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

Follow this and additional works at: https://www.j-saudi-heart.com/jsha

Part of the Cardiology Commons

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

Turan Erdoğan [a], Mustafa Çetin [a], Göksel Çinier [b], Savaş Özer [c], Ahmet Seyda Yõlmaz [a,*], Ozan Karakişi [d], Tuncay Kõrõş [e]

[a] Department of Cardiology, RTE University, Faculty of Medicine, Rize, Turkey
[b] Department of Cardiology, Kackar State Hospital, Rize, Turkey
[c] Department of Cardiology, RTE Education and Research Hospital, Rize, Turkey
[d] Department of Cardiovascular Surgery, RTE University, Faculty of Medicine, Rize, Turkey
[e] Department of Cardiology, Katip Çelebi Üniversity, Atatürk Educational and Research Hospital, İzmir, Turkey

Abstract

Background: Long-term mortality rate following coronary artery bypass grafting (CABG) procedure is still considered to be high despite advances in surgical techniques and perioperative management. Identifying high-risk patients by using cost-effective and clinically useful parameters is needed.

Methods: Patients who were admitted to our cardiology clinic with the diagnosis of coronary artery disease and underwent CABG between January 2008 and August 2010 were included. Study patients were followed-up for 112.6 ± 17.8 months for major adverse cardiac events (MACE) which were defined as all-cause mortality and new-onset decompensated heart failure (HF).

Results: Patients in MACE (+) group were older ($p < 0.001$), had higher additive Euroscore ($p < 0.001$), and lower left ventricular ejection fraction ($p < 0.001$). Multivariate Cox regression analysis showed that additive Euroscore [odds ratio (OR) = 1.601; 95% confidence interval (CI) = 1.374−1.864; $p < 0.001$)] and blood urea nitrogen-to-left ventricular ejection fraction ratio (BUNEFr; OR = 1.028; 95% CI = 1.006−1.050; $p = 0.011$) independently predicted MACE. Receiver operating characteristic curve analysis demonstrated that BUNEFr had an area under curve of 0.794 and BUNEFr >33 had a sensitivity and specificity of 74% and 64%, respectively.

Conclusion: BUNEFr is a clinically useful and cost-effective parameter for the prediction of long-term mortality and new-onset decompensated HF in patients undergoing CABG.

Keywords: Blood urea nitrogen, Coronary artery bypass grafting, Left ventricular ejection fraction, Major adverse cardiac event

1. Introduction

Coronary artery bypass grafting (CABG) surgery still remains a treatment of choice for revascularization of diffuse coronary artery disease (CAD) and three-vessel disease involving the left anterior descending artery [1]. Despite improvements in periprocedural care, surgical techniques, and operator's experience, in-hospital and long-term mortality rates following CABG are still relatively high. Identifying those with a high risk for mortality is of utmost importance for

tailoring guideline-directed therapy and for stricter follow-up. Several risk scores are developed for predicting both short- and long-term mortality, but the ideal risk score still remains debatable.

Renal functions are well-known prognostic factor for CAD [2]. In daily practice, elevated serum creatinine (sCr) level and decreased glomerular filtration rate (GFR) are considered as worsening in renal functions. Blood urea nitrogen (BUN) is another blood marker that is associated with renal functions, but its sensitivity and specificity is less compared with sCr and GFR. However, in addition to reflecting GFR, BUN may rise independent of changes in GFR or sCr owing to enhanced proximal tubular reabsorption of urea under the activation of the sympathetic nervous and renin–angiotensin–aldosterone systems (RAAS) [3]. Thus, BUN may reflect neurohormonal dysregulation in patients with depressed left ventricular ejection fraction (LVEF) [4–6] and is found to be a predictor for long-term mortality following CABG [7].

In the present study, we investigated the predictive value of the ratio of BUN to LVEF (BUNEFr) for the occurrence of all-cause mortality and new-onset decompensated heart failure (HF) following CABG.

