Does Baseline BUN Have an Additive Effect on the Prediction of Mortality in Patients with Acute Pulmonary Embolism?

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Abstract

Background: In patients with heart failure, elevated levels of blood urea nitrogen (BUN) is a prognostic factor. In this study, we investigated the prognostic value of elevated baseline BUN in short-term mortality among patients with acute pulmonary embolism (PE).

Methods: Between 2007 and 2014, cardiac biomarkers and BUN levels were measured in patients with acute PE. The primary endpoint was 30-day mortality, evaluated based on the baseline BUN (≥14 ng/L) level in 4 groups of patients according to the European Society of Cardiology’s risk stratification (low-risk, intermediate low-risk, intermediate high-risk, and high-risk).

Results: Our study recruited 492 patients with a diagnosis of acute PE (mean age=60.58±16.81 y). The overall 1-month mortality rate was 6.9% (34 patients). Elevated BUN levels were reported in 316 (64.2%) patients. A high simplified pulmonary embolism severity index (sPESI) score (OR: 5.23, 95% CI: 1.43–19.11; P=0.012), thrombolytic or thrombectomy therapy (OR: 2.42, 95% CI: 1.01–5.13; P=0.021), and elevated baseline BUN levels (OR: 1.04, 95% CI: 1.01–1.03; P=0.029) were the independent predictors of 30-day mortality. According to our receiver-operating characteristics analysis for 30-day mortality, a baseline BUN level of greater than 14.8 mg/dL was considered elevated. In the intermediate-low-risk patients, mortality occurred only in those with elevated baseline BUN levels (7.2% vs. 0; P=0.008).

Conclusion: An elevated baseline BUN level in our patients with PE was an independent predictor of short-term mortality, especially among those in the intermediate-risk group.

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Introduction

Acute pulmonary embolism (PE), with a fatality rate of 7% to 11%, is a potentially life-threatening disease that requires urgent medical or invasive intervention; a delay in its diagnosis can, therefore, lead to increased morbidity and mortality. After the diagnosis of acute PE, risk stratification for appropriate management is necessary, particularly among patients with unstable hemodynamics. A combination of biomarkers for comprehensive risk stratification and clinical and imaging risk scores will yield a more desirable strategy for the selection of higher-risk patients from the point of view of management and follow-up. Currently, a measurement of cardiac troponins, especially high-sensitivity cardiac troponin T (hs-cTnT), natriuretic peptides, and heart-type fatty-acid-binding protein, is recommended for risk stratification and management. Research has previously confirmed that an elevated level of blood urea nitrogen (BUN) is a prognostic factor in patients admitted for decompensated heart failure. Even a mild elevation in BUN levels may be predictive of a worse outcome in patients with acute heart failure. This elevation may reflect the cumulative effects of systemic hemodynamic and neurohormonal changes, leading to renal hyperperfusion. On the other hand, an increase in sympathetic activity and hemodynamic changes is common in the acute PE setting. In patients with acute PE, not least in those with massive PE, postulating that elevated levels of BUN could be associated with poor clinical outcomes in patients with acute PE, we sought to determine the prognostic value of elevated BUN levels in short-term mortality among such patients.

Methods

The present observational study was conducted on 492 consecutive patients with a diagnosis of acute PE admitted to our center, a tertiary care teaching hospital, between January 2007 and October 2014. Patients who developed PE during their hospitalization in our center were not included. The local institutional review board approved the study.

The PE diagnosis was confirmed via a pulmonary spiral computed tomography angiography (CTA) scan by the demonstration of partial or complete filling defects in the pulmonary circulation in the majority of the patients. Otherwise, the diagnosis was confirmed through a ventilation perfusion scan. Those who had clinical contraindications to pulmonary spiral CTA scans underwent ventilation perfusion scan. Two-dimensional and Doppler echocardiographic examinations were performed within 48 hours after admission by experienced operators. RV dysfunction was defined as an RV mid-cavity diameter of greater than 35 mm or a tricuspid regurgitation gradient of greater than 30 mmHg on transthoracic echocardiography or an RV-to-left ventricular diameter ratio of equal to or greater than 1 on transthoracic echocardiography or CTA. The simplified pulmonary embolism severity index (sPESI) was calculated for all the patients. Patients with an sPESI score of 0 were considered low-risk and those with scores equal to or greater than 1 were considered high-risk. After peripheral venous blood collection, the levels of hs-cTnT and the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were determined via a fully-automated electrochemiluminescent assay with the Elecsys 2010 (Roche Diagnostics, Indianapolis, IN), and urea was measured photometrically with a Cobas Integra 400 plus chemistry analyzer (Roche Company). BUN was determined by converting urea to BUN in mg/dL with the following formula: BUN (mg/dL) = urea (mg/dL) / 2.14. Elevated biomarkers were regarded as either a minimum level of hs-cTnT of 14 ng/L or an NT-proBNP level of 600 pg/mL or greater.

