Blood urea nitrogen is associated with long-term all-cause mortality in stable angina pectoris patients: 8-year follow-up results

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Background
Elevation of blood urea nitrogen (BUN) indicates renal dysfunction and is associated with increased mortality in cardiovascular diseases. We investigated the relationship between the BUN concentration measured at hospital admission and the long-term all-cause mortality in patients with stable angina pectoris (SAP).

Methods
The mortality rate of 344 patients who underwent coronary angiography (CAG) in our clinic due to SAP was analyzed during a mean follow-up period of 8 yrs.

Results
Age (p<0.001), male gender (p=0.020), waist circumference (p=0.007), body-mass index (p=0.002), fasting glucose (p=0.004), BUN (p<0.001), serum creatinine (Cr) (p<0.001), hemoglobin (p=0.015), triglyceride concentrations (p=0.033), and the Gensini score (p<0.001) were related to all-cause mortality as shown by univariate Cox regression analysis. Age (OR 1.056, 95 % CI 1.015–1.100, p=0.008), fasting glucose (OR 1.006, 95 % CI 1.001–1.011, p=0.018), BUN, (OR 1.077, 95 % CI 1.026–1.130, p=0.003), and the Gensini score (OR 2.269, 95 % CI 1.233–4.174, p=0.008) were significantly related with mortality as shown by multivariate Cox regression analysis. According to receiver operating characteristic analysis of the sensitivity and specificity of BUN and Cr for predicting mortality, the area under the curve values of BUN and Cr were 0.789 (p<0.001) and 0.652 (p=0.001), respectively. BUN had a stronger relationship with mortality than Cr. A concentration of BUN above 16.1 mg/dl had 90.1 % sensitivity and 60 % specificity for predicting mortality (OR=2.23).

Conclusion
In patients who underwent CAG due to SAP, the BUN concentration was associated with all-cause mortality during a mean follow-up period of 8 yrs.

Keywords
Stable angina pectoris; blood urinary nitrogen; long term mortality

For citation
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Introduction
Urea is the primary metabolite derived from turnover of dietary and tissue protein. Blood urea nitrogen (BUN) is about one-half (0.446) of the blood urea. The BUN concentration is determined by protein intake, endogenous protein catabolism, hydration status, hepatic urea synthesis, and renal urea excretion [1]. In addition, increased renin-angiotensin system activation, sympathetic activity, and antidiuretic hormone increase the BUN concentration by its passive absorption from renal proximal tubules [2–4]. This increase may cause an elevation of BUN in heart failure patients [5].

Renal dysfunction is a poor prognostic factor in cardiovascular diseases [6]. Serum creatinine (Scr) and estimated glomerular filtration rate (eGFR) are generally used for both prognosis and optimization of medical therapy. Although the BUN concentration is an essential indicator of neuroendocrine activation in left ventricular dysfunction, unlike Cr and eGFR, it does not have a strong relationship with renal function. [2–5] Elevation of the BUN concentration is an indicator of increased cardiovascular mortality during long-term follow-up, and it is associated with extremity ischemia and the extent of coronary artery disease (CAD) [7–10].

There has been no investigations of the relationship between BUN and long-term all-cause mortality in patients with stable angina pectoris (SAP). We evaluated the relationship between BUN and the long-term prognosis of patients who underwent coronary angiography (CAG) due to SAP.

Material and Methods
Study Population
This was a prospective, observational, cohort study. A total of 344 consecutive patients who presented with chest pain or...
The study was performed according to the Declaration of Helsinki, and it was approved by the local Ethics Committee. Informed consent was obtained from all patients before examination.

**Exclusion criteria**

The exclusion criteria were diagnosis of acute coronary syndrome in the past month, moderate or severe valvular heart disease, nonischemic cardiomyopathy, malignancy, history of coronary artery bypass graft surgery, acute or chronic liver disease, chronic renal failure (eGFR <30 ml/min/1.73 m²), chronic inflammatory diseases, and severe comorbid disorders.

