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Original Article

Blood urea nitrogen level in patients with chronic total occlusion predicts long-term mortality independent of estimated glomerular filtration rate and serum creatine level: (9-year follow-up results)

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Abstract

Aim: Increased serum blood urea nitrogen (BUN) level is an indicator of neurohormonal and renal dysfunction, and is associated with the major adverse cardiovascular events (MACE). Chronic total occlusion (CTO) is a typical coronary artery disease diagnosed by coronary angiography. We established and tested the hypothesis that there might be a relationship between serum BUN level and long-term prognosis in patients with CTO.

Materials and Methods: The study consisted of 124 patients diagnosed with CTO. The patients were followed up for a mean of 9.2 (7.4-9.5) years, and all-cause mortality was determined.

Results: Patients were divided into two groups according to mortality outcome. During the follow-up, 38 of 124 patients died. Univariate Cox analysis showed that age (p=0.002), BUN (p=0.001), and serum creatinine levels (p=0.039) were associated with mortality. BUN level (OR: 1.074; 95% CI: 1.018-1.134; p=0.009) and age (OR: 1.043; 95% CI: 1.001-1.087, p=0.043) were independently associated with mortality in multivariate Cox analysis. In the ROC analysis, the AUC values for BUN and estimated glomerular filtration rate were 0.689 (p=0.002) and 0.650 (p=0.001), respectively. When the cutoff value for BUN level was considered >16 mg/dL, the sensitivity was 68%, and the specificity was 53% (OR:1.38) to predict mortality. When the cutoff value was considered >20 mg/dL, the sensitivity diminished to 40%, while the specificity increased to 90% (OR:3.9).

Conclusion: In patients with CTO, BUN level is associated with increased all-cause mortality during long-term following. This relationship is independent of renal dysfunction.

Keywords: BUN; chronic total occlusion; coronary angiography; mortality; neurohormonal activation

INTRODUCTION

Blood urea nitrogen (BUN) is the nitrogen-containing part of urea synthesized as a result of protein catabolism in the liver and is mainly excreted through the kidneys (1). Urea is filtered in the kidneys and can be absorbed from the proximal tubule, depending on the blood volume, the renin-angiotensin-aldosterone system (RAAS), vasopressin, and sympathetic discharge. Urea shows the level of glomerular filtration rate less than the actual level. Neurohormonal activation and renal dysfunction also affect BUN levels. However, after filtering in the glomerular, serum creatinine is not absorbed from the tubules, and unlike urea, it can be secreted. Therefore, neurohormonal activity is less affected than urea and may show estimated glomerular filtration (eGFR) more than it is, compared to glomerular filtration calculated with insulin (2,3).

In patients with left ventricular dysfunction, increased BUN level is typically due to neurohormonal activity and hypersensitivity to vasopressin (4). BUN plays a role as an indirect indicator of neurohormonal activity in heart failure (5,6). The increased BUN level is also a poor prognostic marker in other cardiovascular diseases (7).

Chronic total occlusion (CTO) is a coronary artery disease diagnosed with coronary angiography (CAG) and is hard to treat. Although many factors have been investigated to determine long-term prognosis, there is no data associated with BUN. We investigated the relationship between the BUN level measured at hospitalization before CAG procedure and long-term all-cause mortality in patients diagnosed with CTO.

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MATERIALS and METHODS

The study is an observational, single-center, retrospective, cohort trial. A total of 124 consecutive patients with stable angina pectoris, who underwent CAG between 03.15.2010 and 11.15.2011 and diagnosed with CTO, were included in the study. Study groups consisted of patients with failed percutaneous coronary intervention or who were scheduled for medical treatment. The research was carried out under the Declaration of Helsinki, and the local ethics committee approved the study protocol (R.T.E. University Non-Interventional Clinical Researches Ethics Committee, 16.06.2020, 2020/101).

The standard selective CAG procedure was performed using the Judkins technique. Total coronary artery occlusion was defined as 100% occlusion of the coronary artery with TIMI 0-1 flow. Total occlusion lasting more than three months was considered chronic.

Patients with CTO in at least one major coronary artery were included in the study. Two experienced interventional cardiologists blinded to the study evaluated the patient's coronary angiograms in terms of collateral development. Totally occluded vessels were graded in terms of collateral development. The grading was done according to the vessel with better collaterals in a patient with CTO and collateral vascular development in more than one vessel.

