VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2018, Vol. 25, No. 3, 371–376
DOI: 10.5603/CJ.a2017.0075

ISSN 1897–5593

Blood urea nitrogen in the prediction of in-hospital mortality of patients with acute aortic dissection

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Abstract

Background: *Blood urea nitrogen (BUN) has been shown to be associated with adverse cardiovascular disease outcomes. The aim of the present study was to evaluate the prognostic role of BUN in patients with acute aortic dissection (AAD). Hypothesis: BUN has correlation with in-hospital mortality of patients with AAD.*

Methods: *Patients admitted to the emergency room within the first 24 h of onset of AAD were included in the study. BUN levels were measured on admission and the endpoints were mortality during hospitalization after receiving surgical or endovascular repair.*

Results: *A total of 192 patients with AAD were enrolled. During hospitalization, 19 patients died and 173 patients survived. Increased levels of BUN (8.9 [7.0–9.7] vs. 6.0 [5.1–7.2] mmol/L, $p < 0.001$) were found in non-survivors compared with those survived. Using multivariable logistic analysis, BUN was an independent predictor of in-hospital mortality in patients with AAD (OR 1.415, 95% CI 1.016–1.971, $p = 0.040$). Furthermore, using receiver operating characteristic analysis, the optimal cutoff value for BUN was 6.95 mmol/L. Under this value, the area under the curve was 0.785 (95% CI 0.662–0.909, $p < 0.001$) and the sensitivity and specificity to predict in-hospital mortality was 78.9%, and 72.2%, respectively.*

Conclusions: *Admission BUN levels were an independent predictor for in hospital mortality in patients with AAD.* (Cardiol J 2018; 25, 3: 371–376)

Key words: blood urea nitrogen, acute aortic dissection, in-hospital mortality

Introduction

The relationship between renal dysfunction and adverse cardiovascular disease outcomes have been well established in patients with coronary artery disease (CAD) [1] and in those with heart failure [2]. Prior studies utilizing serum creatinine, estimates of glomerular filtration rate (eGFR) or blood urea nitrogen (BUN) to investigate the prognostic role of renal dysfunction in cardiovascular disease have found that BUN is more sensitive than creatinine and eGFR in predicting poor clinical outcomes [1, 3, 4]. In fact, BUN has also been demonstrated to be a valid biomarker for disease severity and prognosis in many other conditions such as community-acquired pneumonia [5], acute pancreatitis [6] and acute intracerebral hemorrhage [7].

Acute aortic dissection (AAD) is a life-threatening disorder that necessitates immediate management. Previous studies have demonstrated that kidney injury is a risk factor for both short and long term mortality in patients with AAD [8, 9]. However, these studies used serum creatinine

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Received: 08.03.2017 Accepted: 20.05.2017

as a surrogate marker for renal dysfunction and whether BUN could also provide some prognostic significance in these patients is unknown. Hence, the aim of the present study was to evaluate the relationship between BUN and in hospital mortality in patients admitted with AAD.

Methods

Study population

Herein is retrospectively investigated the medical records of patients with AAD admitted to the First Affiliated Hospital of Wenzhou Medical University between December 2012 and June 2016. The study was reviewed and approved by the ethics committee of the hospital and informed consent was waived due to its retrospective nature.

The diagnosis of AAD was confirmed by multidetector computed tomography scan and the type of AAD was classified in accordance with Stanford University criteria. Patients were included in the present study if they fulfilled the following criteria: (1) the time interval between symptoms onset and hospital admission of ≤ 24 h; (2) receiving surgical or endovascular repair for AAD during hospitalization. Exclusion criteria included: (1) presence of AAD for more than 24 h; (2) diagnosis with Marfan syndrome; (3) prior history of aortic dissection (AD).

Treatment

For patients with confirmed diagnosis of AD, urapidil, sodium nitroprusside or nitroglycerine were was administered intravenously to reduce systolic blood pressure (SBP) to 100–120 mmHg. Beta-blocker was administered to all patients except those with the contraindication.

All type A AD patients and a small part of type B AD patients underwent surgery repair via cardiopulmonary bypass. Endovascular repair was performed using commercially available endografts with the patients under general anesthesia.

Data collection

The following clinical data were collected on admission: age, sex, presence of hypertension, CAD, dyslipidemia, diabetes mellitus (DM), smoking and drinking habits, type of AAD, aortic diameter, blood pressure, heart rate, and laboratory data.

Endpoint

The study endpoint was defined as all-cause mortality during hospitalization.

