Blood urea nitrogen to left ventricular ejection fraction ratio is associated with long-term mortality in the stable angina pectoris patients

A.G. ÖZYILDIZ[1], E. KALAYCIOĞLU[2], A. ÖZYILDIZ[1], T. TURAN[2], M. ÇETIN[1]

[1]Department of Cardiology, Recep Tayyip Erdogan University, Training and Research Hospital, Rize, Turkey
[2]Department of Cardiology, University of Health Sciences, Trabzon Ahi Evren Chest and Cardiovascular Surgery Education and Research Hospital, Trabzon, Turkey

Abstract. – OBJECTIVE: Left ventricle (LV) dysfunction remains a significant cause of morbidity and mortality in patients with stable angina pectoris (SAP) and has prognostic significance. However, new prognostic indicators may be more useful in clinical practice. There is a growing interest in the role of blood urea nitrogen (BUN) in cardiovascular diseases. Blood urea nitrogen is an indicator of cardiac dysfunction and neurohormonal activation. We aimed to determine the relationship of BUN/LV ejection fraction ratio (BUNLVEFr) with long-term mortality and de novo decompensated heart failure (HF) in SAP patients.

PATIENTS AND METHODS: The study comprised 603 consecutive SAP patients who underwent coronary angiography. The median duration of the follow-up period was 112.6±17.8 months. All-cause mortality and de novo decompensated HF were determined as the endpoints.

RESULTS: Adverse cardiac events were observed in 141 patients (23.3%), including mortality in 103 (17.1%) and decompensated HF in 38 (6.3%) of them during the follow-up period. Age (*p*=0.027), BUNLVEFr (*p*=0.001), glucose (*p*=0.043), hemoglobin (*p*=0.035), and Gensini score (*p*=0.012) were found as independent predictors of mortality and decompensated HF. BUNLVEFr was superior to BUN alone (BUNLVEFr *vs.* BUN: Z=5.715, *p*<0.001) and LVEF alone (BUNLVEFr *vs.* LVEF: Z=4.075, *p*<0.001) in predicting endpoints. In addition, BUNLVEFr >29 predicted all-cause mortality/decompensated HF with high sensitivity (78%) and low specificity (68%).

CONCLUSIONS: BUNLVEFr may provide better prognostic information than either BUN or EF can give alone in determining therapeutic strategies for SAP patients.

Key Words:
   Blood urea nitrogen to left ventricular ejection fraction ratio, All-cause mortality, Decompensated heart failure, Stable angina pectoris.

Introduction

Stable angina pectoris (SAP) is one of the common reasons for admission to the cardiology clinic. The therapy goals in SAP patients are to ease symptoms, delay or prevent the disease's progression, and eliminate the risk of adverse outcomes such as death, heart failure (HF), or myocardial infarction[1]. Patients have a survival benefit from revascularization based upon the lesion's location and severity, the number of diseased vessels, and left ventricular (LV) dysfunction[2]. Although LV dysfunction is a crucial cause of morbidity and mortality in SAP patients, some risk stratifications are needed[3].

Recently, studies[4,5] demonstrating the role and prognostic importance of blood urea nitrogen (BUN) in cardiovascular (CV) diseases have been considerable. A high BUN level at admission is the top predictor of long-term mortality in acute HF and acute coronary syndrome patients, and BUN serves as an essential biomarker in critically ill patients free of HF[4,5]. Blood urea nitrogen level is associated with renal dysfunction; however, this relationship is weak compared to serum creatinine (Cr) and estimated glomerular filtration rate (eGFR). Blood urea nitrogen level may increase independently from eGFR or serum Cr owing to enhanced proximal tubular reabsorption seconder to the activation of the sympathetic nervous system (SNS) and rennin-angiotensin-aldosterone system (RAAS)[6-8]. Therefore, BUN shows neurohormonal activity in patients with LV systolic or diastolic dysfunction[9]. In contrast, the association of serum Cr and eGFR with neurohormonal activation is weak[8]. Studies[10,11] focus on the hypothesis that BUN increase has a predictive role due to its effect on cardiovascular diseases through neurohormonal activation, and it has been reported

Corresponding Author: Ali Gökhan Özyıldız, MD; e-mail: aligokhanozyildiz@gmail.com

that this role is independent of the type of coronary artery disease. Oxidative stress and neurohormonal activation are two of the possible underlying mechanisms of stable angina and BUN is a nonspecific marker for both of them[10,11]. However, the relationship between stable angina with the RAAS, oxidative stress, and inflammation is unclear and needs further investigation.