An experienced cardiologist used the Cohen-Rentrop method to determine the degree of collateral development. Grade 0-1 collateral development was regarded weak collaterals, and grade 2-3 collateral development was considered good collaterals (8,9).

Blood samples were obtained for routine blood chemistry analyses before the CAG procedure, eight hours of fasting. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were analyzed by standard methods and recorded.

Patients with peripheral vascular disease, prior coronary revascularization, non-ischemic dilated cardiomyopathy, ongoing infection or inflammation, hepatic disease, acute coronary syndrome (within three months before enrollment), hematological disorders, and malignancy were excluded from the study.

Patient's echocardiographies were performed by a cardiologist unaware of the study data with GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway). Ejection fraction was calculated by the modified Simpson method in apical four-chamber imaging (10). The mortality information of the patients was obtained from the health registration system.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as percentages. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether the data are normally distributed. The Student t-test was used to compare normally distributed parameters among the mortality groups. The Mann-Whitney U-test tests were conducted to compare not normally distributed parameters among the mortality groups. A p-value <0.05 was considered as a statistically significant result. Cross-tabulations were used for comparison of the proportions of patients with categorical variables. The Chi-square or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts) was used to compare in different groups. For multivariate analysis, the possible factors identified with univariate analyses were further entered into the Cox regression analysis to determine independent predictors of mortality. We used the Hosmer-Lemeshow goodness-of-fit statistic was used to evaluate model fit and 5% type-I error level to derive statistical significance. Data were statistically analyzed using the SPSS software (Version 23.0, SPSS, Inc., Chicago, IL).

RESULTS

The analysis included 124 patients (102 male) with an average of 62 (55.25-70) years. During a follow-up of 9.2 (7.4-9.5) years, 38 (30.6%) of 124 patients died. Patients were analyzed in two groups in terms of mortality outcomes. According to coronary angiography evaluations, there were two patients with 3-vessel disease in both groups (p=0.099). Chronic total occlusion in LAD artery and its branches was observed in 14 patients in the mortality group and 46 patients in the survival group (p=0.098). Total occlusion in CX artery and its branches was observed in 17 patients in the mortality group and 30 patients in the survival group. Total occlusion in RCA was observed in six patients in the mortality group and eight patients in the survival group. In the univariate analysis, age (p=0.002), BUN (p=0.001), and serum creatinine (p=0.039) levels were higher; on the contrary, eGFR was lower (p=0.025) in the mortality group. Left ventricular ejection fraction (p=0.238) was lower in the mortality group, but it was not significant. There was no difference in collateral grade between the groups (p=0.812) (Table 1).

Factors that have a significant relationship with mortality were evaluated using the enter method, first by univariate and then by multivariate cox regression analysis. As a result of this analysis, age (OR 1.043, 95% CI 1.001-1.087, p=0.043) and BUN level (OR 1.074, 95% CI 1.018-1.134, p=0.009) were determined as independent predictors of long-term mortality in patients with CTO (Table 2). In the ROC analysis, the AUC values for BUN and eGFR were 0.689 (p=0.002) and 0.650 (p=0.001), respectively (Figure 1). When the cutoff value for BUN level was considered >16 mg/dL, the sensitivity was 68%, and the specificity was 53% (OR:1.38) to predict mortality. When we designated the cutoff value as >20 mg/dL, the sensitivity decreased to 40%, while the specificity increased to 90% (OR:3.9). In the Kaplan Meier graphic, created according to the mean BUN value of 17.7 mg/dL, survival decline in the high BUN level group started to become evident from the second year (Figure 2).

Table 1. Univariate analysis of demographic, laboratory and angiographic parameters