Statistical analysis

Normality of continuous data was assessed using the Shapiro-Wilk test. Continuous variables are presented as the mean ± standard deviation or median and interquartile range according to whether they follow normal distributions. Categorical variables are presented as proportions. Comparisons between groups were performed with unpaired Student t tests for normally distributed continuous variables and Wilcoxon Mann-Whitney tests for non-normally distributed continuous variables. Categorical variables were compared by χ^2 tests or Fisher's exact test when appropriate. Univariate analysis and multiple logistic regression analysis were used to identify the predictors of in-hospital mortality. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value for BUN in predicting in-hospital mortality with high sensitivity and specificity. A p value < 0.05 was considered to be statistically significant. All the statistical analyses were performed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical characteristics

Six hundred twenty six patients were identified with a diagnosis of AD, of whom 251 were admitted within 24 h after onset of symptoms. Among them, 8 patients diagnosed with Marfan syndrome, 9 patients with prior history of AD and 42 patients died during hospitalization with conservative treatment were excluded from analysis. A total of 192 patients met our eligibility criteria and were included in the present study. During hospitalization, 19 patients died and 173 patients survived.

Patient characteristics are shown in Table 1. There were no significant differences in sex, hypertension, CAD, dyslipidemia, DM, smoking, alcohol use, aortic diameter, heart rate and neutrophil counts between the two groups. Compared with survivors, the non-survivors were older (62 [50–66] vs. 50 [44–60] years, p = 0.03), had a higher percentage of type A AD (78.9% vs. 43.9%, p = 0.003). The non-survivors had a significantly lower SBP (116.2 ± 26.0 vs. 145.6 ± ± 26.0 mmHg, p < 0.001), diastolic blood pressure (DBP; 66.6 ± 15.5 vs. 80.2 ± 18.6 mmHg, p = 0.003), and hemoglobin (122 [111–133] vs. 132 [122–144] g/L, p = 0.006) on admission. In addition, white blood cell counts (14.8 [13.1–18.0] vs. 13.2 [11.2–15.8] $\times 10^9$/L, p = 0.047), creatinine

Table 1. Baseline characteristics of the patients.

Variable	All patients (n = 192)	Survivor (n = 173)	Non-survivor (n = 19)	P
Age [years]	51 (44-62)	50 (44-60)	62 (50-66)	**0.03**
Male	151 (78.6%)	135 (78.0%)	16 (84.2%)	0.388
Hypertension	137 (71.4%)	122 (70.5%)	15 (78.9%)	0.316
Coronary artery disease	1 (0.5%)	1 (0.6%)	0 (0%)	0.901
Dyslipidemia	1 (0.5%)	1 (0.6%)	0 (0%)	0.901
Diabetes mellitus	7 (3.6%)	6 (3.5%)	1 (5.3%)	0.524
Smoking	66 (34.4%)	61 (35.3%)	5 (26.3%)	0.612
Alcohol use	41 (21.4%)	39 (22.5%)	2 (10.5%)	0.181
Type A AD	91 (47.4%)	76 (43.9%)	15 (78.9%)	**0.003**
SBP [mmHg]	142.7 ± 27.4	145.6±26.0	116.2 ± 26.0	**< 0.001**
DBP [mmHg]	78.8 ± 18.7	80.2 ± 18.6	66.6 ± 15.5	**0.003**
Aortic diameter [mm]	39 (36–43)	39 (36–43)	41 (35–45)	0.329
Heart rate [bpm]	80.9 ± 16.6	80.5±16.3	84.4 ± 19.0	0.333
White blood cell [$\times 10^9$/L]	13.5 (11.2–16.0)	13.2 (11.2–15.8)	14.8 (13.1–18.0)	**0.047**
Neutrophil [$\times 10^9$/L]	12.0 ± 3.7	11.8 ± 3.6	13.3 ± 4.3	0.100
Hemoglobin [g/L]	132 (122–144)	132 (122–144)	122 (111–133)	**0.006**
Creatinine [mmol/L]	78.0 (64.0–102.8)	76.0 (63.0–96.0)	127.0 (83.0–150.0)	**< 0.001**
BUN [mmol/L]	6.1 (5.2–7.6)	6.0 (5.1–7.2)	8.9 (7.0–9.7)	< 0.001

Data are expressed as mean ± standard deviation, median (25th–75th percentile) or the number (percentages) of patients. The bold values indicate statistical significance; AD — aortic dissection; BUN — blood urea nitrogen; DBP — diastolic blood pressure; SBP — systolic blood pressure

Table 2. Univariable logistic regression for in-hospital mortality.