According to the guidelines of the European Society of Cardiology (ESC), the patients were classified into 4 groups based on the short-term mortality risk: low-risk, intermediate low-risk, intermediate high-risk, and high-risk. Those with shock or hypotension (blood pressure <90 mmHg) were classified as high-risk. Normotensive patients with an sPESI score of 1 or greater were regarded as the intermediate-risk group. In this group, those with evidence of both RV dysfunction (by echocardiography or CTA) and elevated cardiac biomarker levels in the circulation were classified as intermediate high-risk. Patients with a normal RV and/or normal cardiac biomarker levels were considered to be intermediate low-risk. Finally, if the abovementioned parameters were normal, the patients were categorized as low-risk. Thereafter, short-term (30-day) mortality in each group was evaluated based on the baseline BUN level to determine whether an elevated baseline level of BUN had additive values for the prediction of short-term mortality. Short-term mortality was defined as death from any cause during a period of 30 days from admission.

The continuous variables were described as the mean±the standard deviation (SD), and the categorical variables were expressed as frequencies and percentages. All the patients were followed to evaluate short-term mortality (30-day mortality). A logistic regression model was applied to evaluate the univariate effects of baseline BUN and other variables on 30-day mortality. Moreover, a multivariable logistic regression model was used to assess the adjusted effects of baseline BUN on 30-day mortality controlling
for potential confounders. Variables with a P value of less than 0.2 in the univariate analyses were considered potential confounders. The adjusted and unadjusted effects of baseline BUN on 30-day mortality were reported through odds ratios (ORs) with 95% confidence intervals (CIs). The receiver-operating characteristics (ROC) curve and the Youden index were utilized to find the optimum cutoff point for the BUN level able to prognosticate short-term mortality.

The continuous and categorical variables were compared between the BUN-level groups using the Student t-test, the χ² test, or the Fisher exact test, whichever one was appropriate. IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp.), was applied to conduct the analyses.

Table 1. Baseline characteristics of the patients (N=492)*

| Variable                        | Alive (n=458)        | Dead (n=34)       | OR (95% CI)** | P     |
|---------------------------------|----------------------|-------------------|---------------|-------|
| Age (y)                         | 60.3±16.87           | 64.0±15.96        | 1.01 (0.99-1.04) | 0.224 |
| Male                            | 245 (53.5)           | 15 (44.1)         | 1.46 (0.72-2.93) | 0.293 |
| Heart rate (bpm)                | 100.7±19.4           | 107.5±17.7        | 1.01 (1.00-1.04) | 0.048 |
| Systolic blood pressure (mmHg)  | 130.8±22.6           | 124.2±15.6        | 0.98 (0.97-1.00) | 0.096 |
| Dyspnea                         | 406 (88.6)           | 31 (91.2)         | 1.32 (0.39-4.48) | 0.652 |
| Pleuritic chest pain            | 142 (31.0)           | 9 (26.5)          | 1.29 (0.52-3.22) | 0.582 |
| Syncope                         | 50 (10.9)            | 2 (5.9)           | 0.51 (0.12-2.19) | 0.366 |
| sPESI score (per 1 mg/dL)       | High 268 (58.5)      | 31 (91.2)         | 7.33 (2.21-24.31) | 0.001 |
| Low 190 (41.5)                  |                      |                   |               |       |
| Diabetes mellitus               | 84 (18.3)            | 6 (17.6)          | 0.92 (0.38-2.38) | 0.954 |
| Hypertension                    | 195 (42.6)           | 12 (35.3)         | 0.74 (0.35-1.52) | 0.408 |
| Smoking                         | 95 (20.7)            | 6 (17.6)          | 0.82 (0.33-2.03) | 0.667 |
| Immobility ≥ 3d                 | 128 (27.9)           | 7 (20.6)          | 0.67 (0.28-1.57) | 0.356 |
| Malignancy                      | 20 (4.4)             | 5 (14.7)          | 3.78 (1.32-10.78) | 0.013 |
| Surgery during the preceding 4 weeks | 65 (14.2)           | 3 (8.8)           | 0.58 (0.17-1.97) | 0.387 |
| RV dysfunction                  | 318 (69.4)           | 27 (79.4)         | 1.70 (0.72-3.99) | 0.225 |
| Elevated biomarkers (hs-cTnT or NT-proBNP) | 319 (71.5)       | 29 (85.3)         | 2.31 (0.87-6.10) | 0.091 |
| Serum BUN (mg/mL)               | 19.16±9.40           | 24.01±11.76       | 1.04 (1.01-1.070) | 0.006 |
| Serum hemoglobin (mg/mL)        | 13.6±2.3             | 14.0±2.3          | 1.06 (0.91-1.24) | 0.428 |
| Thrombolytic or thrombectomy    | 99 (21.6)            | 15 (44.1)         | 2.86 (1.40-5.83) | 0.004 |

