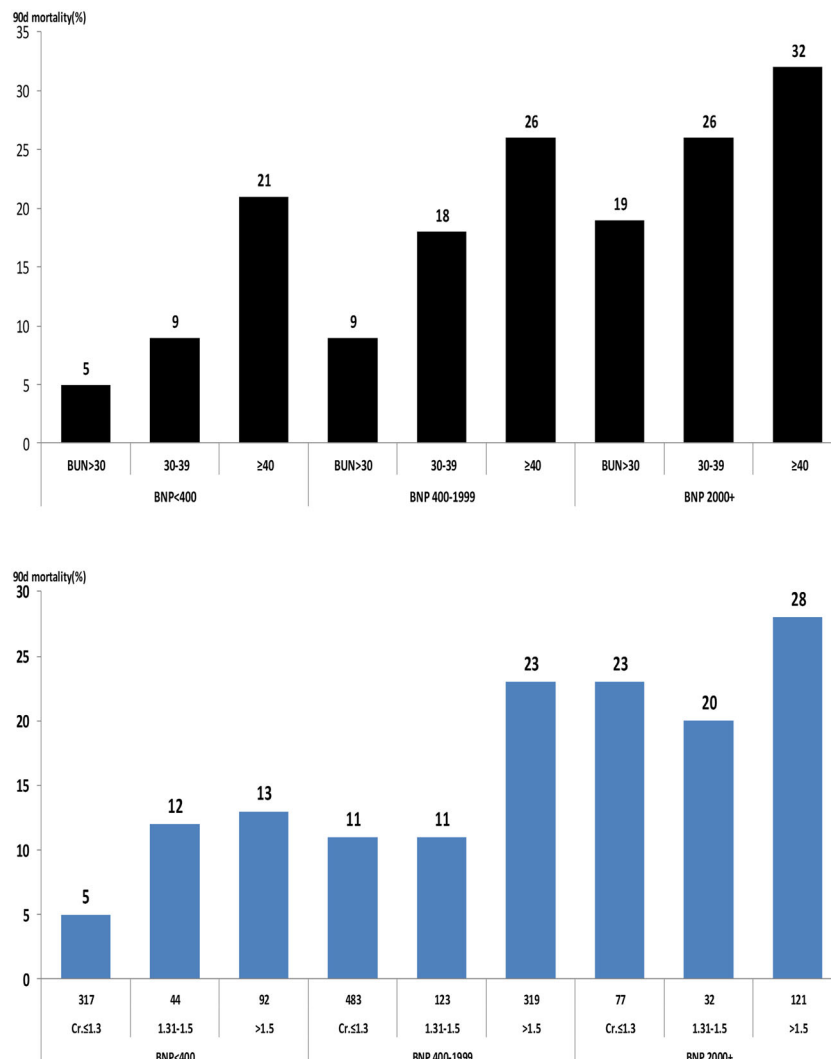
performed, showing a higher mortality rate in the higher BUN on admission groups; this observation was noted in all BNP groups. When the same analysis was finished using creatinine, this correlation was not demonstrated (*Figure 5*).

Long-term mortality

A Kaplan–Meier curve for 36 month mortality follow-up shows a higher survival rate in patients with normal BUN on admission and on discharge, followed by high BUN on either admission or discharge, and then the lowest survival for those who were admitted and discharged with elevated BUN levels, all statistically significant with $P < 0.001$ (*Figure 6*).
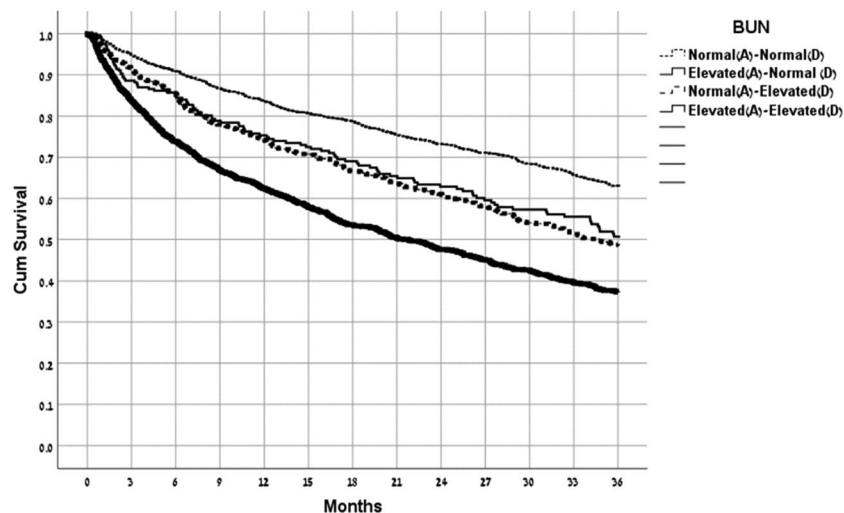
Discussion