**Demographical and laboratory data**

The patients were evaluated in terms of age and demographical properties. Arterial hypertension was defined as antihypertensive drug usage or documented blood pressure over 140/90 mmHg. Diabetes mellitus was described as a fasting plasma glucose concentrations over 126 mg/dl or glucose concentration over 200 mg/dl at any measurement or active antidiabetic treatment. Patients who were using tobacco products or who had quit smoking within the last year were considered as smokers. A family history of CAD was defined as either CAD or sudden cardiac death in a first-degree relative, before the age of 55 for men and 65 for women. C-reactive protein and routine biochemistry, including glucose, BUN, and lipids, were measured. Serum C-reactive protein was measured with a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0–0.8 mg/dl).

**Coronary angiography**

Standard selective CAG with at least four views of the left coronary system and two views of the right coronary artery was performed using the Judkins technique. Coronary angiograms were recorded on compact discs in DICOM format. Two experienced observers who were blinded to the patient’s clinical characteristics assessed the CAG images. Finally, the Gensini score was calculated [11].

**Mortality data acquisition**

The mortality data of patients were obtained from the official Population Administration.

**Statistical analysis**

Normality distribution patterns of variables were evaluated with the Kolmogorov-Smirnov test. Continuous, normally distributed variables are presented as mean values (standard deviation [SD]). Non-normally distributed variables are presented as medians with ranges. Categorical variables are expressed as percentages. The variables were compared with a 2-tailed, student t-test for continuous variables with a normal distribution or with the Mann–Whitney U test for those with a non-normal distribution. A Chi-Square test was used for categorical variables. Age and gender were adjusted using the General Linear Model or the Cox proportional hazards model for continuous variables and for selected time durations. A logistic regression model was used for categorical variables. The effects of the various variables on mortality were calculated by univariate Cox regression analysis. In these analyses, the variables with unadjusted p<0.1 were identified as confounding factors. These factors were included in the multivariate regression analyses to determine independent predictors of mortality. The predictive values of BUN and Cr were estimated by the areas under the receiver operating characteristic (ROC) curve. We used the DeLong test to compare the area under the curve (AUC) for each of these parameters. All the statistical tests were 2-tailed, and a p<0.05 value was considered significant. All the analyses were performed with SPSS version 16 (SPSS, Inc., Chicago, Illinois).

**Results**

A total of 223 male and 121 female patients were included in the study. Of the 344 patients who had CAG, 60 patients (17.4%) died at a mean follow-up period of 92.2±20 mos. Groups of patients were compared according to the mortality outcome. The mean age, male gender, BUN, Cr, fasting glucose, and Gensini score were higher in the mortality group. Waist circumference, BMI, triglyceride, and hemoglobin were lower in this group. White blood cell count (WBC) tended to be high in the mortality group. Other laboratory and demographic variables did not differ significantly (Table 1).

In the univariate analysis using Cox regression, age, male gender, waist circumference, BMI, fasting glucose, BUN, Cr, hemoglobin, triglyceride, and Gensini score were related to all-cause mortality. WBC did not reach statistical significance. Age, fasting glucose, BUN, and the Gensini score had the strongest relationships with mortality in the multivariate Cox regression analysis (Table 2).

Comparisons of the sensitivity and specificity of BUN and Cr for predicting mortality with the ROC analysis showed that the AUC values of BUN and Cr were 0.789 (p<0.001) and 0.652 (p=0.001), respectively. The BUN concentration seemed to have a stronger relationship with mortality than did the Cr concentration (Figure 1). A cut off value of BUN >16.1 mg/dl had 90.1% sensitivity and 60% specificity (OR=2.23) for predicting mortality according to the ROC analysis. In patients with BUN >16.1 mg/dl, mortality was higher on the Kaplan–Mayer chart (Figure 2).

**Discussion**

At 92 mos follow-up, age, BUN, fasting glucose, and the Gensini score had independent relationships with long-term mortality in SAP patients who underwent CAG.
The relationship between the BUN concentration and all-cause mortality was independent of the Cr concentration. Our study is the first to show the relationship between pretreatment BUN and long-term mortality in patients with SAP. An increase in Cr also had a significant relationship with long-term mortality.