	Mortality (-) (n=86)	Mortality (+) (n=38)	p value
Age (years)	61.01±9.7	66.8±8.1	0.002
Body-mass index	28.4±4.2	28.3±4.6	0.846
Male gender n (%)	69(80.2)	33(86.8)	0.379
Diabetes Mellitus n (%)	35(40.7)	14(36.8)	0.688
Hypertension n (%)	48(55.8)	26(68.4)	0.190
Dyslipidemia n (%)	62(72.1)	31(81.6)	0.264
Current smoker n (%)	41(47.7)	21(55.3)	0.440
LV EF (%) *	52.5(40-61)	45(40-55)	0.206
Fast. Glucose (mg/dL) *	106.5(94.25-128.7)	104(97-142)	0.738
BUN (mg/dL)	16.04±3.9	20.8±8.1	**0.001**
Creatinine (mg/dL) *	0.90(0.80-1.00)	1.00(0.84-1.20)	**0.039**
eGFR ml/min/1.73m^2	83.5±17.35	75.6±17.6	**0.025**
Total cholesterol (mg/dl)	186.1±47.2	200±51.1	0.275
Triglyceride (mg/dL)	150.2±86.4	151.5±59.5	0.816
HDL (mg/dL) *	38(31-41)	38(32-41)	0.703
LDL (mg/dL)	122.2±36.9	127.1±34.6	0.515
WBC (10^3/mm^3)	8.07±2.3	8.17±2.2	0.816
Hemoglobin (mg/dL)	13.5±1.39	13.6±1.5	0.682
Acetylsalicylic acid n (%)	82(95)	37(98)	0.881
Clopidogrel n (%)	4(5)	3(8)	0.547
Beta-blocker n (%)	63(73)	23(61.1)	0.194
ACE/ARB n (%)	40(47)	22(58)	0.254
CCB n (%)	9(11)	6(15)	0.242
Statin n (%)	80(93)	34(89)	0.124
Number of CTO ≥2 n (%)	14(18.7)	7(25.9)	0.295
Rentrop grade 2-3 n (%)	54(62.8)	7(25.9)	0.295
3-vessel disease n (%)	2(2.4)	2(5.3)	0.099
Total occlusion n (%)			
LAD - branches	46(54.1)	14(36.8)	0.098
CX - branches	30(35.1)	16(42.1)	0.112
RCA	8(10.8)	6(15.7)	0.157

ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin-II receptor blocker, BUN: Blood urea nitrogen, CCB: Calcium channel blocker, CTO: Chronic total occlusion, CX: Circumflex artery, eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, LAD: Left anterior descending artery, LDL: Low-density lipoprotein, LV EF: Left ventricular ejection fraction, RCA: Right coronary artery, WBC: White blood cell, Fast: Fasting * Median, inter-quartile range (range, [25% percentile-75% percentile])

Table 2. Multivariate cox regression analysis

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	1.053	1.017-1.090	0.004	1.043	1.001-1.087	0.043
BUN	1.081	1.035-1.129	0.001	1.074	1.018-1.134	0.009
Creatinine	2.262	0.824-6.211	0.063			
eGFR	0.981	0.963-0.999	0.042	0.999	0.973-1.025	0.918

BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate

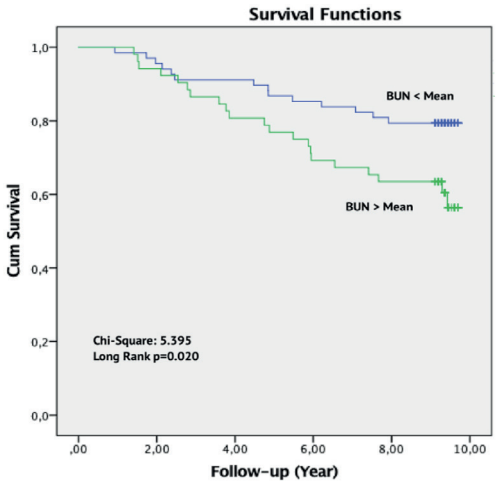

Figure 1. Kaplan-Meier survival curve

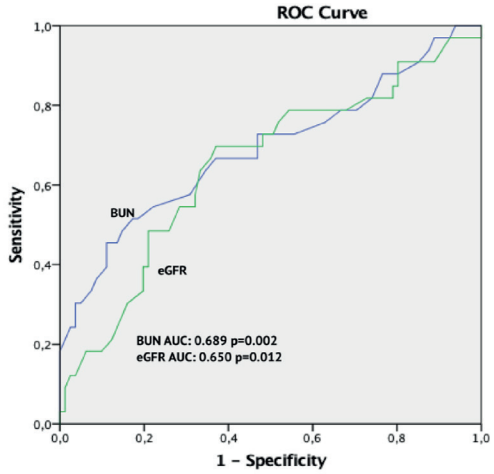

Figure 2. ROC Curve comparison of eGFR and BUN

DISCUSSION

The current study suggests that BUN level at hospital admission has the potential to independently predict long-term mortality in CTO patients. This relationship between BUN and mortality in CTO has not been discussed in previous studies. Bun also continued to provide prognostic information after adjusting either eGFR or creatinine in multivariate analysis.

