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BLOOD UREA NITROGEN-TO-LEFT VENTRICULAR EJECTION FRACTION RATIO AS A PREDICTOR FOR CONTRAST INDUCED NEPHROPATHY IN ACUTE CORONARY SYNDROME PATIENTS WHO WERE TREATED WITH PERCUTANEOUS CORONARY INTERVENTIO

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Abstract

Background: Blood urea nitrogen (BUN) is an informative marker for both renal and cardiac performance in addition to the neurohormonal activity associated with their impairment. The aim of this study was to investigate the predictive value of the blood urea nitrogen-to-left ventricular ejection fraction ratio (BUN/EF) for the development of contrast induced nephropathy (CIN) in patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI). A total of 100 patients with ACS who were planning to attend PCI were enrolled in this observational study. The serum creatinine, BUN and LVEF were measured on the same day before contrast medium exposure. BUN/EF was determined for all patients. Serum creatinine was measured after PCI (48–72 hours) to detect development of CIN.

Results: CIN had been developed in 14 cases (14%). Patients who developed CIN were older, had higher frequency of diabetes mellitus, higher frequency of hypertension and higher GENSINI Scores than those who had not develop CIN. BUN values were greater in the CIN group than those in the non-CIN one (22.8 ± 3 mg/dl vs 13.6±2.97 mg/dl, $p<0.001$). LVEF was lower in CIN group than the non-CIN one. (37.6±1.6% vs 49.4±7.3%, $p<0.001$). BUN/EF was greater in the CIN cases than the no-CIN cases (0.61±0.1 vs 0.3±0.1, $p<0.001$). BUN/EF cutoff value >0.47 had sensitivity of 92.8% and specificity of 98.8% to predict CIN in ACS patients after PCI ($p< 0.001$). BUN/EF was independent risk factor in a multivariate logistic regression analysis for the development of CIN (OR 469.6, confidence interval: 25.74-8568.5, $p<0.001$).

Conclusion: In addition to common risk factors of acute kidney injury initiated by contrast exposure during coronary intervention, BUN/EF could predict development of contrast induced nephropathy in patients with ACS who underwent coronary intervention.

Keywords: Acute coronary syndrome, Contrast-induced nephropathy, Blood urea nitrogen, left ventricular ejection fraction.

Background

The risk of CIN in patients with ACS who were treated with primary PCI is about 12% of all patients.[1] CIN results in a longer

stay in the hospital, higher medical expenses and increased morbidity and mortality.[2] Patients with acute myocardial infarction who developed contrast induced acute kidney injury had higher rate of in-hospital mortality.[3] CIN is described as a 25% rise in creatinine concentration of serum from baseline level or an absolute rise in serum creatinine of at least 0.5 mg/dl throughout 2-3 days following administration of contrast.[4] CIN risk factors include chronic renal impairment, systolic heart failure, elderly, reduced hemoglobin, high plasma glucose level, and increasing contrast medium volume.[5,6] BUN which represents compromised cardiac performance, neurological and hormonal activity could be used as an informative and predictor factor for CIN.

Aim of the study

The aim of this study was to investigate the predictive value of the blood urea nitrogen-to-left ventricular ejection fraction ratio (BUN/EF) for the development of contrast induced nephropathy after PCI.

Methods

It was observational study that included 100 patients who were admitted by ACS and underwent PCI in the period between March 2019 and June 2020. Patients on renal dialysis, patients had reduced glomerular filtration rate (GFR) <30 mL/minute/1.73 m^2, patients had prior exposure to contrast within 48 hours before PCI were excluded from the study. All the patients have signed a written informed consent. The study was reviewed and approved by the institutional review board of our university (IRB approval number: 4/19419CARD) in accordance to the declaration of Helsinki. All the patients were subjected to complete medical history including cardiovascular risk factors and physical examination including body mass index and vital signs.