The prediction of morbidity and mortality in determining SAP treatment strategy is critical. In the present study, we hypothesized that the ratio of BUN and LV ejection fraction might be superior in predicting clinical outcomes than BUN and LVEF alone could provide; and we examined the relationship of BUN to LVEF ratio (BUNLVEFr) to long-term mortality and *de novo* decompensated HF in SAP patients who underwent coronary angiography (CAG).

Patients and Methods

Study Population

The present research is an observational cohort study and consisted of 603 consecutive SAP patients who underwent CAG between January 2008 and August 2010. The diagnosis of SAP was based on whether the patient had typical chest pain or chest pain equaling symptoms. We planned to evaluate the predictive value of BUN (in the normal range or slightly increased level) of the remaining patients in long-term cardiovascular events. Therefore, patients with eGFR <45 mL/min/1.73 m^2 (moderate to severe renal failure) were considered exclusion criteria, as they would contaminate the study population. The median duration of the follow-up period was 112.6±17.8 months. All-cause mortality and *de novo* decompensated HF were determined as the endpoints. Congestive heart failure was defined as hospital admission requiring intravenous drug therapy due to the worsening of heart failure. Patients who were already diagnosed with decompensated heart failure based on symptoms and echocardiographic findings were not included in the study. Patients' mortality information was provided through the official national population registration system, and medical data was provided through the medical record system, face-to-face, and telephone interviews. The study was performed under the principles stated in the Declaration of Helsinki. The local Ethics Committee approved the study protocol. Informed consent was obtained from all individual participants included in the study.

History of acute or chronic renal failure (eGFR <45 mL/min/1.73 m^2), moderate-to-severe heart valve disease, history of coronary artery bypass graft operation, decompensated HF, non-ischemic dilated cardiomyopathy, chronic liver disease, chronic inflammatory disease, severe comorbid conditions such as chronic obstructive sleep apnea, hematologic disorders, and malignancy were determined as exclusion criteria.

Blood urea nitrogen and routine biochemistry analysis were performed from the fasting blood samples taken from the patients before the CAG procedure. Coronary angiography images were recorded at a database of the institution. Two experienced cardiologists, blinded to the research data, assessed the CAG images. The Gensini score was calculated using the relevant scoring system[12]. Body mass index (BMI) was calculated as weight (kg)/height (m^2). eGFR was calculated as 194 × serum creatinine (–1.094) × age (–0.287) (× 0.739 if female). Medical treatment of patients was performed according to current guidelines.

Standard transthoracic and Doppler echocardiography examinations were performed by a 3.25-MHz transthoracic transducer connected to a Vivid 5 System (GE Vingmed Ultrasound AS, Horten, Norway). Two echocardiographers, blinded to the data, performed the examinations according to the American Society of Echocardiography guideline[13].