A decrease in cardiac output secondary to diastolic and systolic dysfunction leads to the activation of peripheral receptors. As a compensatory mechanism, this activation induces the sympathetic nervous system and RAAS and aggravates inflammation (11,12). This process causes changes in heart rate and contractility, salt and water retention, and constriction of the peripheral blood vessels. These 'neurohormonal' systems induce some pathways in the kidneys, heart, and vasculature to maintain cardiovascular homeostasis in the short-term. However, in the long term, these responses result in hemodynamic stress and exert deleterious effects on the heart and circulation. Neurohormonal activation is a vital mechanism underlying heart failure progression; thus, neurohormonal system blockade is the primary goal of heart failure treatment. Renal dysfunction, as well as reducing long-term survival, causes peripheral vasoconstriction and left ventricular remodeling (12,13).

Chronic total occlusion is identified in up to 20% of coronary artery disease patients. However, the CTO procedural success rate (50% to 90%) is lower compared with the non-CTO percutaneous coronary intervention (PCI) success rate (98%) (14,15). Myocardial viability is one of the most important predictors of survival, and myocardial tissue is affected at various levels in patients with CTO (16). Left ventricular systolic and diastolic dysfunction is typical in the presence of ischemic myocardial tissue, decreases the success rate of revascularization, and leads to poor prognosis (17,18).

Neurohormonal activation is triggered in acute and chronic myocardial ischemia. The severity of ischemia can enhance the spread of necrosis and the response of neurohormonal activation (12). Chronic total occlusion is one of the causes of coronary ischemia. Although percutaneous coronary procedures can reverse ischemia, survival benefit remains unclear, even if complete revascularization is achieved. Fractional flow-reserve shows the presence of chronic ischemia in CTO despite sufficient collaterals (19). Although BUN is an unideal, nonspecific marker of kidney function, it can indicate neurohormonal and hemodynamic impairment. Chronic total occlusion can lead to neurohormonal disruption by causing chronic ischemia. Therefore, it can be assumed that BUN may be a prognostic indicator for the CTO. Richter et al. showed that BUN could be a useful prognostic tool for long-term mortality in AMI patients, independent of GFR. (7) This finding supports the BUN-mortality relationship we stated in CTO patients.

In patients with left ventricular systolic dysfunction, the BUN level increases due to neurohormonal activity, indicating a poor prognosis (6,20). Diastolic dysfunction, as in left ventricular systolic dysfunction, increases the BUN level in proportion to its severity (21). Otsuka et al. showed an impaired diastolic function in the early stage of renal failure (22). This finding may explain the relationship between BUN increase and diastolic dysfunction. Xiaohong et al. demonstrated the correlation between BUN and brain natriuretic peptide (BNP) in patients with acute decompensated heart failure (23). The relationship of BUN with left ventricular systolic and diastolic dysfunction may be a reason for the association of BUN increase with long-term mortality in patients with CTO.

Renal dysfunction adversely affects the prognosis of cardiovascular diseases (24-26). The BUN level shows glomerular filtration less than it is due to absorption from tubules. Although it is not a reliable indicator, the BUN level is affected by renal dysfunction (1). Therefore, high BUN levels due to renal dysfunction may indicate a mortality increase in CTO patients.

In conclusion, the high BUN level determined in CTO patients before the CAG procedure is associated with increased long-term mortality. Evaluation of BUN levels may be cost-effective in predicting the long-term risk of CTO patients.

LIMITATIONS

The study was conducted on a relatively limited and single ethnic group. Researches on a larger population can better prove the accuracy of the results. Laboratory data are the one that obtained during the first hospital application. We cannot exclude the possible impact of the laboratory data on the patients during their follow-up in the long-term. It should be kept in mind that BUN is affected by various neurohormonal and hemodynamic factors (systolic and diastolic dysfunction) and drugs. Although there is no significant difference between systolic functions between the groups, the effect of diastolic dysfunction cannot be interpreted from the data of our study. Besides, the treatment method applied to CTO patients after the CAG procedure was not available. Therefore, the study does not provide information about the effectiveness of treatment modalities.

CONCLUSION

In patients with CTO, the BUN level measured before coronary angiography procedure is a predictor of all-cause mortality in the long term. The BUN level at the hospital admission may help identify the possible long-term risks of CTO patients and guide them to a more aggressive therapeutic approach.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: Recep Tayyip Erdogan University Non-Interventional Clinical Researches Ethics Committee, 16.06.2020, 2020/101.

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