Electrocardiogram:

ST segment elevation myocardial infarction (STEMI) was diagnosed by new ST-elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥ 2mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age. Non-STEMI was defined by elevated cardiac enzymes without persistent ST elevation or with ST depression.[7]

Blood sampling and echocardiographic analysis:

Serum creatinine and urea nitrogen levels were assessed at the time of

admission. Baseline GFR was calculated using the modification of diet in renal disease (MDRD-4) equation.[8]

The modified Simpson's method has been used to measure the LVEF after estimating the end-diastolic and end-systolic left ventricular volumes in the apical 4-chamber and 2-chamber views.[9] Both LVEF and BUN were measured on the same day before coronary angiography. Serum creatinine was measured 2–3 days following the procedure to detect patients who developed CIN. CIN is described as a 25% rise in creatinine concentration of serum from baseline level or an absolute rise in serum creatinine of at least 0.5 mg/dl throughout 2-3 days following administration of contrast.[4] Patients had been classified into 2 groups according to the presence or absence of CIN. Mehran risk score [10] (Mehran Score for Post-PCI Contrast Nephropathy - MDCalc) was used to assess the risk of developing CIN. The severity of heart failure in the studied patients was graded by Killip Classification [11] (Killip Classification for Heart Failure - MDCalc).

Angiographic Analysis:

Primary PCI was done for STEMI patients, immediate invasive strategy (within 2 hours) was applied to very high risk NSTMI patients, early invasive strategy was applied to high-risk patients (within 24 hours) while invasive PCI within 72 hours was applied to intermediate risk NSTEMI patients.[12] Assessment of angiographic lesion severity was done by Modified GENSINI score.[13] Non-ionic low-osmolar contrast were used for all patients.

Statistical analysis

The Statistical Package of Social Sciences (SPSS) version 21 for Windows has been utilized to analyze the data (SPSS, Inc., Chicago, IL, USA). For quantitative variables and/or patients' number, the median, mean, and standard deviation have been used, although percent has been used for qualitative variables. The Kolmogorov-Smirnov test for normality was used to analyze the distribution of the measured variables. The significance of variations among continuous values was calculated using an independent samples t test for parameters with a normal distribution and a Mann-Whitney test for parameters that were not distributed normally. When comparing qualitative variables, the chi-square or Fisher exact test has been used, as applicable. After performing a univariate study to identify significant factors that influenced mortality, a multivariate logistic regression test was used to analyze four significant factors, which included a combination of socioeconomic, medical, and lab factors.

Results

Patients were divided into 2 groups, the first group included patients who developed CIN (14 patients, 14%) and the second represent those who did not develop CIN (86 patients, 86%). Patients who developed CIN were older, had higher frequency of cardiovascular risk factors (diabetes mellitus, hypertension, smoking), lower BMI than those who had not developed CIN (Table 1). BUN values on admission were greater in the CIN group than those in the non-CIN one (22.8±2.94 mg/dl vs 13.6±3 mg/dl, p<0.001). LVEF at admission was lower in CIN group than the non-CIN one (37.9±1.6% vs 49.4±7.3%, p <0.001). BUN/EF was greater in the CIN cases than the no-CIN cases (0.6±0.1 vs 0.3±0.1, p<0.001). Cases with CIN received more contrast volume than non-CIN cases (301.4 ± 55.2 ml vs 179.1 ± 58.7 ml, p<0.001). Patients who developed CIN had higher Killip classification, higher Mehran and higher GENSINI Scores than who did not develop. Table 2, figure 1.