Statistical Analysis

Continuous variables were presented as mean values [standard deviation (SD)] or medians with ranges, and the categorical variables were expressed as percentages. The variables were compared using a 2-tailed Student's *t*-test for the continuous variables of a normal distribution or the Mann-Whitney U test for the continuous variables of non-normal distribution. The Chi-Square test was used for the categorical variables. The effects of the various variables on mortality and decompensated heart failure were calculated by univariate regression analysis. The variables with unadjusted *p*<0.1 were identified as confounding factors and included in the multivariate regression analyses to determine the independent predictors of mentioned adverse cardiac events. The predictive values of BUN, LVEF, and BUNLVEFr 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) with these parameters[14]. All the statistical tests were 2-tailed, and a *p*<0.05 value was considered significant. All the analyses were carried out using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the study population was 59±10.3 years and 70% of the patients were male. Adverse cardiac events developed in 141 (23.3%) patients, including 103 (17.1%) mortality and 38 (6.3%) *de novo* HF during the follow-up period. Patients were divided into two groups according to the primary outcomes. Age (*p*<0.001), male predominance (*p*=0.028), diabetes mellitus (DM) prevalence (*p*=0.007), BUN (mg/dl, *p*<0.001), Cr (mg/dl, *p*<0.001), BUNLVEFr (*p*<0.001), and Gensini score (*p*<0.001) were higher in the primary outcome (+) group, while LVEF (*p*<0.001) was lower for this group (Table I).

Table I. Baseline characteristics of the study population.

Variables	Mortality/ decompensated HF (-) (n=462)	Mortality/ decompensated HF (+) (n=141)	All Patient (n=603)	*p*
Age (year)	57.2±9.9	64.8±9.6	59±10.3	<0.001
Gender (Male)	314 (68)	109 (76.8)	423 (70)	0.028
Diabetes mellitus (n, %)	118 (25.5)	54 (38)	172 (28.5)	0.007
Hyperlipidemia (n, %)	340 (73.6)	101 (71.1)	441 (73)	0.316
Current smoker (n, %)	141 (30.5)	41 (28.9)	182 (30.1)	0.394
Hypertension (n, %)	258 (55.8)	86 (60.6)	344 (57)	0.185
Family history of CAD (n, %)	103 (22.3)	25 (17.6)	128 (21.2)	0.232
Stable HF (n, %)	20 (4.3)	63 (44.7)	83 (13.8)	<0.001
BMI (kg/m^2)	29.5±4.9	28.1±4.6	29.2±4.8	0.007
LVEF %	59.9±10.5	50.5±13.8	57.1±12.4	<0.001
BUN (mg/dl)	15.8 (13.3-18.7)	18.6 (15.4-22.2)	16.5(13.8-19.6)	<0.001
BUNLVEFr	26.7±8.5	45.8±21.1	32.6±16.2	<0.001
Creatinine (mg/dl)	0.87±0.17	0.94±0.22	0.89±0.19	<0.001
Fast plasma glucose (mg/dl)	116.1±38	128.4±61.6	119.1±45	0.003
Total cholesterol (mg/dL)	193.1±45.6	187.5±47	191.8±46	0.215
Triglycerides (mg/dl)	123 (91-174)	120 (84-163)	122 (89-171)	0.233
HDL- cholesterol (mg/dl)	41.5±10.3	39.9±10.8	41.2±10.4	0.133
LDL- cholesterol (mg/dl)	123.3±37.3	118.2±38	122.1±37	0.856
White blood cell (10^3/µL)	7.3±1.9	7.7±2.2	7.4±2.01	0.089
Hemoglobin (g/dL)	13.9±1.4	13.6±1.6	13.8±1.4	0.015
Gensini Score	3.3 (0-16)	17 (1.5-52.7)	6.7 (0.4-25.2)	<0.001
CAD severity				
<50%	276 (61.2)	56 (41.6)	332 (56.7)	0.001
1 vessel	64 (14.2)	22 (16.3)	86 (14.7)	
≥2 vessel	111 (24.6)	57 (42.2)	168 (28.7)	
PCI (n, %)	159 (34.4)	69 (%48.9)	228 (37.8)	0.001
ASA n (%)	278 (60.2)	101 (71.1)	379 (62.7)	0.011
Beta-blockers (n, %)	204 (44.2)	72 (50.7)	276 (45.7)	0.139
RAAS inhibitors (n, %)	269 (58.2)	90 (63.4)	359 (59.4)	0.160
Clopidogrel (n, %)	102 (16.2)	43 (30.3)	145 (24)	0.031
Calcium-channel-blockers (n, %)	68 (14.8)	31 (21.8)	99 (16.4)	0.273
OAD/Insulin (n, %)	106 (22.9)	54 (38)	160 (26.5)	0.001
Statin (n, %)	249 (53.9)	73 (51.4)	322 (53.3)	0.336
Nitroglycerin	89 (19.3)	22 (15.6)	111 (18.4)	0.403
Death (n, %)	0	103 (72.5)	103 (17.1)	<0.001
Decompensate HF	0	38 (27.4)	38 (6.3)	<0.001