Variable	OR	95% CI	P
Age	1.037	0.999–1.075	**0.0054**
Type A AD	4.786	1.526–15.011	**0.007**
SBP [mmHg]	0.957	0.929–0.976	**< 0.001**
DBP [mmHg]	0.960	0.934–0.987	**0.004**
White blood cell [$\times 10^9$/L]	1.116	0.997–1.249	0.057
Hemoglobin [g/L]	0.965	0.940–0.992	**0.010**
Creatinine [mmol/L]	1.005	1.000–1.010	**0.037**
BUN [mmol/L]	1.330	1.118–1.582	**0.001**

CI — confidence interval; OR — odds ratio; rest abbreviations as in Table 1

(127.0 [83.0–150.0] vs. 76.0 [63.0–96.0] mmol/L, $p < 0.001$) and BUN (8.9 [7.0–9.7] vs. 6.0 [5.1–7.2] mmol/L, $p < 0.001$) levels were higher in the non-survivor group than in the survivor group.

Predictors for in-hospital mortality

Logistic regression was performed to identify potential predictors for in-hospital mortality in patients with AAD. Variables included in the univariable logistic regression analysis for in-hospital mortality were age, type A AD, SBP, DBP, white blood cell counts, hemoglobin, creatinine and BUN. Except for white blood cell counts, all variables included were significantly associated with in-hospital mortality in univariable logistic regression (Table 2). The multivariable logistic regression model for in-hospital mortality included all variables from the univariable analysis. The only variables that remained as independent predictors of in-hospital mortality were age (odds ratio [OR] 1.059, 95% confidence interval [CI] 1.003–1.119, $p = 0.039$), SBP (OR 0.962, 95% CI 0.928–0.998,

Table 3. Multivariable logistic regression for in-hospital mortality.

Variable	OR	95% CI	P
Age	1.059	1.003–1.119	**0.039**
Type A AD	2.099	0.451–9.774	0.345
SBP [mmHg]	0.962	0.928–0.998	**0.037**
DBP [mmHg]	1.000	0.955–1.047	0.992
White blood cell [$\times 10^9$/L]	1.113	0.946–1.310	0.196
Hemoglobin [g/L]	0.983	0.943–1.026	0.435
Creatinine [mmol/L]	0.996	0.984–1.007	0.469
BUN [mmol/L]	1.415	1.016–1.971	**0.040**

CI — confidence interval; OR — odds ratio; rest abbreviations as in Table 1.

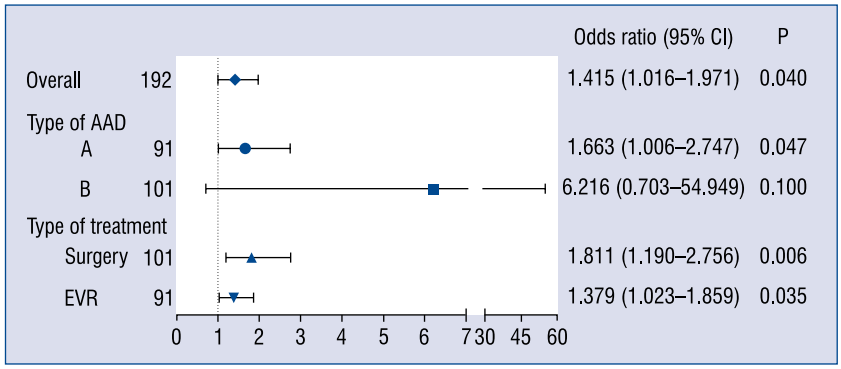

Figure 1. Odds ratios of blood urea nitrogen for predicting in-hospital mortality according to the type of acute aortic dissection (AAD) and treatment; CI — confidence interval; EVR — endovascular repair.

Table 4. Diagnostic value of blood urea nitrogen for in-hospital mortality.

AUC	Cut-off value	SE	95% CI	P	Sensitivity	Specificity
0.785	6.95	0.063	0.662–0.909	< 0.001	0.789	0.722

AUC — area under the curve; CI — confidence interval; SE — standard error

p = 0.0037) and BUN (OR 1.415, 95% CI 1.016––1.971, p = 0.040) (Table 3).

Given the high mortality rates in patients with type A AD and those who undergo surgery treatment, subgroup analysis was performed by the type of AD and treatment. In patients with type A AD, BUN was associated with high risk of in-hospital mortality (OR 1.663, 95% CI 1.006–2.747, p = 0.047). For patients with type B AD, BUN was not an independent predictor for in-hospital mortality. As for the subgroup, stratified by surgical or endovascular repair, BUN independently predicted in-hospital mortality (OR 1.811, 95% CI 1.190–2.756, p = 0.006; OR 1.379, 95% CI 1.023–1.859, p = 0.035, respectively) (Fig. 1).

ROC analysis

ROC analysis yielded an area under the curve (AUC) statistic of 0.785 (95% CI 0.662–0.909, p < 0.001) and the cut-off value of BUN to predict in-hospital mortality was 6.95 (sensitivity 78.9%, specificity 72.2%) (Table 4, Fig. 2).

