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Original Article

Blood Urea Nitrogen, Creatinine and Urea Nitrogen-to-creatinine Ratio as Predictors of In-Hospital Adverse Cardiac Events in Acute Myocardial Infarction

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ABSTRACT

Background: Kidney dysfunction affects cardiovascular outcome in patients with acute myocardial infarction. Creatinine, urea nitrogen and urea nitrogen-to-creatinine ratio (UCR) are kidney biomarkers routinely measured in patients with acute myocardial infarction. Their implication in acute myocardial infarction has not been validated. **Aims:** The study aims to investigate the association between urea nitrogen, creatinine and UCR and in-hospital adverse cardiac events in patients with acute myocardial infarction. **Methodology:** The study design was cohort. Subjects were patients with acute myocardial infarction. Blood urea nitrogen and creatinine were measured on admission. The UCR was calculated as ratio of urea nitrogen to creatinine. The observation was performed during hospitalization in ICCU to detect the adverse cardiac events, i.e. death, acute heart failure, cardiogenic shock, reinfarction and rescucitated ventricular arrhytmia. The ROC curve was designed to determine the cut-off point of high urea nitrogen, creatinine and UCR. The bivariate and multivariable analysis were performed to establish the independent predictors of adverse cardiac events. A p value < 0.05 was a limit of statistics significance. **Results:** The subjects of this research were 424 patients. Among them, 96 subjects (22.6 %) developed in-hospital adverse cardiac events. Subjects with adverse cardiac events had significantly higher level of urea nitrogen, creatinine and UCR. The bivariate analysis showed that high urea nitrogen, high creatinine and high UCR were associated with adverse cardiac events. The multivariable analysis showed only high urea nitrogen as an independent predictor for adverse cardiac events (adjusted OR 3.14 (95 % CI:1.37-7.19, p value 0.007)). **Conclusion:** High urea nitrogen, creatinine and UCR were associated with increased in-hospital adverse cardiac events. Only high urea nitrogen was an independent predictor for in-hospital adverse cardiac events in patients with acute myocardial infarction.
Key words: Urea nitrogen, Urea nitrogen to creatinine ratio, Adverse cardiac events, Acute myocardial infarction.

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INTRODUCTION

Acute kidney injury and chronic kidney disease have been proven to affect short and long term cardiovascular outcome in patients with acute coronary syndrome and acute myocardial infarction.[1] Serum creatinine level has became popular biomarker for establishing the acute injury or chronic impairment of the kidney. Creatinine clearance calculation has been routinely used to predict outcome in acute myocardial infarction.[2-4] Furthermore, creatinine level has been incorporated in the risk prediction in patients admitted with non ST elevation acute myocardial infarction.

In addition to creatinine and creatinine clearance, urea nitrogen is a omnipresent kidney biomarker which is routinely measured in patients with acute myocardial infarction. Urea nitrogen also reflects glomerular filtration rate, however its increase is autonomous to the alteration of glomerular filtration rate or serum creatinine level.[5] Activation of renin-angiotensin-aldosterone (RAA) system and neurohormonal system, two proven biological systems prevail in acute myocardial infarction, may cause enhanced kidney proximal tubular reabsorbtion and, therefore, increased urea nitrogen in the blood circulation.[5]

Increased blood urea nitrogen due to RAA and neurohormonal system activation may greatly exceed the increase of creatinine level due to intrinsic kidney disease. The urea nitrogen-to-creatinine ratio (UCR) is a widely used marker of prerenal kidney dysfunction rather than intrinsic parenchymal kidney disease.[6] This ratio has been used to differentiate prerenal azotemia from renal azotemia, due to intrinsic kidney disease, in various clinical settings.[6] In heart failure, the low renal perfusion is associated with prerenal dysfunction due to the increase of neurohormonal activation and therefore higher UCR.[7] In acute myocardial infarction, its role is still unknown. The study aims to investigate the association between urea nitrogen, creatinine and UCR and in-hospital adverse cardiac events in patients hospitalized with acute myocardial infarction.