CAD: coronary artery disease; BMI: body mass index; LVEF: left ventricular ejection fraction; BUN: blood urea nitrogen; BUNLVEFr: blood urea nitrogen to left ventricular ejection fraction ratio; HDL: high density lipoprotein; HF: heart failure; LDL: low density lipoprotein; ASA: acetylsalicylic acid, RAAS: rennin-angiotensin-aldosterone system; OAD: oral anti-diabetic, HF: Heart failure, PCI: percutaneous coronary intervention.

In univariate analysis age (*p*<0.001), LVEF (*p*<0.001), BUN (*p*<0.001), BUNLVEFr (*p*<0.001), creatinine (*p*=0.001), and Gensini score (*p*<0.001) were related to all-cause mortality/*de novo* decompensated HF. In multivariate analysis age [odds ratio (OR): 1.047, 95% confidence interval (CI) 1.005-1.090, *p*=0.027], BUNLVEFr (OR: 1.037, 95% CI 1.024-1.050, *p*=0.001), and Gensini score (OR: 1.009, 95% CI 1.003-1.015 *p*=0.012) were the independent predictors of adverse cardiac events (Table II).

Sensitivity and specificity of BUN, LVEF, and BUNLVEFr for mortality were compared with ROC analysis, and AUC was found as 0.697, 0.699, and 0.819, respectively. The efficacy of BUNLVEFr for predicting survival was superior to BUN (BUNLVEFr *vs.* BUN: Z=5.715, *p*<0.001) or LVEF (BUNLVEFr *vs.* LVEF: Z=4.075, *p*<0.001) alone (Table III). BUNLVEFr ≥29 predicted mortality with high sensitivity (78%) but low specificity (68%) (Figure 1). We observed a correlation with survival from the first months of follow-up in the Kaplan-Meier graph, which was created by taking 29 as cut-off point for BUNLVEFr (Figure 2).

Discussion

The present study demonstrates that BUNLVEFr is an independent predictor of long-term mortality and *de novo* decompensated HF in a 10-year follow-up of SAP patients undergoing CAG. BUNLVEFr was superior to BUN or LVEF alone in predicting mentioned adverse cardiac events.

Both the SNS and RAAS activation can promote water and sodium absorption and cause passive reabsorption of BUN in the renal tubules. This activation may lead to renal vasoconstriction and decreased excretion of eGFR and BUN. In addition, insufficient blood volume stimulates the release of arginine vasopressin, facilitating the reabsorption of BUN in the collecting duct. However, Cr is freely filtered through the glomerulus

Table II. Univariate and Multivariate logistic regression analysis for mortality/decompensated heart failure.

Variables	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	1.080	1.054-1.106	<0.001	1.047	1.005-1.090	0.027
Gender (male)	1.428	0.966-2.111	0.074			
Diabetes mellitus	1.569	1.117-2.205	0.009			
BMI (kg/m²)	0.948	0.909-0.987	0.010			
LVEF%	0.955	0.941-0.969	<0.001			
BUN (mg/dl)	1.073	1.048-1.100	<0.001			
BUNLVEFr	1.042	1.034-1.050	<0.001	1.037	1.024-1.050	0.001
Creatinine (mg/dl)	5.868	2.154-15.98	0.001			
Fast plasma glucose (mg/dl)	1.004	1.001-1.017	0.010	1.005	1.00-1.011	0.043
White blood cell (10³/µL)	1.141	0.991-1.252	0.071			
Hemoglobin (g/dL)	0.892	0.797-0.999	0.047	0.811	0.667-0.985	0.035
Gensini Score	1.011	1.005-1.018	<0.001	1.009	1.003-1.015	0.012
CAD severity	1.422	1.180-1.715	0.001			

BMI: body mass index; LVEF: left ventricular ejection fraction; BUN: blood urea nitrogen; BUNLVEFr: blood urea nitrogen to left ventricular ejection fraction ratio; CAD: coronary artery disease.