Table 1: Epidemiological and clinical characteristics of the study population

	No CIN (n = 86)	CIN (n = 14)	Test of Sig.	p
Age (yr.)	54.7 ± 11.1	66.5 ± 8.5	t=3.804*	<0.001*
Female gender (n, %)	11 (12.8%)	7 (50%)	$\chi2$=11.294*	p=0.003*
BMI (kg/m^2)	29.1 ± 4.1	23.9 ± 5.4	t=4.179*	<0.001*
Diabetes mellitus (n, %)	48(55.8%)	12(85.7%)	$\chi2$=4.485*	0.034*
Hypertension (n, %)	42(48.8%)	11(78.6%)	$\chi2$=4.273*	0.039*
Smoking (n, %)	71 (82.6%)	7 (50%)	$\chi2$=7.438*	p=0.012*
Type of ACS				
NSTEMI (n, %)	11(12.8%)	3 (21.4%)	$\chi2$=2.896	p=0.263
STEMI (n, %)	75(87.2%)	11 (78.6%)		
Killip class				
I	46 (53.5%)	0 (0%)		
II	29 (33.7%)	2 (14.3%)	$\chi2$=34.393*	p<0.001*
III	11 (12.8%)	9 (64.3%)		
IV	0 (0%)	3 (21.4%)		

CIN: contrast induced nephropathy, BMI: body mass index, ACS: acute coronary syndrome, χ^2: Chi square test, t: Student t-test, *: Statistically significant at p ≤ 0.05

The sensitivity of baseline BUN/EF as a predictor of CIN was 92.86% and specificity of 98.84%, with a high statistically significant p value. By using ROC curve analysis, the predictive value of BUN/EF for development of CIN in the studied patients was better than serum creatinine alone (the area under curve for BUN/EF was 0.999, while for serum creatinine was 0.888, p<0.001), LVEF alone (the area under curve for LVEF was 0.96, p<0.001), and BUN alone (the area under curve for BUN was 0.981, p<0.001). Table 3, figure 2.

Table 2: Laboratory data of the study population

	No CIN (n = 86)	CIN (n = 14)	Test of Sig.	p
Hemoglobin (gm/dl)	13.4 ± 1.2	9.1 ± 0.3	t=30.010*	<0.001*
BUN at admission (gm/dl)	13.6 ± 3	22.8 ± 2.9	t=10.748*	<0.001*
eGFR at admission (mL/minute/1.73 m^2)	114.6 ± 40	66.8 ± 15.5	U=109.50*	<0.001*
Admission serum creatinine (mg/dl)	0.8 ± 0.2	1.1 ± 0.2	U=227.50*	<0.001*
post PCI serum creatinine (mg/dl)	0.9 ± 0.2	2 ± 0.3	U=0.0*	<0.001*
LVEF %	49.4 ± 7.3	37.6 ± 1.6	t=13.191*	<0.001*
BUN/EF	0.3 ± 0.1	0.6 ± 0.1	t=15.167*	<0.001*
CIN risk score (points)	5.1 ± 2.8	16.4 ± 5.3	U=26.50*	<0.001*
Gensini score (points)	61.1 ± 34	89.4 ± 39.3	U=336.0*	0.008*
Contrast volume (ml)	179.1 ± 58.7	301.4 ± 55.2	U=59.50*	<0.001*

CIN: contrast induced nephropathy, BUN: blood urea nitrogen, GFR: glomerular filtration rate (mL/minute/1.73 m2), LVEF: left ventricular ejection fraction, BUNEF: blood urea nitrogen-to-left ventricular ejection fraction ratio, t: Student t-test, U: Mann Whitney test, *: Statistically significant at p ≤ 0.05