MATERIALS AND METHODS

The study design is a cohort study. It comprises in-hospital observation of patients with acute myocardial infarction. Subjects were patients with acute myocardial infarction, both ST elevation and non ST elevation acute myocardial infarction, whom were hospitalised in Dr. Sardjito Hospital, Yogyakarta, Indonesia. The subjects were enrolled consecutively from July 2013 until April 2015. The inclusion criteria were as follows: (1) diagnosis of ST elevation and non ST elevation acute myocardial infarction, (2) age between 30 and 75 years, (3) onset of anginal pain less than 24 hrs for ST elevation acute myocardial infarction and (4) agree to participate in the study by signing an informed consent. The exclusion criteria were as follows: (1) history of chronic kidney disease stage V, chronic heart failure NYHA ≥ II, hepatic cirrhosis and malignancy, (2) comorbidites of acute infection and sepsis, (3) previous revascularisation before reaching the hospital, (4) creatinine level ≥ 2.5 mg/dL on admission, (5) comorbidities of upper gastrointestinal bleeding and (6) history of valvular heart disease. All subjects were given an informed consent. The study has been approved by ethics committee of Faculty of Medicine, Universitas Gadjah Mada.

Subjects were admitted, assessed and managed in emergency unit based on the diagnosis. The diagnosis of ST elevation and non ST elevation acute myocardial infarction were defined according to international guideline

criteria based on angina symptom, appearance of electrocardiogram and elevated cardiac enzyme.[8] The initial management comprised of loading dose of double antiplatelet, nitrate and/or revascularisation procedure, i.e. primary percutaneous coronary intervention or fibrinolytic. Subjects were admitted and treated to intensive cardiac care unit (ICCU) until discharge. The treatment strategy of each subject was in the discretion of attending cardiologists.

The blood sample was withdrawn on admission from antecubital veins, before the revascularisation procedure performed, if indicated. The routine hematology and blood chemistry examination were performed in hospital central laboratory, including blood urea nitrogen and creatinine measurement. The urea nitrogen-to-creatinine ratio (UCR) was calculated as ratio of urea nitrogen level to creatinine level. Cardiac enzyme measurement, i.e. CK-MB and Troponin I, was performed using similar blood sample. The characteristics of subjects were recorded during intensive hospitalisation in ICCU. The observation was performed during intensive hospitalisation in ICCU to identify the outcome.

The outcome of this research was adverse cardiac events occurring during intensive hospitalisation in ICCU. The adverse cardiac event was a composite of all cause of death, acute heart failure, cardiogenic shock, reinfarction and ventricular arrhythmia requiring rescuscitation. All cause of death was determined as death from any etiology during intensive hospitalisation. Acute heart failure was determined as the clinical symptom and sign of breathlesness due to lung congestion with the concominant use of intravenous nitrates or diuretics. Cardiogenic shock was determined as systolic blood pressure < 90 mmHg and the signs of low perfusion with the concomitant use of vasopressor drugs. Reinfarction was determined as the re-occurrence of chest pain, ST-segment elevation and increased of creatine kinase-MB after subjects subsided clinically. Ventricular arrhytmia was determined as ventricular tachycardia/fibrillation episodes requiring cardiopulmonary rescucitation. The outcomes were assessed by attenting cardiologists.

The statistics analysis was conducted to asses the association between the level of urea nitrogen, creatinine and UCR and the adverse cardiac events. Subjects were divided into two groups, i.e. subjects with adverse cardiac events and those without adverse cardiac events. The continuos data was tested for normality distribution in each group and compared between group. The comparison was statistically tested with Student *t* test for normally distributed data or Mann Whitney test for not normally distributed data. The comparison of categorical data was statistically tested with Chi-square test. The receiver operator characteristics (ROC) curve was constructed to determine the accuracy of urea nitrogen, creatinine and UCR for predicting the adverse cardiac events and to determine the best cut-off point of the prediction. Based on the cut-off point, the level of urea nitrogen and creatinine and the value of UCR were determined as high and low. The bivariate analysis was performed to assess the association between high urea nitrogen, creatinine and UCR and adverse cardiac events. The multivariable analysis, i.e. logistic regression test, was performed to establish whether high urea nitrogen, creatinine and UCR were the independent predictors of adverse cardiac events. In all statistics analysis, a p value < 0.05 was determined as statistical significance.