Table III. Statistical comparison of AUCs.

Variables	AUC Dif.	SE	95% CI	Z statistic	*p*
BUNLVEFr to BUN	0.160	0.028	0.104-0.212	5.715	<0.001
BUNLVEFr to LVEF	0.121	0.029	0.062-0.179	4.075	<0.001

BUN: blood urea nitrogen; LVEF: left ventricular ejection fraction; BUNLVEFr: blood urea nitrogen to left ventricular ejection fraction ratio.

Figure 1. Comparison of sensitivity and specificity of BUNLVEFr and LVEF in determining mortality/de novo decompensated heart failure.
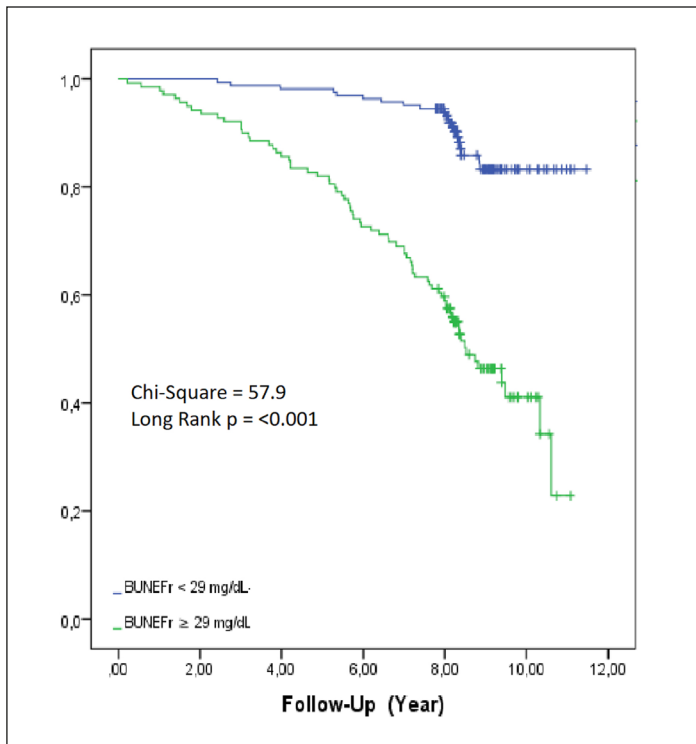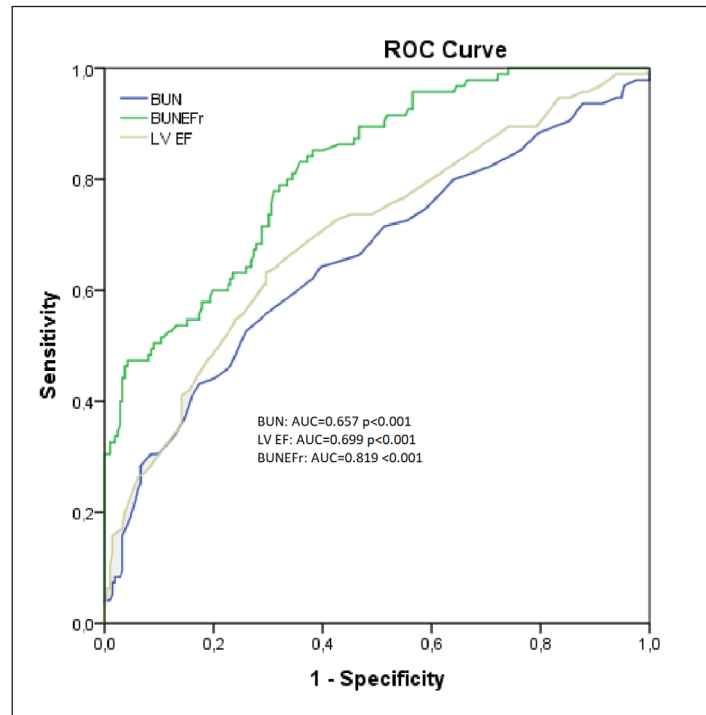