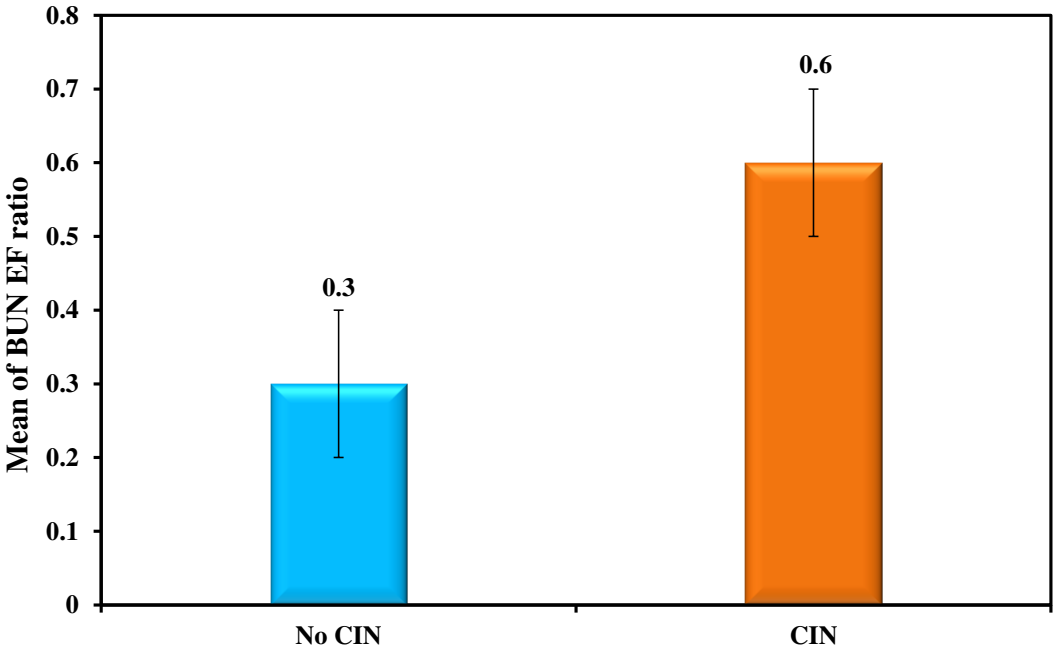

Figure 1: Difference in BUN/EF among both studied groups

Table 3: Validity (AUC, sensitivity, specificity) for different parameters to predict CIN in the studied patients

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
LVEF %	0.960	<0.001*	0.923 – 0.997	≤39	85.71	94.19	70.6	97.6
Serum creatinine	0.811	<0.001*	0.711 – 0.911	>0.8	92.86	56.98	26.0	98.0
BUN	0.981	<0.001*	0.959 – 1.0	>18	85.71	96.51	80.0	97.6
BUN/EF	0.999	<0.001*	0.996 – 1.0	>0.47	92.86	98.84	92.9	98.8

LVEF: left ventricular ejection fraction, BUN: blood urea nitrogen, BUN/EF: blood urea nitrogen-to-

left ventricular ejection fraction ratio, AUC: Area Under a Curve, p value: Probability value, CI: Confidence Intervals, PPV: Positive predictive value, NPV: Negative predictive value, *: Statistically significant at p ≤ 0.05