RESULTS

The subjects of this research were 424 patients. During intensive hospital observation, 96 subjects (22.6 %) developed adverse cardiac events. The subjects with adverse cardiac events were significantly older ($p < 0.001$), had lower systolic blood pressure ($p = 0.012$), had higher heart rate ($p < 0.001$), had greater leukocyte count ($p = 0.002$), had higher glucose level ($p < 0.001$), had higher urea nitrogen level ($p < 0.001$) and had higher creatinine ($p < 0.001$) level as compared to subjects without cardiac events. The UCR was also significantly higher in subjects with adverse cardiac events. The proportion of diabetes mellitus was significantly higher in subjects with adverse cardiac events, whereas subjects with active smoking was lower. A significant increased of cardiac enzymes (CK-MB and troponin) was observed in subjects with adverse cardiac events. The proportion of ST elevation myocardial infarction was significantly higher among subjects with adverse cardiac events. Table 1 shows the compared characteristics of subjects with adverse cardiac events and those without adverse cardiac events.

Table 1: Characteristics of subjects based on the presence and absence of in hospital adverse cardiac events.

Characteristics	Presence of Adverse Cardiac Events n = 96	Absence of Adverse Cardiac Events n = 328	*P* value
Demographic, means±SD			
Male gender, n (%)	74 (77.1)	271 (82.6)	0.221
Years of age	61.0±9.4	57.0±8.9	<0.001
Body mass index	23.7±3.2	24.1±3.1	0.314
Risk factors, n (%)			
Hypertension	69 (71.9)	206 (62.8)	0.102
Diabetes mellitus	35 (36.5)	73 (22.3)	0.005
Active smoker	39 (40.6)	171 (52.1)	0.047
Stabil IHD	7 (7.3)	49 (14.9)	0.052
Clinical, mean±SD			
Systolic BP	123.9±26.9	132.3±23.5	0.012
Diastolic BP	77.2±16.5	80.0±13.9	0.201
Heart rate	86.5±22.6	75.5±14.9	<0.001
STEMI, n (%)	83 (86.5)	247 (75.5)	0.023
Laboratory, mean±SD			
Haemoglobin	13.5±2.0	13.9±1.9	0.090
Leukocytes	13.9±4.5	12.3±3.8	0.002
Platelet	256.9±78.7	266.0±89.6	0.378
Glucose	231.4±120.8	167.5±84.1	<0.001
Urea nitrogen	19.7±9.7	14.3±5.6	<0.001
Creatinine	1.4±0.5	1.2±0.3	<0.001
UCR	14.4±5.1	12.7±4.8	0.002
CK-MB	169.6±177.9	115.3±142.5	0.003
Troponin I	7.2±9.5	4.8±8.2	0.024
Management, n (%)			
Primary PCI	38 (39.6)	89 (27.1)	0.019
Fibrinolytic	33 (34.4)	106 (32.3)	0.706
Heparinisation			0.712
LMWH	4 (4.2)	26 (7.9)	
UFH	83 (86.5)	276 (84.1)	
Fondaparinux	6 (6.2)	16 (4.9)	
ACE-I/ARB	77 (80.2)	274 (83.5)	0.447
Beta blockade	45 (46.9)	210 (64.0)	0.003

SD is Standard Deviation, IHD is Ischemic Heart Disease, BP is Blood Pressure, STEMI is ST Elevation Myocardial Infarction, UCR is Urea Nitrogen-to-Creatinine Ratio, CK-MB is Creatine Kinase MB, PCI is Percutaneous Coronary Intervention, LMWH is Low Molecular Weight Heparin, UFH is Unfractionated Heparin, ACE-I is Angiotensin Converting Enzyme inhibitor, ARB is Angiotensin Receptor Blocker.