Figure 2. Kaplan-Meier primary endpoint (mortality/decompansated heart failure) curves for BUNLVEFr >29 and <29 for the 10-year follow-up.

and is not reabsorbed from the tubules[15]. The relationship between BUN level with mortality and decompensated HF was revealed, but we found no relationship between Cr and primary outcomes. This conclusion can be explained by the view that, although Cr is freely filtered, several factors raise the level of BUN. In concordance with our study, Richter et al[16] reported that BUN was superior to eGFR in predicting long-term mortality of patients with acute myocardial infarction.

End-diastolic volume and heart rate are determinants of cardiac output, alongside ejection fraction (EF). Considering that comorbidities such as hypertension and diabetes can also cause renal dysfunction, in contrast to the limitations of EF, BUNLVEFr may be a superior marker to LVEF alone. In addition, BUNLVEFr reflects the influence of cardiac function on the kidney not only through LV systolic function but also through diastolic function. BUNLVEFr can act as an indicator in predicting survival and new-onset heart failure[17]. In a way that supports these findings, Kiriş et al[18] demonstrated that BUNLVEFr could be a useful new predictor of contrast-induced nephropathy in acute coronary syndrome patients treated with percutaneous coronary intervention (PCI), and they suggested that BUNLVEFr may reflect the systemic effects of LV dysfunction.

Studies[19,20] have shown that increased BUN level is associated with the risk of CV events and mortality in acute and chronic HF with LV systolic dysfunction. In HF-preserved EF patients, LV diastolic dysfunction increases LV end-diastolic pressure, which causes HF symptoms and increases mortality[21]. Left ventricular diastolic dysfunction – although not as prominently as LV systolic dysfunction – contributes to neurohormonal activation[22]. In addition, LV systolic dysfunction often accompanies LV diastolic dysfunction[23]. McKie et al[24] reported that patients with preclinical diastolic dysfunction showed impaired renal cyclic guanosine monophosphate activation, contributing to weakened natriuresis, resulting in higher BUN reabsorption and elevated serum BUN levels. Zhou et al[9] indicated that higher BUN levels were correlated with LV diastolic dysfunction. In the present study, LV-diastolic dysfunction, closely related to CAD, might have increased the BUNLVEFr.

Increased BUN levels were associated with a high mortality rate in acute coronary syndrome patients[15]. However, few studies[4] have been conducted on stable CAD. Kawabe et al[4] demonstrated that a BUN level >25 mg/dl was associated with long-term mortality independent of traditional CV risk factors in CAD patients who underwent PCI. They reported that high BUN levels correlated with multi-vessel disease. In concordance with this study[4], we found a correlation between BUNLVEFr with Gensini score and increased CAD burden. Akanda et al[25] found a significant association between BUN level and CAD. They suggested that measuring the BUN level could provide significant prognostic benefits in CV risk assessment and patient management. In a cohort study of over 15,000 participants, Jiang et al[10] classified the patients into three groups according to their initial BUN levels and reported that the incidence of coronary heart disease increased in patients with high BUN levels compared to those with low BUN levels during long-term follow-up. Çetin et al[26] showed a correlation between the BUN level and long-term mortality in stable-angina patients with no chronic kidney disease. We found that BUN to LVEF ratio predicted mortality in stable-angina patients with no chronic renal failure, which is consistent with a previous research[26].