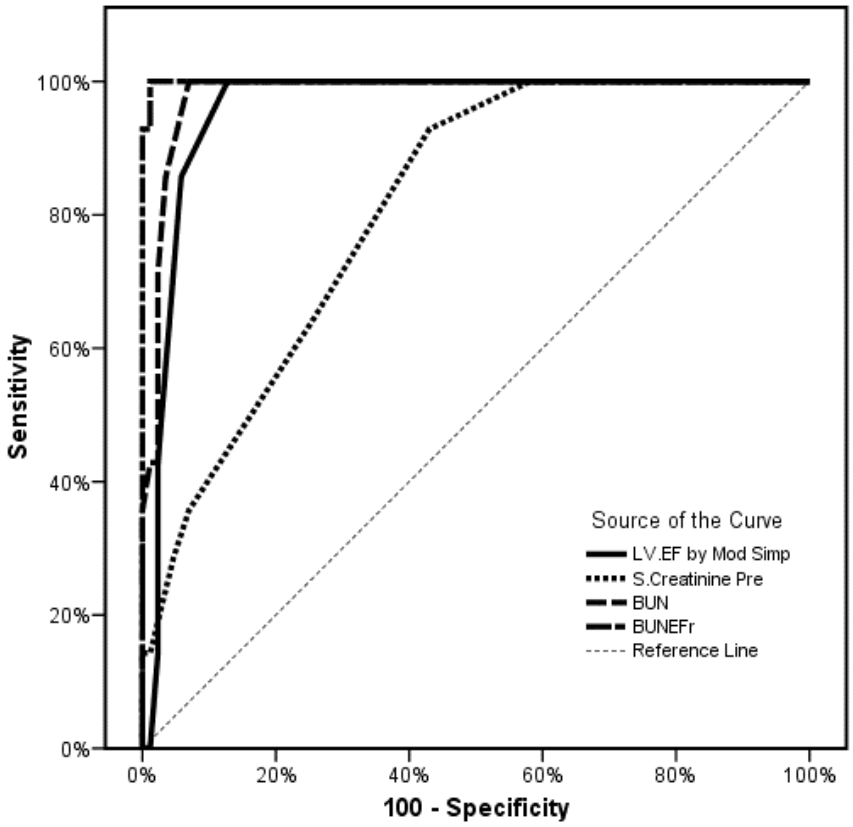

Figure 2: ROC curve for different parameters to predict CIN in the studied patients. BUN: blood urea nitrogen, LVEF: left ventricular ejection fraction, BUN/EF: blood urea nitrogen-to-left ventricular ejection fraction ratio

BUN/EF and other factors associated with development of CIN (age, female sex, diabetes and hypertension were evaluated in a multivariate logistic regression analysis. BUN/EF was independent risk factor for the development of CIN (odds ratio 469.660, confidence interval: 25.74 – 8568.49, p<0.001). Table 4. Correlation of BUN/EF with different variables are demonstrated in table 5.

Table 4: Univariate and multivariate Logistic regression analysis for the parameters affecting CIN

	Univariate		Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
Age (years)	0.001*	1.138(1.054 – 1.229)	0.377	1.083(0.907 – 1.293)
Sex (female)	0.002*	6.818(2.005 – 23.185)	0.418	4.138(0.133 – 129.087)
Diabetes mellitus	0.049*	4.750(1.002 – 22.520)	0.561	3.786(0.043 – 335.753)
Hypertension	0.049*	3.841(1.001 – 14.741)	0.961	1.092(0.030 – 39.164)
BUN/EF	<0.001*	1105.0(65.04 – 18773.43)	<0.001*	469.660(25.74 – 8568.49)

OR: Odd`s ratio, C.I: Confidence interval, BUN/EF: blood urea nitrogen-to-left ventricular ejection fraction ratio, *: Statistically significant at p ≤ 0.05

Table 5: Correlation between BUN/EF and different parameters in the studied patients

	BUN/EF	
	r value	P value
Age	0.438	<0.001*
Body mass index	-0.286	0.004*
LVEF	-0.689	<0.001*
Creatinine Pre-PCI	0.619	<0.001*
Creatinine Post-PCI	0.872	<0.001*
BUN	0.928	<0.001*
GFR	-0.618	<0.001*
Serum Hemoglobin	-0.721	<0.001*
Gensini score	0.285	0.004*
CIN risk score	0.706	<0.001*
Contrast volume	0.510	<0.001*

BUN: blood urea nitrogen, LVEF: left ventricular ejection fraction, BUN/EF: blood urea nitrogen-to-left ventricular ejection fraction ratio, GFR: glomerular filtration rate, r: Pearson coefficient, *: Statistically significant at p ≤ 0.05

Discussion

CIN was defined by a rise in serum creatinine of 0.5 mg/dl (26.5 mol/l) within 2-3 days; or rise in creatinine level to 25% of baseline within the previous 7 days.[14] CIN is a common complication of coronary interventions. Its development had been linked with increasing both in-hospital and long-term morbidity and mortality.[15] It is a severe renal damage executed by the injection of radio-opaque contrast media intravascularly. The contrast media induced intramedullary vasoconstriction leading to hypoxia of renal medulla with subsequent nephrotoxicity. A 3rd of all inpatient acute renal insult is caused by CIN, and it effects around 1% -2% of the general public.[16]