*Data are presented as mean±SD or n (%)

**Age OR per 1 y; Heart rate OR per 1 bpm; Systolic blood pressure OR per 1 mmHg; Serum BUN OR per 1 mg/dL; Serum hemoglobin OR per 1 mg/dL; PE, Pulmonary thromboembolism; BUN, Blood urea nitrogen; NT-BNP, N-terminal prohormone of brain natriuretic peptide; hs-cTnT, High-sensitivity cardiac troponin T; sPESI, Simplified pulmonary embolism severity index; RV, Right ventricle

Table 2. Adjusted analyses for the evaluation of the associations between various variables and 30-day mortality

| Variable                        | OR (95% CI)**     | P     |
|---------------------------------|-------------------|-------|
| High sPESI score                | 5.23 (1.43-19.11) | 0.012 |
| Thrombolytic or thrombectomy    | 2.42 (1.14-5.13)  | 0.021 |
| Baseline BUN (per 1 mg/dL)      | 1.04 (1.01-1.07)  | 0.029 |
| Elevated biomarkers             | 1.49 (0.54-4.11)  | 0.437 |
| Malignancy                      | 2.93 (0.96-8.92)  | 0.058 |
| Systolic blood pressure (per 1 mmHg) | 0.99 (0.97-1.01) | 0.392 |
| Heat rate (per 1 bpm)           | 1.00 (0.98-1.02)  | 0.865 |

sPESI, Simplified pulmonary embolism severity index; BUN, Blood urea nitrogen

**Result**

The study population consisted of 492 patients at a mean age of 60.58±16.81 years. The overall mortality rate during the 30-day period was 6.9% (34 patients). The baseline characteristics of the patients, divided into alive and dead after the 30-day period, are illustrated in Table 1. The patients who died had significantly higher heart rates, sPESI scores, and serum BUN levels. They also more frequently received thrombolytic or thrombectomy therapy. Our adjusted analyses revealed that higher baseline sPESI scores and serum BUN levels were associated with 30-day mortality (OR: 5.23, 95% CI: 1.43–19.11; P=0.012) and (OR: 1.04, 95% CI: 1.01-1.07; P=0.006).
95% CI: 1.01–1.03; P=0.029), respectively. In addition, the mortality rate was significantly higher among those who received thrombolytic or thrombectomy therapy during the 30 days of follow-up (OR: 2.42, 95% CI: 1.014–5.13; P=0.021) (Table 2).

Thirty patients died in the group with high baseline BUN levels, while only 4 patients expired in the group with normal baseline BUN levels (9.5% vs. 2.3%; P=0.002). For a better evaluation of the association between the baseline level of BUN and 30-day mortality, we used the ROC analysis to identify the optimal BUN cutoff value for short-term mortality (Figure 1). According to the ROC analysis, a BUN level of greater than 14.8 mg/dL was considered elevated. Based on the baseline BUN level, the patients were divided into 2 groups. Totally, 316 (64.2%) patients had high BUN levels (>14.8 mg/mL). Those with higher baseline BUN had higher mortality during the short-term follow-up (Figure 2).