Discussion

The main findings of the present study were that admission BUN levels were independently associated with in-hospital mortality in patients with AAD admitted within 24 h after onset of symptoms. When BUN was ≥ 6.95 mmol/L, the sensitivity and specificity for in-hospital mortality were 78.9% and 72.2%, respectively.

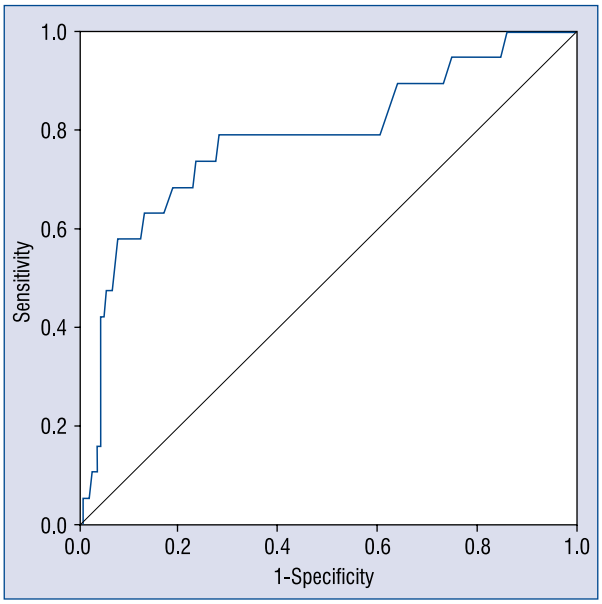

Figure 2. Receiver operating characteristic curve of blood urea nitrogen for predicting in-hospital mortality in patients with acute aortic dissection.

Urea is synthesized in liver via protein catabolism and blood urea is freely filtered at the glomerulus and undergoes tubular reabsorption. In the absence of enhanced protein catabolism, such as severe infection and burning, trauma, glucocorticoids therapy or high protein diet, urea levels in blood is determined by the GFR and tubular reabsorption. In the setting of AAD, hemodynamic disturbances lead to activation of the neurohormonal axis, resulting in increased sympathetic nervous system [10] and renin–angiotensin–aldosterone system activity [11]. Increased angiotensin and adrenergic stimulation decrease renal urea excretion via effects on vascular, glomerular, and tubular effects on the kidney. These neurohormonal responses cause renal vasoconstriction, decreases in glomerular ultrafiltration, and increases in proximal tubular sodium and water reabsoption. Consequently, the fluid delivery in the collecting conduct will decrease and urine flow will slow. Because urea reabsorption in the distal tubule is urine flow dependent, the decreased slowing of tubular flow will enhance urea reabsorption [12]. Besides, AAD can cause low cardiac output by forming pericardial effusion or myocardial ischemia secondary to coronary artery involvement. In order to preserve systemic perfusion, arginine vasopressin (AVP) is released as a compensatory mechanism. AVP can rapidly increase urea permeability in the collecting duct through phosphorylation and apical plasma-membrane accumulation of the urea transporter A1 (UT-A1) and subsequently lead to increased reabsorption of urea in the collecting duct [13]. Therefore, increased BUN level could be regarded as a surrogate marker for hemodynamic and neurohormonal alternations in AAD.

The prognostic implication of increased BUN has been evaluated in patients with acute decompensated heart failure (ADHF). Studies have demonstrated that in the setting of ADHF, patients with high admission BUN level had low cumulative survival rate [14, 15]. In addition, Miura et al. [16] have shown that in patients admitted for ADHF, a BUN increase during hospitalization also indicated worse long-term prognosis, independent of renal function. Moreover, increased BUN is also associated with worse prognosis in a wide spectrum of patients with acute coronary syndromes [1, 17]. However, few data are available on the relationship between BUN and clinical outcomes in patients with AAD. The present findings indicate for the first time that in patients with AAD receiving surgical or endovascular repair, high admission BUN levels were associated with high in-hospital mortality. BUN may be a promising marker for risk stratification in patients with AAD.

Limitations of the study

This study has several limitations. First, because of its observational nature, some factors that may have influenced the outcome of AD were unavailable, such as D-dimer and C-reactive protein. Second, this study was carried out in patients receiving surgical or endovascular repair for AAD, excluding those receiving conservative treatment, which could limit results to extrapolate to a wider group of patients. Furthermore, this study was carried out in a single institution and enrolled a relatively small number of patients, which precluded subgroup analysis. A future prospective study with a larger sample size is required to confirm these findings.

Conclusions

In summary, the present study found that elevated BUN levels were an independent predictor of in-hospital mortality in patients with AAD receiving surgical or endovascular repair. Serum BUN may serve as a simple marker to identify high risk patients.

Funding: This study was supported by a grant from the Natural Science Foundation of Zhejiang Province (LQ17H020005).

Conflict of interest: None declared

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