**Table 1.** Correlation analysis of SAP patients with and without mortality

| Variable                          | Mortality (-), n=284 | Mortality (+), n=60 | p       | p*     |
|-----------------------------------|----------------------|---------------------|---------|--------|
| Age (yr)                          | 57.1±10              | 66.4±10.4           | <0.001  | NA     |
| Gender (male)                     | 62.5%                | 78.3%               | 0.019   | NA     |
| Hypertension                      | 58.6%                | 63.3%               | 0.506   | 0.762  |
| DM                                | 29.5%                | 38.3%               | 0.108   | 0.384  |
| Dyslipidemia                      | 74.3%                | 61.6%               | 0.047   | 0.138  |
| Family history (CAD)             | 38%                  | 26%                 | 0.106   | 0.225  |
| Current smoker                    | 23%                  | 20%                 | 0.616   | 0.979  |
| Waist circumference (cm)          | 106.5±18.9           | 99.1±18.7           | 0.010   | 0.323  |
| BMI (kg/m²)                       | 30.1±5               | 27.8±6.2            | 0.003   | 0.528  |
| BUN (mg/dl)                       | 16.26±4.5            | 21.4±7.08           | <0.001  | <0.001 |
| Cr (mg/dl)                        | 0.83±0.17            | 0.96±0.25           | <0.001  | 0.187  |
| Uric acid (mg/dl)                 | 5.1±1.4              | 5.4±1.6             | 0.194   | 0.110  |
| Glucose (fasting) (mg/dl)         | 114.5±37.7           | 132.1±71            | 0.006   | 0.420  |
| Total Cholesterol (mg/dl)         | 199.5±42.6           | 192.4±44.5          | 0.249   | 0.251  |
| LDL Cholesterol (mg/dl)           | 127.7±36.9           | 123.6±34.9          | 0.499   | 0.678  |
| HDL Cholesterol (mg/dl)           | 42.6±10.2            | 43.1±12.7           | 0.742   | 0.874  |
| TG (mg/dl)                        | 144.6±74.9           | 120.9±58.3          | 0.024   | 0.808  |
| WBC (10³/µl)                      | 7.1±2.02             | 7.6±2.3             | 0.093   | 0.414  |
| Hemoglobin (g/dl)                 | 13.9±0.7             | 13.4±1.9            | 0.015   | 0.135  |
| CRP (mg/dl)                       | 0.39 (0.24–0.63)     | 0.38 (0.22–0.74)    | 0.958   | 0.980  |
| Gensini Score*                    | 3.5 (0–22.2)         | 14.5 (1–52.6)       | <0.001  | <0.001 |
| ASA (dis.)                        | 75%                  | 78%                 | 0.821   | 0.357  |
| Clopidogrel (dis.)                | 53%                  | 56%                 | 0.402   | 0.629  |
| ACEI/ARB (dis.)                   | 47.2%                | 50.4%               | 0.696   | 0.943  |
| Beta blocker                      | 39.5%                | 41.6%               | 0.765   | 0.850  |
| CCB (dis.)                        | 14.2%                | 16.6%               | 0.637   | 0.764  |
| OAD/Insulin                       | 29%                  | 37%                 | 0.202   | 0.915  |
| Nitroglycerin                     | 14.2%                | 10.1%               | 0.384   | 0.086  |
| Statin                            | 73%                  | 60%                 | 0.766   | 0.609  |

* – adjusted for age and gender.