A comparison of the baseline characteristics of the patients based on their baseline BUN levels is shown in Table 3. The patients in the group with high BUN levels were significantly more frequently male and older. Moreover, in this group, syncope, high sPESI scores, diabetes mellitus, hypertension, dyslipidemia, and RV dysfunction were significantly more frequent. Additionally, a history of receiving thrombolytic or thrombectomy was significantly more common among the patients with a high BUN level. However, surgery during the preceding 4 weeks was more frequent in those with a normal baseline BUN level.

Figure 1. Receiver-operating characteristics (ROC) curve for 30-day mortality for the baseline blood urea nitrogen (BUN) level. The best cutoff...
value of BUN to predict mortality was 14.8 mg/dL with 88.2% sensitivity and 62.4% specificity (AUC: 0.64; 95% CI: 0.55–0.73; P=0.006).

According to the guidelines of the ESC, the patients were classified into 4 groups based on short-term mortality risks: 47 (9.6%) in the low-risk group, 250 (50.8%) in the intermediate low-risk group, 192 (39.0%) in the intermediate high-risk group, and 3 (0.6%) in the high-risk group. There was no 30-day mortality in the low- and high-risk groups. Mortality occurred in 11 (7.2%) patients in the intermediate low-risk group with elevated baseline BUN levels, whereas there was no mortality in the group with normal baseline BUN levels (P=0.008). The mortality rate was also higher in the intermediate high-risk patients with elevated baseline BUN levels than in those with normal baseline BUN levels; nevertheless, this difference did not constitute statistical significance (13.5% vs. 7.8%; P=0.288) (Table 4).

**Discussion**

Our results showed that patients with high baseline sPESI scores, high serum BUN levels, and history of thrombolytic or thrombectomy therapy had a higher rate of 30-day mortality. Not only were those with elevated baseline BUN levels (>14.8 mg/mL) significantly more frequently male and older but also they more frequently had syncope, high sPESI scores, diabetes mellitus, hypertension, dyslipidemia, and RV dysfunction. We found that the baseline BUN level had an additive value in the ESC’s classification among the intermediate-risk patients with acute PE, especially among those with intermediate low-risk. There was no mortality among the intermediate low-risk patients with normal baseline BUN levels, whereas 7.2% of the patients with elevated baseline BUN levels in this group died (P=0.008). This trend was also observed in the intermediate high-risk group, but the difference was not statistically significant.

Apart from the demonstrated and guideline-approved biomarkers, including troponin and natriuretic peptides, search for finding higher-risk patients based on new biomarkers was undertaken in previous studies. Voelkel et al. showed that the severity of pulmonary hypertension was associated with uric acid elevation. In another study, Nagaya et al. demonstrated that long-term mortality was higher in patients with primary pulmonary hypertension and high serum uric acid levels. Scherz et al. found that hyponatremia in patients presenting with PE was an independent predictor of short-term mortality and hospital readmission. Yazıcı et al. reported that red cell distribution width, together with cardiac troponin, was an independent predictor of short-term mortality in patients with PE. Babaoglu et al. investigated the importance of biomarkers in the risk stratification of patients with PE and found that the mean of the blood urea level in the low-risk group was significantly lower than that in the high-risk group; however, after analysis of covariance for age, the significance did not persist.

Previous research has confirmed that the level of BUN is a prognostic factor in patients admitted for decompensated heart failure. Indeed, even a mild elevation in the BUN level is predictive of a worse outcome in these patients. An increase in concentration-dependent urea reabsorption in proximal tubules secondary to a rise in the renin-angiotensin-aldosterone system activity, an increase in flow-dependent urea reabsorption in distal tubules secondary to a rise in the sympathetic nervous system activity, and the upregulation of urea transporters in the inner medullary collecting ducts secondary to an increase in arginine vasopressin release are the major pathophysiologic mechanisms of increased BUN levels in the heart failure setting.

Fonarow et al. in a large study showed that a BUN level of equal to or greater than 43 mg/dL was the most important predictor of increased in-hospital mortality in patients with acute decompensated heart failure. Elsewhere, Filippatos et
Moreover, the rate of short-term mortality was significantly higher in the intermediate low-risk patients with elevated baseline BUN levels. Although this trend was also observed in the intermediate high-risk group, the difference was not statistically significant. More studies with larger sample sizes and longer follow-up durations are required to evaluate the effects of this marker on the adverse outcomes of patients with acute PE.

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