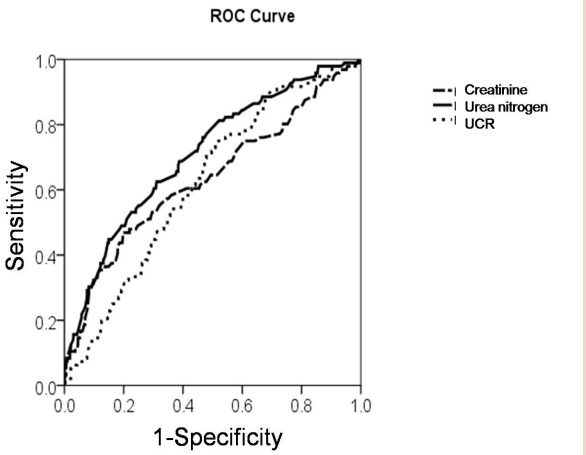

Figure 1: The ROC curve of creatinine, urea nitrogen and urea nitrogen-to-creatinine ratio to predict in-hospital adverse cardiac events.

Table 2: Area under the curve and cut-off point based on ROC curve of creatinine, urea nitrogen and UCR.

	Area under curve	Cut off value	Sensitivity	Specificity
Creatinine	63.5 %	1.19	60.4 %	58.8 %
Urea nitrogen	70.8 %	15.35	62.5 %	68.9 %
UCR	62.3 %	12.26	61.5 %	55.8 %

UCR is urea nitrogen-to-creatinine ratio

The ROC curve is shown in Figure 1. It indicates that area under the curve of urea nitrogen was the highest (70.8 %), followed by area under the curve of creatinine level (63.5 %) and UCR (62.3 %).The cut-off point of best prediction value was set based on ROC curve. The best value of sensitivity and specificity among urea nitrogen, creatinine and UCR is shown in Table 2.

The bivariate analysis showed that the value above cut-off point for urea nitrogen (high urea nitrogen), creatinine (high creatinine) and UCR (high UCR) were associated with the adverse cardiac events. The unadjusted OR were 3.69 (95% CI: 2.29-5.94, *p* value < 0.001), 2.18 (95% CI: 1.37-3.47, *p* value 0.001) and 2.01 (95% CI: 1.26-3.21, *p* value 0.003) respectively (shown in Table 3). Other variables which associate with adverse cardiac events (*p* value < 0.200) in bivariate analysis were further analyzed in the multivariable analysis.

The logistic regression analysis showed that only high urea nitrogen emerged as an independent predictor for adverse cardiac events with adjusted OR 3.14 (95 % CI: 1.37-7.19, *p* value 0.007). The high creatinine level and UCR did not significantly pose as independent predictors for in-hospital adverse cardiac events. Other independent predictors were increasing age, reduced systolic blood pressure and increased heart rate (shown in Table 3).

DISCUSSION

Several findings of our study are as follows: (1) the mean value of blood urea nitrogen was within normal range in subjects with adverse cardiac events and those without (normal range: 7–20 mg/dL), (2) the mean value of creatinine was above the normal range in both groups (normal range (men): 0.84 to 1.20 mg/dL), (3) the mean value of UCR was within normal range in both groups (normal ratio: 10-20), (4) higher value of urea nitrogen, creatinine and UCR were associated with increased incidence of in-hospital adverse cardiac events and (5) only higher value of urea nitrogen was an independent predictor for in-hospital adverse cardiac events in patients with acute myocardial infarction.

Table 3: Univariat and multivariable analysis to identify the predictor of in-hospital adverse cardiac events.