Data are mean ± SD, median with range, median with 25%–75% percentiles where indicated by, or as percentages. BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; dis, discharge; ASA, acetylsalicylic acid; OAD, oral antidiabetic; CHF, congestive heart failure; WBC, white blood cell; CRP, C-reactive protein; TG, triglycerides; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensinogen converting enzyme inhibitor; ARB, angiotensinogen receptor blocker; CCB, calcium channel blocker.
The neurohumoral response to arterial underfilling secondary
Therefore, GFR calculated by BUN may be lower than it actually
On the contrary, the urea is freely filtered at the glomerulus, but
Cr is filtered freely at the glomerulus. Renal tubules do not
then it can be absorbed back into the blood from the collecting
tubules. Neurohormonal mechanisms, including arginine
vasopressin, play an important role in this absorption [12].
This decreases GFR and enhances urea reabsorption
with diastolic dysfunction and that the BUN / Cr ratio was
has been mostly investigated in patients with systolic heart
failure patients, both vasopressin concentration and
is and may not adequately demonstrate renal dysfunction. In
heart failure patients, both vasopressin concentration and
vasopressin-sensitive aquaporin-2 channels are increased, and
this is highly correlated with the BUN concentration [13].
The neurohormonal response to arterial underfilling secondary to
decreased cardiac output involves not only arginine vasopressin but also stimulation of the renin – angiotensin –
aldosterone system and the sympathetic nervous system [14, 15]. This decreases GFR and enhances urea reabsorption in
the distal tubules. The decrease in the BUN concentration and the clinical outcome with use of angiotensin-converting
enzyme inhibitors in the OPTIME-CHF study are consistent with this mechanism [16].

Although the relationship between BUN and heart failure has been mostly investigated in patients with systolic heart failure, diastolic heart failure may also cause an increase in BUN by inducing neurohumoral activation [17]. Zhou et al. found that BUN and Cr concentrations were high in patients with diastolic dysfunction and that the BUN/Cr ratio was independently associated with diastolic dysfunction [18]. Both systolic and diastolic heart failure were associated with increased cardiovascular mortality. As in kidney dysfunction, the BUN concentration has a stronger correlation with both systolic and diastolic heart failure than does Cr. Thus, BUN may be a useful prognostic marker in cardiovascular diseases [17, 19]. Qian et al. reported that an increased BUN/Cr ratio was associated with an increase in long-term mortality in patients with acute myocardial infarction complicated by heart failure [20]. Brisco et al. showed that an increase in the BUN/Cr ratio was associated with increased death in patients with decompensated heart failure [21]. These studies emphasized that the increase of BUN in heart failure is more predictive in prognosis than is the Cr concentration.

The findings of the current investigation are consistent with reports that have demonstrated the prognostic significance of BUN in CAD. Richter et al. showed a correlation of BUN concentration with mortality, NT-proBNP, left ventricular dysfunction, and decreased eGFR. In 1332 patients with acute myocardial infarction, BUN was an independent predictor of mortality during a 8.6 yr follow-up period [22]. They speculated that neurohumoral activation played a role in this relationship. Arsalan et al. found that BUN and Cr were associated with increased mortality in acute coronary syndrome patients [23]. Jiang et al. showed that increased BUN was related to an increased incidence of CAD [24]. Martinson et al. demonstrated that increased BUN was associated with postoperative stroke in patients who underwent cardiac surgery [25]. Arthur et al. reported that an increase in BUN before surgery was a sign of long-term mortality [26]. Kawabe et al. found that BUN >25 mg/dl was associated with long-term mortality in patients treated with percutaneous coronary intervention [27].

In summary, the BUN concentration provides information about the prognosis of patients with SAP, as it does in those with heart failure. Including BUN in models to determine long-term risk may help to predict the prognosis more accurately. Since BUN is a component of routine biochemical tests that are cheap and readily available, predicting prognosis with the BUN concentration can be a practical approach at little cost.
Limitations

The study had a relatively small sample size and was performed in a specific region. Further studies are required to reevaluate our findings. Different types of drugs can affect the BUN concentration. Effects of drugs other than those used for CAD and diabetes have not been studied in detail. The BUN concentrations were not measured during the follow-up period. Such measurements might show more accurately the relationship of BUN with long-term mortality.

Conclusion

The BUN concentration measured before CAG in patients with SAP is an independent predictor of long-term all-cause mortality.

No conflict of interest is reported.

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