This study shows that BUN is a predictor of short-term (90 day) and long-term mortality (up to 36 months) in patients with first admission of ADHF. BUN both on admission and on discharge showed a correlation with 90 day mortality and mortality during the first 36 months following admission; however, worst prognosis was seen in patients with elevated BUN on both admission and discharge.

The results show that worse prognosis is seen if the BUN levels deteriorate or even did not improve during hospital stay, regardless of BUN admission levels: patients with normal BUN levels on admission have worse prognosis if discharged with elevated levels as compared with normal levels on discharge; also, patients with elevated BUN on admission have worse prognosis if discharged with elevated levels as compared with normal levels on discharge. For short-term prognosis, worse BUN variation correlates with worse prognosis.

The BUN seems to have a prognostic value beyond kidney function. First, the BUN had a better correlation with prognosis than do creatinine and GFR as seen in the ROC curves; second, when BUN levels were divided to creatinine levels below and above 1.5 mg/dL, the predictive value was maintained in both groups. The exact mechanism by which BUN is correlated with prognosis is not fully understood. However, it is thought that BUN can be a marker of neurohormonal activation: urea undergoes free filtration and then is reabsorbed in the renal tubules,[12] which is influenced by the urine flow rate, and the arginine vasopressin influence on the urea transporter in the collecting ducts.[10,12–14] On the other hand, creatinine is freely filtered in the glomeruli but does not undergo further reabsorption. Our study shows that patients who were discharged with elevated BUN levels after admission for HF had worse prognosis, regardless of the BUN admission levels. The reason behind this is not fully known; however, it is conceivable to presume that failure to normalize BUN could be a sign of difficulty to achieve optimal control of extravascular volume without causing intravascular blood volume depletion with consequent activation of the hormonal axis and worsening of kidney function. Loop diuretics are the cornerstone of ADHF treatment[15]; however, this treatment activates the renin–angiotensin–aldosterone system.[15,16] Patients treated with high loop diuretic doses, mostly to control volume overload, might have deterioration in kidney function and also hormonal dysregulation.[15] High vasopressin levels in these patients may also contribute to higher BUN levels.[17]

Figure 6 Survival curves of different BUN variation groups. Elevated(A)-Elevated(D), elevated BUN on admission, elevated on discharge; Elevated(A)-Normal(D), elevated BUN on admission, normal on discharge; Normal(A)-Elevated(D), normal BUN on admission, elevated on discharge; Normal(A)-Normal(D), normal BUN on admission, normal on discharge.

The prognostic effect of BUN on admission is well established.[18–20] Recently, Kajimoto *et al.* showed that BUN on discharge has a prognostic value as well.[10] However, to our knowledge, this is the first study to discuss the prognostic value of BUN variation.

Our study has several limitations: this is a retrospective single-centre study; however, it is among the largest studies in this field. Furthermore, the study examined the correlation of BUN only on admission and on discharge, regardless of the levels during the hospital stay. Not less important, the endpoint of the hospitalization and the accumulative doses of diuretics were not uniform for the different patients.

In conclusion, BUN variation is a reliable prognostic predictor for both short and long outcomes in patients with ADHF, with worst prognosis seen in patients with elevated BUN in both admission and discharge. Worsening in BUN levels during hospitalization should be an alert for optimizing medical treatment before discharge and close follow-up.

Conflict of interest

The authors declare no conflict of interest.

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