Variables	Unadjusted OR(95% CI)	*P* value	Adjusted OR (95% CI)	*P* Value
Years of age	1.05 (1.02-1.08)	<0.001	1.09 (1.04-1.13)	< 0.001
Hypertension	1.51 (0.92-2.49)	0.10	2.02 (0.94-4.39)	0.71
Diabetes mellitus	2.00 (1.23-3.27)	0.005	1.54 (0.69-3.41)	0.29
Active smoker	0.63 (0.39-0.99)	0.05	1.11 (0.54-2.28)	0.77
Stabil IHD	0.45 (0.19-1.02)	0.06	0.53 (0.15-1.92)	0.34
Systolic BP	0.98 (0.97-0.99)	0.01	0.96 (0.94-0.99)	0.004
Diastolic BP	0.99 (0.97-1.01)	0.16	1.03 (0.99-1.07)	0.16
Heart rate	1.04 (1.02-1.05)	<0.001	1.04 (1.02-1.07)	<0.001
STEMI	2.06 (1.09-3.89)	0.03	3.09 (1.06-8.99)	0.38
Haemoglobin	0.90 (0.80-1.02)	0.09	1.07 (0.88-1.29)	0.53
Leukocytes	1.10 (1.04-1.16)	0.001	1.05 (0.96-1.16)	0.27
High glucose	2.52 (1.54-4.11)	<0.001	1.57 (0.74-3.34)	0.24
High urea nitrogen	3.69 (2.29-5.94)	<0.001	3.14 (1.37-7.19)	0.007
High creatinine	2.18 (1.37-3.47)	0.001	0.76 (0.34-1.67)	0.49
High UCR	2.01 (1.26-3.21)	0.003	1.02 (0.44-2.33)	0.97
CK-MB	1.00 (1.00-1.01)	0.005	1.00 (0.99-1.00)	0.91
Troponin I	1.03 (1.00-1.06)	0.026	1.01 (0.95-1.06)	0.83

CI is Convidence Interval, OR is Odds Ratio, IHD is Ischemic Heart Disease, BP is Blood Pressure, STEMI is ST Elevation Myocardial Infarction, UCR is Urea nitrogen-to-Creatinine Ratio, CK-MB is Creatine Kinase MB

The implication of kidney disturbance in acute myocardial infarction has been widely investigated.[1] Various parameters have been applied in the measurement of kidney function. Creatinine level has been utilized to stratify the risk and predict the adverse cardiac events following non ST-elevation acute myocardial infarction (NSTEMI).[9] Using creatinine level dynamic alteration during hospitalisation, acute kidney injury is associated with adverse outcomes after acute ST elevation myocardial infarction (STEMI).[10] Our previous study showed that increased creatinine and estimated glomerular filtration rate (eGFR) were associated with in-hospital adverse cardiac events in patients with acute myocardial infarction.[11] In the previous study, more than 50% subjects had moderate to severe kidney dysfunction based on eGFR calculation at admission.[11] In this study, we found that increased creatinine level doubled the risk to develop in-hospital adverse cardiac events. However, after the adjustment for covariates, increased creatinine level did not independently predict in-hospital adverse cardiac events. Other parameter, urea nitrogen, was the independent predictor for in-hospital adverse cardiac events.

In acute myocardial infarction, kidney disturbance partly represents hemodynamic impairment or pre-renal dysfunction. The factors that play crucial role in the hemodynamic impairment in acute myocardial infarction and induce pre-renal dysfunction are the drop of cardiac output, the treatment with angiotensin converting-enzyme inhibitors or diuretics, the administration of contrast media during revascularization proce-

dures and the activation of neurohormonal and sympathetic nervous systems.[12] In our study, these factors co-exist and are interrelated. The use of angiotensin converting enzyme and angiotensin receptor blocker are comparable between subjects with presence of adverse cardiac events and those without. Primary PCI with the utilisation of contrast media was mostly performed in subjects with adverse cardiac events, however the procedure was completed after blood creatinine or urea nitrogen measurements, therefore their on admission levels were not affected by the utilisation of contrast media. The reduced cardiac output and subsequent left ventricular dysfunction due to acute myocardial infarction might be responsible for increased level of kidney biomarkers.