Left ventricular dysfunction is a significant cause of morbidity and mortality in patients with coronary artery disease. Although decreased LVEF leads to systemic effects and symptoms of HF, the primary cause of mortality is ventricular arrhythmias, and sudden cardiac death is closely associated with low LVEF[27]. In the current study, we evaluated BUNLVEFr, a powerful new marker that can be used in the further prognostic evaluation of SAP patients undergoing CAG.

Limitations

The study was conducted with a relatively small number of patients. Studies with larger participants may better determine the cross-sectional value and long-term prognostic significance of BUNLVEFr. The fact that information on adherence was not included in our data is one of the limitations of the study. The lack of strict monitoring on drug usage data during follow-up might have affected the findings of the study.

Conclusions

BUNLVEFr can provide further prognostic information superior to BUN or LVEF alone to identify risk groups and therapeutic strategies in the long-term follow-up of SAP patients. The predictive strength of BUNLVEFr in SAP patients needs to be investigated in large prospective long-term studies.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

The study was performed under the principles stated in the Declaration of Helsinki. Recep Tayyip Erdoğan University Faculty of Medicine Non-interventional Clinical Research Ethics Committee approved the study protocol.

References

1) Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, Velazquez E, Diegeler A, Sigusch H. PCI and CABG for Treating Stable Coronary Artery Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2019; 73: 964-976.

2) Voudris KV, Kavinsky CJ. Advances in Management of Stable Coronary Artery Disease: The Role of Revascularization? Curr Treat Options Cardiovasc Med 2019; 21: 15.

3) Siontis GC, Branca M, Serruys P, Silber S, Räber L, Pilgrim T, Valgimigli M, Heg D, Windecker S, Hunziker L. Impact of left ventricular function on clinical outcomes among patients with coronary artery disease. Eur J Prev Cardiol 2019; 26: 1273-1284.

4) Kawabe M, Sato A, Hoshi T, Sakai S, Hiraya D, Watabe H, Kakefuda Y, Ishibashi M, Abe D, Takeyasu N, Aonuma K. Impact of blood urea nitrogen forlong-term risk stratification in patients with coronary artery disease undergoing percutaneous coronary intervention. Int J Cardiol Heart Vessel 2014; 4: 116-121.

5) Arihan O, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig J, Masyuk M, Lauten A, Schulze PC, Hoppe UC, Kelm M, Jung C. Blood Urea Nitrogen (BUN) is independently associated with mortality in critically ill patients admitted to ICU. PLoS One 2018; 13: e0191697.

6) Ren X, Qu W, Zhang L, Liu M, Gao X, Gao Y, Cheng X, Xu W, Liu Y. Role of blood urea nitrogen in predicting the post-discharge prognosis in elderly patients with acute decompensated heart failure. Sci Rep 2018; 8: 13507.

7) Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. Circ Heart Fail 2008; 1: 2-5.

8) Kato A, Klein JD, Zhang C, Sands JM. Angiotensin II increases vasopressin-stimulated facilitated urea permeability in rat terminal IMCDs. Am J Physiol Renal Physiol 2000; 279: 835-840.

9) Zhou J, Cui X, Jin X, Zhou J, Zhang H, Tang B, Fu M, Herlitz H, Cui J, Zhu H, Sun A, Hu K, Ge J. Association of renal biochemical parameters with left ventricular diastolic dysfunction in a community-based elderly population in China: a cross-sectional study. PLoS One 2014; 9: e88638.

10) Jiang H, Li J, Yu K, Yang H, Min X, Chen H, Wu T. Associations of estimated glomerular filtration rate and blood urea nitrogen with incident coronary heart disease: the Dongfeng-Tongji Cohort Study. Sci Rep 2017; 7: 9987.

11) Javid AZ, Haybar H, Denghan P, Haghighizadeh MH, Mohaghegh SM, Ravanbakhsh M, Mohammadzadeh A. The effects of Melissa officinalis (lemon balm) in chronic stable angina on serum biomarkers of oxidative stress, inflammation and lipid profile. Asia Pac J Clin Nutr 2018; 27: 785-791.