2. Methods

In this prospective, observational, cohort study, patients who were admitted to our cardiology clinic with the diagnosis of CAD between January 2008 and August 2010 were included. The diagnosis of CAD constituted stable CAD, unstable CAD, ST-segment elevation myocardial infarction, and non-ST segment elevation myocardial infarction. Only patients who underwent CABG procedure following initial admittance to the hospital and subsequent coronary artery angiography (CAG) were evaluated in the final analysis. The decision for CABG or percutaneous coronary intervention was made by the careful evaluation of the patients by cardiology and cardiovascular surgery teams. Informed consents were obtained from all of the participants of the study.

Study patients were followed-up for 112.6 ± 17.8 months for major adverse cardiac events (MACE) which were defined as all-cause mortality and new-onset decompensated HF. After surgery, all patients were followed for MACE during the postoperative period. Data for MACE were obtained from the national and institutional databases, hospital records, routine clinical visits, or by phone interviews with patients and their families. The

Abbreviation	
ASA	Acetylsalicylic acid
BUN	Blood urea nitrogen
BMI	Body mass index
Cr	Creatinine
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
Dis	Discharge
SAP	Stable angina pectoris
USAP	Unstable angina pectoris
NSTEMI	Non ST Elevation MI
STEMI	ST Elevation MI
LVEF	Left ventricular ejection fraction
LMCA	Left main coronary artery
OAD	Oral antidiabetic

study was performed in accordance with the principles stated in the Declaration of Helsinki. The local ethics committee approved the study protocol.

Clinical characteristics, which consisted of multiple descriptors from each patient's medical history and physical examination, were collected by physicians from the cardiology clinic for each patient prior to CAG and were stored in the database of coronary angiography laboratory in our institution. We recorded the baseline characteristics, including hypertension, diabetes mellitus, smoking history, family history for CAD, and blood's parameters. Preoperative BUN value, which was obtained from a sample prior to CABG surgery, was used in our study. Both echocardiography and BUN measurements were performed on the same day before CABG surgery.

Additive Euroscore of each patient was calculated using an online web calculator in the website http://www.euroscore.org/calc.html. Preoperative myocardial infarction (MI) and chronic obstructive pulmonary disease were diagnosed in accordance to the latest guideline documents [8,9]. All patients were evaluated by carotid artery Doppler ultrasonography for the detection of carotid artery stenosis. Extracardiac arthropathy was defined as limb claudication, carotid artery stenosis more than 50%, chronic total occlusion of any artery in extremities, previous history of amputation due to peripheral artery disease (PAD), and previous history of intervention to abdominal aorta, extremities, and carotid arteries for the treatment of PAD.

Exclusion criteria were patients with GFR <30 mL/min/1.73 m^2, those on chronic dialysis, more than moderate valvular heart disease, re-do CABG cases, chronic liver disease, active infection, inflammatory diseases, malignancy, and emergent CABG procedures.

Standard transthoracic and Doppler echocardiographic examinations were performed using a 3.25-MHz transthoracic transducer connected to a Vivid 5 System (GE Vingmed Ultrasound AS, Horten, Norway). Two echocardiographers who were unaware of the study performed the examinations, and they were blinded to the echocardiograms and clinical status of each patient. Left ventricular end-systolic dimension, end-diastolic dimension, wall thickness, and left atrial volume were measured according to the guidelines of the American Society of Echocardiography [10]. Left ventricular end-systolic and end-diastolic volumes and ejection fraction were measured from the apical four- and two-chamber views using the modified Simpson method.

2.1. Statistical analysis

Continuous variables were presented as mean values (standard deviation) or medians with ranges, and the categorical variables were expressed as percentages. The variables were compared using a two-tailed Student t test for the continuous variables of normal distribution or the Mann—Whitney U test for the continuous variables of non-normal distribution. A Chi-square test was used for categorical variables. The effects of various variables on MACE were calculated by univariate regression analysis. In these analyses, 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 MACE. The predictive values of BUN, LVEF, and BUNEFr were estimated by areas under the receiver operating characteristic (ROC) curve. We used the DeLong test to compare the area under the curve (AUC) with each of these parameters [11]. All statistical tests were two-tailed, and a p value <0.05 value was considered significant. All analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