The main finding in this study is the value of BUN/EF at admission in prediction of development of CIN in ACS patients underwent contrast exposure during PCI. The exertion of BUN by the kidney is affected by the changes of glomerular filtration rate and the degree of BUN tubular reabsorption under the control of anti-diuretic hormone. In cases of

reduced LV cardiac output that causes a reduction of glomerular flirtation rate and increased secretion of anti-diuretic hormone resulting in an elevation of serum BUN level. In addition, the activated sympathetic nervous system and renin angiotensin system increase renal tubular reabsorption of BUN so elevates its serum level. Accordingly, BUN could be used as an index for both renal and cardiac function.[17-19] The impaired LV systolic function is eventually leading to worsening of renal perfusion. The authors, in this study, reported higher BUN values and lower LVEF prior to exposure to contrast in patients who developed CIN in comparison to those who did not. Previous studies reported lower LVEF in patients who developed CIN. [20-23]
The current study showed that sensitivity of BUN/EF level as a predictor of CIN was 92.86% and specificity of 98.84%. The predictive value of BUN/EF for development of CIN was better than serum creatinine alone, LVEF alone and BUN alone.

This study reported that age is statistically significant correlator with CIN development. It is in agreement with Kiris et al.[24] Also, this study reported a decrease in hemoglobin level was associated with development of CIN. In comparison, Kaya A et al reported no significant association between serum hemoglobin level and development of CIN.[25]

The current study reported a difference of statistical significance in the contrast volume utilized during PCI in patients who had CIN in comparison with those who had not. This finding is in agreement with Marenzi et al.[26] Similarly, Narula et al reported that volume of contrast is an efficient indicator of acute kidney injury development.[27] Furthermore, the current study reported higher Gensini score in patients who developed CIN in comparison with those who did not. High Gensini score means multiple and significant vessel affection that necessitate further views for better and accurate assessment of lesion significance and furthermore multiple injections of contrast media. This finding coincides with Acet et al [28] and Li et al [29] who reported similar results regardless of other clinical variables.

Mehran introduced one of the most common risk scores in prediction of CIN. The Mehran score included 8 parameters hypotension requiring inotropes, use of intra-aortic balloon pump, heart failure, old age, anemia, diabetes mellitus, contrast volume and glomerular filtration rate.[10] The Mehran score can be used in the primary angioplasty setting and can forecast CIN as well as stratify patients for poor clinical results in both the short and long term.[30,31] As the score increased, the risk of CIN increased exponentially. The authors, in the current study, reported higher Mehran score points in patients who

developed CIN. Furthermore, there was a significant correlation between Killip class and development of CIN. Similar results were reported by Kiris T et al[24] and Kaya A et al.[25]

In regard to these findings, we could use BUN/EF to predict and hence, to prevent the occurrence of CIN. All measures which were recommended to decrease risk of CIN should be introduced for those patients such as suitable contrast type [32], use of IVUS (zero-/ultra-low-contrast-volume PCI protocol)[33], use of Renal Guard system [34] and remote ischemic conditioning.[35]

Conclusion

In addition to common risk factors of acute kidney injury initiated by contrast exposure during coronary intervention, BUN/EF could predict development of contrast induced nephropathy in patients with ACS who underwent coronary intervention.

Limitations

The pre-admission medications, which may affect the development of CIN were not included in the study. We didn't record factors that might affect serum BUN level like starvation, protein diet before BUN venous sampling. The relatively small patients' sample is another limitation.

Abbreviations

BUN, blood urea nitrogen; BUN/EF ratio, urea nitrogen-to-left ventricular ejection fraction ratio; CIN, contrast induced nephropathy; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate.

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