12) Avci A, Fidan S, Tabakçı MM, Toprak C, Alizade E, Acar E, Bayam E, Tellice M, Naser A, Kargın R. Association between the Gensini Score and Carotid Artery Stenosis. Korean Circ J 2016; 46: 639-645.

13) Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019; 32: 1-64.

14) DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44: 837-845.

15) Qian H, Tang C, Yan G. Predictive value of blood urea nitrogen/creatinine ratio in the long-term prognosis of patients with acute myocardial infarction complicated with acute heart failure. Medicine (Baltimore) 2019; 98: e14845.

16) Richter B, Sulzgruber P, Koller L, Steininger M, El-Hamid F, Rothgerber DJ, Forster S, Goliasch G, Silbert BI, Meyer EL, Hengstenberg C, Wojta J, Niessner A. Blood urea nitrogen has additive value beyond estimated glomerular filtration rate for prediction of long-term mortality in patients with acute myocardial infarction. Eur J Intern Med 2019; 59: 84-90.

17) Erdoğan T, Çetin M, Çinier G, Özer S, Yilmaz AS, Karakişi O, Kırış T. Preoperative blood urea nitrogen-to-left ventricular ejection fraction ratio is an independent predictor of long-term major adverse cardiac events in patients undergoing coronary artery bypass grafting surgery. J Saudi Heart Assoc 2020; 32: 79-85.

18) Kırış T, Avcı E, Çelik A. Association of the blood urea nitrogen-to-left ventricular ejection fraction ratio with contrast-induced nephropathy in patients with acute coronary syndrome who underwent percutaneous coronary intervention. Int Urol Nephrol 2019; 51: 475-481.

19) Jujo K, Minami Y, Haruki S, Matsue Y, Shimazaki K, Kadowaki H, Ishida I, Kambayashi K, Arashi H, Sekiguchi H, Hagiwara N. Persistent high blood urea nitrogen level is associated with increased risk of cardiovascular events in patients with acute heart failure. ESC Heart Fail 2017; 4: 545-553.

20) Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop

diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. J Am Coll Cardiol 2011; 58: 375-382.

21) Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res 2019; 124: 1598-1617.

22) Heinzel RF, Hegemann N, Hohendanner F, Primessnig U, Grune J, Blaschke F, de Boer RA, Pieske B, Schiattarella GG, Kuebler WM. Left ventricular dysfunction in heart failure with preserved ejection fraction-molecular mechanisms and impact on right ventricular function. Cardiovasc Diagn Ther 2020; 10: 1541-1560.

23) Aziz F, Tk LA, Enweluzo C, Dutta S, Zaeem M. Diastolic heart failure: a concise review. J Clin Med Res 2013; 5: 327-334.

24) McKie PM, Schirger JA, Costello-Boerrigter LC, Benike SL, Harstad LK, Bailey KR, Hodge DO, Redfield MM, Simari RD, Burnett Jr JC, Chen HH. Impaired natriuretic and renal endocrine response to acute volume expansion in pre-clinical systolic and diastolic dysfunction. J Am Coll Cardiol 2011; 58: 2095-2103.

25) Akanda M,Choudhury K, Ali M, Kabir M, Begum L, Sayami L. Serum Creatinine and Blood Urea Nitrogen Levels in Patients with Coronary Artery Disease. Cardiovasc J 2013; 5: 141-145.

26) Çetin M, Erdoğan T, Özyıldız AG, Özer S, Ayhan AÇ, Kırış T. Blood urea nitrogen is associated with long-term all-cause mortality in stable angina pectoris patients: 8-year follow-up results. Kardiologiia 2021; 61: 66-70.

27) Tan NY, Roger VL, Killian JM, Cha YM, Noseworthy PA, Dunlay SM. Ventricular Arrhythmias Among Patients With Advanced Heart Failure: A Population-Based Study. J Am Herat Assoc 2022; 11: e023377.