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Impact of blood urea nitrogen for long-term risk stratification in patients with coronary artery disease undergoing percutaneous coronary intervention

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ABSTRACT

Background: Few studies have examined the association between blood urea nitrogen (BUN) and mortality in patients with coronary artery disease (CAD). We investigated the prognostic value of BUN concentration at hospital admission in patients with CAD.

Methods: A total of 3641 patients with CAD who underwent percutaneous coronary intervention (PCI) were included from April 2007 to June 2011. We measured BUN concentration at hospital admission and compared it with long-term clinical outcome. Patients were classified into three groups according to BUN concentration of <20 mg/dl, 20 to 25 mg/dl, or >25 mg/dl. Primary endpoint was all-cause death.

Results: During the follow-up period (median 15 months), 248 (6.8%) patients died. A higher BUN level was associated with multivessel disease, lower ejection fraction, lower systolic blood pressure, and higher prevalence of comorbidities. Cox regression analysis showed that patients with BUN of >25 mg/dl had a hazard ratio (HR) for mortality of 2.73 (95% CI, 1.14 to 6.53; p = 0.023) with an estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73 m^2 and a HR of 2.90 (95% CI, 1.75 to 4.82; p < 0.001) with an eGFR of <45 ml/min/1.73 m^2. Regardless of acute coronary syndrome or stable CAD, BUN of >25 mg/dl was independently associated with higher mortality (HR, 2.58; 95% CI, 1.43 to 4.64; p = 0.004 and HR, 2.16; 95% CI, 1.01 to 4.59; p = 0.044, respectively).

Conclusions: A BUN of >25 mg/dl was associated with long-term mortality in CAD patients who underwent PCI independent of traditional cardiovascular risk factors and eGFR.

1. Introduction

The mortality rate in coronary artery disease (CAD) correlates with the severity of the illness, and some risk stratification is needed. Well-known risk factors include age, multivessel diseases, renal function, systolic blood pressure, anemia, levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP) and troponin, and myocardial viability [1–5]. Recently, there has been a growing concern regarding the importance of blood urea nitrogen (BUN) in cardiovascular disease. Several studies demonstrated that a high level of BUN at admission is the best predictor of in-hospital mortality in patients with acute heart failure [6,7], and BUN also serves as an important biomarker in critically ill patients without heart failure [8,9]. BUN may not only reflect homodynamic deterioration but also neurohormonal activation such as that of the renin–angiotensin–aldosterone system and sympathetic nervous system and arginine vasopressin release [10,11]. However, serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) have shown only a weak association with neurohormonal activation [10]. Although Cr and eGFR are closely associated with short- and long-term mortalities in patients with CAD [2], some studies indicated that BUN more strongly relates to adverse outcomes than do Cr and eGFR in patients with heart failure [12]. However, the prognostic value of BUN in patients with CAD undergoing PCI is unknown. Therefore, we evaluated the impact of BUN concentration measured at hospital admission on long-term mortality in a large cohort of patients with CAD who underwent percutaneous intervention (PCI).

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2. Methods

2.1. Study population

We pooled data from patients enrolled in the Ibaraki Cardiac Assessment Study (ICAS) registry, a multicenter registry involving 12 hospitals in Ibaraki Prefecture, Japan. All traceable personal identifiers were removed from the datasets before analysis to protect patient confidentiality. We enrolled 3941 consecutive patients with CAD who underwent PCI from April 2007 to June 2011. Patients with a BUN value not measured at admission (n = 175) and those who underwent dialysis (n = 125) were excluded. Thus, a total of 3641 patients were included in this study. The study population consisted of 1715 patients with acute coronary syndrome (ACS) and 1926 patients with stable CAD. Bare metal stents were implanted in 782 (21%) patients, drug-eluting stents were implanted in 2529 (70%) patients, and balloon angioplasty without stenting was performed in 330 (9%) patients. ACS was defined as ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina. The diagnosis of ACS was based on the universal definition of myocardial infarction [13]. CAD was diagnosed based on the presence of >70% lumen obstruction of at least one of the three major coronary arteries. Hypertension was defined as the presence of current treatment with antihypertensive drugs or otherwise as a systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg. Dyslipidemia was defined as current treatment with cholesterol-lowering medications or low-density lipoprotein (LDL) cholesterol value of >140 mg/dl and/or high-density lipoprotein cholesterol value of <40 mg/dl. Diabetes mellitus was defined as a fasting glucose level of >126 mg/dl or treatment with oral hypoglycemic agents or insulin. The eGFR was calculated with the following equation: $eGFR = 194 \times (\text{serum creatinine})(-1.094) \times (\text{age})(-0.287)$ ($\times 0.739$ if female) [14]. Generally, a normal value of BUN is 20 mg/dl or less. BUN with 25 mg/dl or more is significantly associated with poor prognosis in patients with myocardial infarction [15]. Therefore patients were categorized into three groups according to BUN concentration measured at hospital admission: BUN of <20 mg/dl, BUN of 20 to 25 mg/dl, and BUN of >25 mg/dl.