3. Results

Between January 2008 and August 2010, 948 patients were admitted to the hospital with the diagnosis of CAD. Among those, 304 patients had undergone CABG surgery, 32 had acute or chronic kidney disease, 30 had more than moderate valvular diseases, four had re-do CABG, five had chronic liver diseases, 12 had active infection, three had inflammatory diseases, four had malignancy, and in 14 patients CABG surgery was performed in emergency settings. These patients were excluded from the study. The remaining 202 patients constituted the study population. The mean age of patients was 61.2 ± 9.8 years and 38 (18.8%) were female. During the follow-up, 64 (31.6%) patients had MACE including 48 (23.7%) died and 16 (7.9%) developed new-onset HF.

Patients were divided into two groups according to MACE. Patients in the MACE (+) group were older ($p < 0.001$), had higher additive Euroscore ($p < 0.001$) and lower LVEF ($p < 0.001$). No significant difference was noted among patients regarding hypertension, diabetes, dyslipidemia, sex, smoke status, and body mass index. The number of patients with coronary artery disease with >50% stenosis was higher in the MACE (+) group ($p = 0.02$), and patients who had severe carotid artery stenosis were more likely to develop MACE ($p = 0.01$). No difference was noted for the presence of stenosis in left main stem. Revascularization using left internal mammary artery was associated with reduced MACE; however, this did not reach statistical significance ($p = 0.082$; Table 1).

The sCr level was higher in patients with MACE (+), but this also did not reach statistical significance ($p = 0.065$). By contrast, both BUN ($p < 0.001$) and BUNEFr ($p < 0.001$) were significantly higher in MACE (+) group (Table 1).

We performed correlation analysis for BUNEFr which revealed that age ($r = 0.269$, $p < 0.001$), additive Euroscore ($r = 0.486$, $p < 0.001$), hypertension ($r = 0.164$, $p = 0.021$), diabetes ($r = 0.145$, $p = 0.042$), diffuse CAD ($r = 0.232$, $p = 0.002$), sCR ($r = 0.324$, $p < 0.001$), and hemoglobin (Hb; $r = -0.212$, $p = 0.003$) levels were significantly correlated with BUNEFr.

Univariate Cox analysis showed that additive Euroscore ($p < 0.001$), number of CAD with >50% stenosis ($p = 0.019$), BUN ($p = 0.003$), BUNEFr ($p < 0.001$), and Hb ($p = 0.010$) levels were associated with MACE (Table 2).

We performed multivariate Cox regression analysis to identify independent predictors for MACE during the follow-up. Additive Euroscore [odds ratio (OR) = 1.601; 95% confidence interval (CI) = 1.374—1.864; $p < 0.001$)] and BUNEFr (OR = 1.028; 95% CI = 1.006—1.050; $p = 0.011$) were found to independently predict MACE (Table 2).

The ROC curve analysis demonstrated that BUNEFr, LVEF, and BUN had an AUC of 0.794, 0.629, and 0.711, respectively (Fig. 1). BUNEFr >33 had a sensitivity and specificity of 74% and 64%, respectively. Comparison of AUCs of BUNEFr, BUN, and LVEF revealed that BUNEFr predicted MACE with greater sensitivity and specificity (BUNEFr to LVEF: $p = 0.0143$; BUNEFr to BUN: $p < 0.001$; Table 3). We created a Kaplan—Meier

Table 1. Baseline characteristics of the study population.

Variable	MACE (−) (n = 138)	MACE (+) (n = 64)	All patients (n = 202)	p
Age (y)	58.8 ± 8.4	65.3 ± 9.7	61.2 ± 9.8	<0.001
Male sex (%)	82.6	79.6	81.6	0.620
Diabetes mellitus (%)	49.2	37.5	48.7	0.119
Hyperlipidemia (%)	75.9	78.1	76.6	0.731
Hypertension (%)	58.7	68.7	46.7	0.173
Current smoking (%)	45.6	51.5	50.3	0.436
BMI (kg/m^2)	28.6	281.1	28.5	0.341
Euroscore	2.8 ± 1.5	4.6 ± 1.8	2.95 ± 1.8	<0.001
Carotid stenosis (%)	2.27	10.9	5.1	0.010
COPD (%)	15.2	20.3	16.8	0.373
Diagnosis (%)				
SAP	65.5	56.9	58	
USAP/NSTEMI	26.8	34.1	33.9	0.392
STEMI	7.5	8.8	8	
LVEF (%)	54.9	44.4	51.6	<0.001
LMCA >%50	10.4	12.6	11.2	0.632
Number of CAD	2.4 ± 0.7	2.6 ± 0.64	2.5 ± 0.68	0.024
Glucose (*Fasting*)	122 ± 35.6	133.4 ± 56	130.1 ± 51	0,038
BUN (mg/dL)	16.1 ± 5.3	18.8 ± 5.5	17.1 ± 5.4	0.001
BUNEFr	31.08 ± 12	45.5 ± 19	35.7 ± 16.1	<0.001
Serum creatinine (mg/dL)	0.96 ± 0.21	1.02 ± 0.21	0.98 ± 0.21	0.065
Total cholesterol (mg/dL)	177 ± 44.8	174.6 ± 45.4	176.8 ± 45	0.621
LDLc (mg/dL)	111.2 ± 37	114.8 ± 35.2	112.6 ± 36.7	0.592
HDLc (mg/dL)	35.5 ± 8.8	35.6 ± 9.4	35.5 ± 8.9	0.951
WBC (10^3/μm^3)	7.9 ± 2	7.9 ± 2.1	7.9 ± 2.03	0.964
Neutrophil (10^3/μm^3)	4.9 ± 1.8	5.03 ± 1.9	4.9 ± 1.8	0.721
Hb (g/dL)	13.5 ± 1.3	13.1 ± 1.4	13.4 ± 1.3	0.020
ASA (*dis.*) (%)	51.7	59.6	56.3	0.332
Clopidogrel (*dis.*) (%)	10.8	15.3	12.2	0.405
ß-Blocker (*dis.*) (%)	71.9	76.9	73.4	0.496
ACE/ARB (*dis.*) (%)	42.5	50	44.9	0.334
CCB (*dis.*) (%)	7.8	6.4	7.4	0.571
OAD/Insulin (*dis.*) (%)	24	18.9	22.6	0.531
Statin (*dis.*) (%)	70.8	61.29	67.7	0.188
Mortality, *n* (%)	0	48 (75)	48 (23.7)	<0.001
New onset HF, *n* (%)	0	16 (25)	16 (7.9)	<0.001
MACE, *n* (%)	0	64 (100)	64 (31.6)	<0.001

Data are presented as % or mean ± SD.

ACE = angiotensin converting enzyme; ARB = angiotensin-reception blocker; ASA = acetylsalicylic acid; BMI = body mass index; BUN = blood urea nitrogen; BUNEFr = blood urea nitrogen-to-left ventricular ejection fraction ratio; CAD = coronary artery disease; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; Dis = discharge; Hb = hemoglobin; HDLc = high-density lipoprotein cholesterol; HF = heart failure; LDLc = low-density lipoprotein cholesterol; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; MACE = major cardiac adverse events; NSTEMI = non-ST elevation myocardial infarction; OAD = oral anti-diabetic; SAP = stable angina pectoris; STEMI = ST elevation myocardial infarction; USAP = unstable angina pectoris; WBC = white blood cell.

Table 2. Cox regression analysis.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Euroscore I	1.480	1.351−1.620	<0.001	1.601	1.374−1.864	<0.001
Number of coronary arteries with significant stenosis	1.770	1.100−2.848	0.019	1.171	0.688−1.994	0.560
BUN	1.059	1.020−1.100	0.003	1.003	0.933−1.079	0.931
Glucose	1.013	1.003−1.028	0.018			
LVEF	0.948	0.929−0.968	<0.001			
BUNEFr	1.043	1.031−1.054	<0.001	1.036	1.019−1.054	<0.001
Serum creatinine	2.734	0.967−7.730	0.058			
Hemoglobin	0.777	0.641−0.943	0.010	1.086	0.869−1.357	0.467

BUN = blood urea nitrogen; BUNEFr = blood urea nitrogen-to-left ventricular ejection fraction ratio; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio.
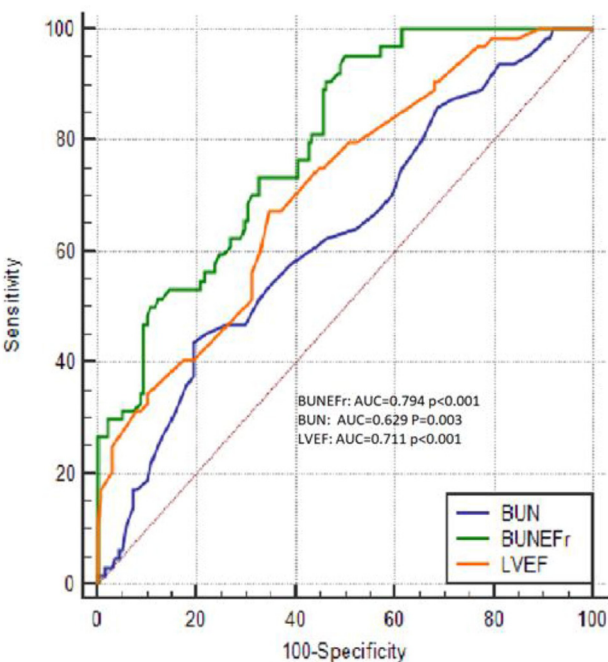
Fig. 1. Sensitivity and specificity of BUNEFr, BUN, and LVEF in predicting major adverse cardiac events. AUC = area under the curve; BUN = blood urea nitrogen; BUNEFr = blood urea nitrogen-to-left ventricular ejection fraction ratio; LVEF = left ventricular ejection fraction.

Fig. 2. Kaplan−Meier analysis for survival when BUNEFr >33 mg/dL. BUNEFr = blood urea nitrogen-to-left ventricular ejection fraction ratio.

graph for BUNEFr cutoff value of 33 which showed increased MACE beginning from even the first months following CABG (Fig. 2).

4. Discussion

In the present study, we found that during 10 years of follow-up, elevated BUNEFr and increased additive Euroscore predicted MACE in patients who underwent CABG procedure. To date, this is the first report to study role of BUNEFr in the prediction of MACE in patients with CAD.

Blood urea nitrogen is a blood parameter whose serum level is influenced by several factors including renal functions, neurohormonal, and sympathetic activity. In particular, serum BUN level increases in patients with HF due to passive reabsorption of urea from renal tubules in response to activation of sympathetic system and RAAS [4−6].

Table 3. Comparison of area under curves of BUNEFr, BUN, and LVEF.

	AUC Dif.	SE	95% CI	Z	p
BUNEFr to LVEF	0.082	0.0338	0.016−0.149	2.450	0.0143
BUNEFr to BUN	0.165	0.0310	0.104−0.225	5.310	<0.001

AUC = area under the curve; BUN = blood urea nitrogen; BUNEFr = blood urea nitrogen-to-left ventricular ejection fraction ratio; CI = confidence interval; LVEF = left ventricular ejection fraction.
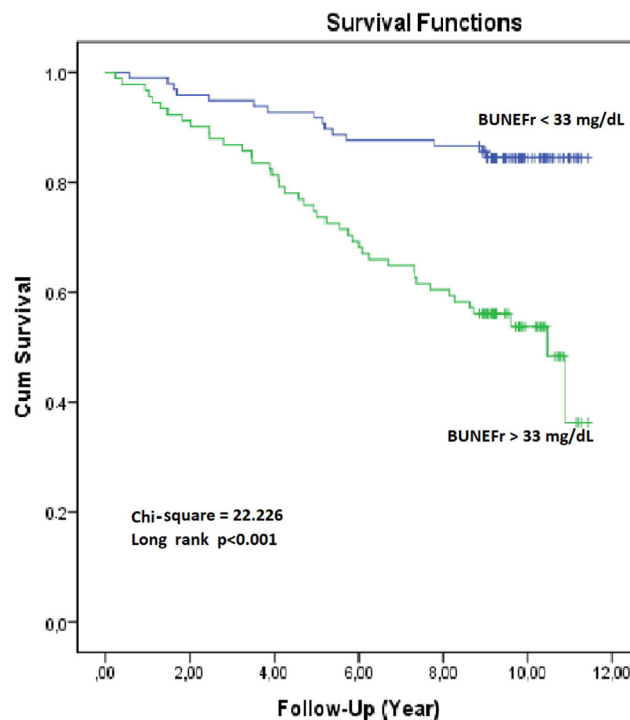
Activation of the neurohormonal system could also lead to renal vasoconstriction and decreased GFR and urea excretion [12,13]. Furthermore, insufficient blood volume secondary to low cardiac output stimulates the release of arginine vasopressin, which can facilitate the reabsorption of BUN in the collecting duct [14,15]. Thus, BUN may serve as an indicator of both cardiorenal dysfunction and neurohormonal activation [16]. BUN has been considered as a prognostic predictor of long-term mortality in acute and chronic HF [17,18]. In addition, data from several recent studies suggested that elevation in serum BUN level predicted worse outcomes in patients with acute MI, acute coronary syndrome, and following elective percutaneous coronary procedures [19−22]. Arnan et al. [23] reported that an increase in the BUN level was associated with an increased risk of stroke during the postoperative period following cardiovascular surgery.

Prior studies mainly included patients with LV systolic dysfunction and subsequent activation in sympathetic system and RAAS. By contrast, diastolic dysfunction can cause activation in both systems in a similar manner, HF symptoms due to elevation in LV end-diastolic filling pressures, and is associated with adverse cardiac outcomes including cardiovascular mortality [24−26]. Diastolic dysfunction can be frequently diagnosed in patients with systolic HF,

and both entities share similar risk factors including diabetes and hypertension [27,28]. This can have an additional impact on activating the neurohormonal system and RAAS leading to elevation in BUN level [6,29]. Importantly, LVEF may have limitations in reflecting the renal functions and thus it is reasonable to consider BUNEFr as a more systemic marker than LVEF alone given the fact that comorbidities including diabetes and hypertension can also cause renal dysfunction and BUNEFr reflects the effect of cardiac function on the renal system not only through LV systolic function but also through a diastolic component [30].

It is important to note that BUN also has limitation in predicting prognosis in cardiovascular diseases because several other conditions can affect its level. Although LVEF has limitations in reflecting systemic mechanisms leading to adverse events, it is still the most reliable predictor of prognosis particularly in HF [31].Thus, combining BUN and LVEF as one parameter could have better accuracy for both a systemic and local marker.

In conclusion, although it is not possible to define precise pathophysiological mechanisms, we found that the BUNEFr value determined during the pre-operative period could predict patients that were a high risk for new-onset HF and all-cause mortality in patients undergoing CABG procedure. It is important to note that both BUN and LVEF are easily obtainable parameters, and BUNEFr could be a cost-effective way to risk stratify patients prior to the CABG procedure.

4.1. Limitation

This is a single-center study with a limited number of patients. Due to inherent characteristics of observational studies, we cannot demonstrate the precise causative mechanism between BUNEFr and MACE.

Conflict of interest

The authors declare no potential conflict of interest.

References

[1] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87—165.

[2] Na KY, Kim CW, Song YR, Chin HJ, Chae DW. The association between kidney function, coronary artery disease, and clinical outcome in patients undergoing coronary angiography. J Korean Med Sci 2009;24:S87—94.

[3] Usberti MA, Federico ST, Di Minno GI, Ungaro BI, Ardillo GI, Pecoraro CA, et al. Effects of angiotensin II on plasma ADH, prostaglandin synthesis, and water excretion in normal humans. Am J Physiol 1985;248:F254—9.

[4] Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. Circ Heart Fail 2008;1:2—5.

[5] 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: F835—40.

[6] Zhou J, Cui X, Jin X, Zhou J, Zhang H, Tang B, et al. 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.

[7] Hartz AJ, Kuhn EM, Kayser KL, Johnson WD. BUN as a risk factor for mortality after coronary artery bypass grafting. Ann Thorac Surg 1995;60:398—404.

[8] Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Circulation 2007;116:2634—53.

[9] Minas M, Dimitropoulos K, Pastaka C, Papadopoulos D, Markoulis N, Gourgoulianis KI. Global initiative for chronic obstructive lung disease for chronic obstructive pulmonary disease: GOLD opportunity for lung disorders. Prev Med 2005;40:274—7.

[10] Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation 2003;108:1146—62.

[11] DeLong ER, DeLong DM, Clarke-Pearson DL. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837—45.

[12] Murata A, Kasai T, Matsue Y, Matsumoto H, Yatsu S, Kato T, et al. Relationship between blood urea nitrogen-to-creatinine ratio at hospital admission and long-term mortality in patients with acute decompensated heart failure. Heart Vessels 2018;33:877—85.

[13] Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819—23.

[14] Georgiopoulou VV, Tang WW, Giamouzis G, Li S, Deka A, Dunbar SB, et al. Renal biomarkers and outcomes in outpatients with heart failure: the Atlanta cardiomyopathy consortium. Int J Cardiol 2016;218:136—43.

[15] Sood MM, Saeed M, Lim V, Cordova F, Komenda P, Malik A, et al. The urea-to-creatinine ratio õs predictive of worsening kidney function in ambulatory heart failure patients. J Card Fail 2015;21:412—8.

[16] Gohbara M, Hayakawa A, Akazawa Y, Furihata S, Kondo A, Fukushima Y, et al. Association between acidosis soon after reperfusion and contrast-õnduced nephropathy in patients with a first-time ST-segment elevation myocardial õnfarction. J Am Heart Assoc 2017;6:e006380.

[17] Jujo K, Minami Y, Haruki S, Matsue Y, Shimazaki K, Kadowaki H, et al. 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—53.

[18] 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—82.

[19] Richter B, Sulzgruber P, Koller L, Steininger M, El-Hamid F, Rothgerber DJ, et al. 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.

[20] Adam AM, Nasir SA, Merchant AZ, Rizvi AH, Rehan A, Shaikh AT, et al. Efficacy of serum blood urea nitrogen,

creatinine and electrolytes in the diagnosis and mortality risk assessment of patients with acute coronary syndrome. Indian Heart J 2018;70:353—9.

[21] Horiuchi Y, Aoki J, Tanabe K, Nakao K, Ozaki Y, Kimura K, et al. A high level of blood urea nitrogen õs a significant predictor for õn-hospital mortality in patients with acute myocardial õnfarction. Int Heart J 2018;59:263—71.

[22] 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 2019;98:e14845.

[23] Arnan MK, Hsieh TC, Yeboah J, Bertoni AG, Burke GL, Bahrainwala Z, et al. Postoperative blood urea nitrogen is associated with stroke in cardiac surgical patients. Ann Thorac Surg 2015;99:1314—20.

[24] Bernal J, Pitta SR, Thatai D. Role of the renin-angiotensin-aldosterone system in diastolic heart failure: potential for pharmacologic intervention. Am J Cardiovasc Drugs 2006;6: 373—81.

[25] Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565—74.

[26] Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1—82.

[27] Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144—50.

[28] Aziz F, Luqman-Arafath TK, Enweluzo C, Dutta S, Zaeem M. Diastolic heart failure: a concise review. J Clin Med Res 2013; 5:327—34.

[29] Metkus TS, Suarez-Pierre A, Crawford TC, Lawton JS, Goeddel L, Dodd-o J, et al. Diastolic dysfunction is common and predicts outcome after cardiac surgery. J Cardiothorac Surg 2018;13:67.

[30] Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. Eur Heart J 2012;33: 2135—42.

[31] Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877—83.