The urea nitrogen concentration is influenced by the equilibrium between urea generation and excretion by the kidney. The urea reabsorption by kidney also influences urea nitrogen concentration in the circulation.[13] The reabsorption of urea is closely related with sodium and water reabsorption in the proximal and distal tubules of the kidney. Therefore, in addition to reflecting GFR, an elevated urea nitrogen concentration in blood circulation can be a sign of kidney hypoperfusion from hypovolemia, reduced cardiac output or renovascular disease.[13] Under this condition, the rise of urea nitrogen is independent to creatinine level and GFR calculation. More enhanced urea reabsorption by the kidney due to activation of renin-angiotensin aldosterone systems and the sympathetic nervous systems are also significantly contributing, which prevail in the setting of acute myoacardial infarction.[13] The increased UCR can be utilized to assess this condition. In our study, the increased UCR was associated with doubled risk to develop in-hospital adverse cardiac events. However, in multivariable analysis, UCR did not signify as independent predictor for in-hospital adverse cardiac events.

The association between urea nitrogen and in-hospital adverse cardiac events was still significant after adjustment with covariables associated with increased adverse cardiac events. With the cut-off value 15.35 mg/dL, high urea nitrogen associated with threefold increased in-hospital adverse cardiac event. Similar to previous study, the association between urea nitrogen and in-hospital adverse cardiac events is apparent at negligible elevations of urea nitrogen.[13] The implication of urea nitrogen concentration as an independent predictor of in-hospital fatal adverse cardiac events among patients with acute myocardial infarction was also reported by Saygitov *et al.* (2010).[14] Other study comprised 2995 subjects, showed that higher level of blood urea nitrogen was associated with stepwise increase of in-hospital mortality, while creatinine level was not.[15] A study by Smith *et al.* (2006) showed that urea nitrogen concentration > 6.1 mmol/L was associated with an increased risk of fatal adverse cardiac events within 1 year after acute myocardial infarction.[16] Other study showed that on-admission urea nitrogen concentration ≥ 25 mg/dL was independently associated with increased probability of fatal adverse cardiac events in early and long term follow up after acute myocardial infarction.[12] Blood urea nitrogen also predicted future adverse events among subjects with acute coronary syndrome and stable coronary artery disease undergoing percutaneous coronary intervention, while GFR was not.[17]

The elevations of blood urea nitrogen may be due to systemic hypoperfusion or pre-renal disturbance rather than intrinsic renal dysfunction.[12] The increased urea nitrogen on admission of acute myocardial infarction is an indicator of the reduction in kidney perfusion due to lower cardiac output associated with abrupt myocardial ischemia. This will be accompanied by increased sodium and water reabsorption which in consequence increase urea reabsorption in the kidney tubules.[12] Our study shows that higher urea nitrogen concentration was associated with subsequent adverse cardiac events. Even after adjustment with covariables, higher urea nitrogen remained the independent factor for developing in-hospital adverse cardiac events. In this condition, elevated blood urea nitrogen is a simple marker that reflects kidney pathophysiologic response to haemodynamic and neurohormonal alterations in the setting of acute myocardial infarction. Furthermore, it may be a marker for left ventricular dysfunction following acute myocardial infarction.

CONCLUSION

The mean value of blood urea nitrogen and UCR were within normal range in subjects with adverse cardiac events and those without. The mean value of creatinine was above the normal range in both groups. The higher value of urea nitrogen, creatinine and UCR were associated with increased in-hospital adverse cardiac events. In multivariable analysis, only higher value of urea nitrogen was an independent predictor for in-hospital adverse cardiac events in patients with acute myocardial infarction.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

RAA: Renin-Angiotensin-Aldosteron; **UCR:** Urea nitrogen-to-creatinine Ratio; **NYHA:** New York Heart Association; **ICCU:** Intensive Cardiac Care Unit; **CKMB:** Creatine Kinase MB; **ROC:** Receiver Operating Characteristics; **IHD:** Ischemic Heart Disease; **PCI:** Percutaneous Coronary Intervention; **LMWH:** Low Molecular Weight Heparin; **UFH:** UnFactionated Heparin; **ACE-I:** Angiotensin Converting Enzyme Inhibitor; **ARB:** Angiotensin Receptor Blocker; **STEMI:** ST Elevation acute Myocardial Infarction; **NSTEMI:** Non ST Elevation acute Myocardial Infarction; **eGFR:** estimated Glomerular Filtration Rate.

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