2.2. Coronary angiography and PCI procedure

PCI was performed according to standard techniques. All patients received treatment with aspirin (100 mg/day) and clopidogrel (75 mg/day following a 300-mg loading dose) or ticlopidine (200 mg/day). A glycoprotein IIb/IIIa receptor inhibitor is not yet available in Japan. Operators selected interventional devices and performed PCI through either the radial, brachial, or femoral artery using 6–7 French catheters. A low osmolality, non-ionic contrast agent was used (iopamidol 350 mgI/ml: Schering AG, Berlin, Germany). Before starting the procedure, heparin 8000 units was given intravenously, and the activated clotting time was maintained at >300 s. The standard of care at discharge was to prescribe clopidogrel for 1 year to all patients treated with drug-eluting stents, whereas clopidogrel was prescribed for at least 3 months to patients treated with bare metal stents. Aspirin was continued indefinitely unless complications occurred. Informed consent was obtained from all patients, and approval for this study was granted by each institution's ethics committee. All adverse events were confirmed by reviewing the medical records of the patients followed at each institution.

2.3. Endpoints and definitions

The primary endpoint of our study was death from any cause. The secondary endpoints included death from cardiovascular causes, congestive heart failure, myocardial infarction, stroke, revascularization, and a composite of these causes. Target vessel revascularization was defined as coronary bypass surgery or repeat PCI performed during the follow-up period because of symptoms or signs of myocardial ischemia in the presence of angiographic restenosis. Congestive heart failure was defined as admission to hospital for worsening heart failure requiring intravenous drug treatment. Stroke was defined as cerebral infarction,

Table 1
Baseline characteristics of the patients.

Characteristic	BUN < 20 mg/dl (n = 2784)	BUN 20–25 mg/dl (n = 527)	BUN > 25 mg/dl (n = 330)	p value
Age (year)	69 [61, 76]	74 [67, 80]	77 [68, 83]	<0.001
Female gender (%)	22.3	23.6	27.0	0.140
BMI (kg/m^2)	24.2 [22.3, 26.5]	23.8 [21.8, 26.2]	23.4 [21.4, 25.5]	<0.001
SBP (mm Hg)	136 [120, 154]	135 [118, 151]	132 [111, 149]	<0.001
DBP (mm Hg)	77 [67, 86]	74 [64, 84]	70 [61, 80]	<0.001
LVEF (%)	63 [51, 68]	61 [48, 67]	55 [41, 65]	<0.001
CRP (mg/dl)	0.16 [0.07, 0.34]	0.16 [0.07, 0.48]	0.37 [0.14, 2.05]	<0.001
eGFR (ml/min/1.73 m^2)	54.3 [46.6, 64.5]	42.4 [35.0, 52.5]	31.3 [23.4, 42.2]	<0.001
LDL cholesterol (mg/dl)	113 [91, 137]	107 [85, 128]	103 [83, 125]	<0.001
Hemoglobin (g/dl)	14.0 [12.8, 15.1]	13.2 [12.0, 14.4]	12.5 [10.8, 14.1]	<0.001
Hypertension (%)	67.4	70.3	74.5	0.018
Dyslipidemia (%)	57.7	51.9	44.0	<0.001
Diabetes mellitus (%)	36.3	41.5	44.7	0.002
Prior MI (%)	17.3	18.6	17.5	0.757
Prior HF (%)	4.1	7.7	14.1	<0.001
Multivessel disease (%)	28.7	33.8	39.6	<0.001
ACS (%)	46.6	47.3	54.4	0.027
Medication on admission				
Beta blockers (%)	43.1	47.8	42.5	0.125
ACE inhibitor (%)	23.8	23.0	28.1	0.188
ARB (%)	35.2	44.2	40.3	<0.001
Statin (%)	70.4	67.8	56.3	<0.001
Diuretics (%)	13.3	29.1	47.6	<0.001

Values are reported as the medians [interquartile range], or %.
ACE = angiotensin converting enzyme, ACS = acute coronary syndrome, ARB = angiotensin receptor blocker, BMI = body mass index, BUN = blood urea nitrogen, CABG = coronary artery bypass graft, Cr = creatinine, DBP = diastolic blood pressure, HF = heart failure, eGFR = estimated glomerular filtration rate, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure.