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BLOOD UREA NITROGEN-TO-CREATININE RATIO AT ADMISSION AS A PREDICTOR OF MAJOR ADVERSE CARDIOVASCULAR EVENT WITHIN 30 DAYS IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

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Abstract
An increase of BUN/Cr Ratio (BCR) shows high neurohormonal activity in patients with acute decompensated heart failure (ADHF). The value of BCR was thought to be able to predict the mortality and readmission rate. An increase of this marker was related to worse outcome during hospitalization. However, the relationship between BCR and Major Adverse Cardiovascular Events (MACEs) in ADHF still controversial. This study aimed to analyze the relationship between BCR and MACEs in ADHF patients.

Methods: Patients were recruited from July 2018 to December 2018. This prospective study involved 96 patients diagnosed with ADHF treated through the emergency unit. Variables, such as comorbidities, drug history, ejection fraction, and laboratory findings were evaluated. MACEs in this study included death, rehospitalization caused by AHF, arrhythmia and stroke. Patients were followed-up for one month since hospital admission. Bivariate analyses were done using Chi-square, independent T-test, and Mann-Whitney. A ROC analysis was performed to assess the BCR and MACEs. Logistic regression, as a multivariate analysis, was also performed in this study.

Results: From 96 patients, 47 (48.9%) patients were having MACEs. Compared to no MACEs patients, nitrate, inotropic, Hb, BUN, Cr, and CrCl were having a statistical significant in univariate analysis (p<0.25). From ROC analysis, weobtained a cut-off value of 16.05 (AUC 62.7%) with 63.8% sensitivity and 56.9% specificity to predict MACEs (p=0.032). A multivariate analysis showed BCR could be an independent variable (OR=2.47, 95% CI= 1.011-6.012; p=0.001).

Conclusion: BCR is an independent variable to predict MACEs in ADHF patients. A prospective design study with large samples was needed to validate this finding.

Introduction
Acute Heart Failure (AHF) is defined as a sudden onset or sudden worsening of heart failure. Intensive and immidiate treatment are needed to overcome excess fluid and stabilze haemodynamic. AHF has a high mortality and hospital readmission rate. Immediate diagnosis in a patient can help the doctor to improve treatment, which in turn increases patient prognosis.[1]

Renal dysfunction is one of the worst complications in acute heart failure and is associated with a poor prognosis. Creatinin (Cr) and Blood Urea Nitrogen (BUN) are nitrogen-end products of proteins, and are freely filtered in the glomerulus. Therefore, both Cr and BUN serum are known as kidney markers. however, the two markers were treated differently in the kidney tubules, while Cr is not reabsorbed, about 40%-50% of BUN is reabsorbed in the tubules. Because this reabsorption process is directly or indirectly regulated by neurohormonal activity, the ratio of BUN-Cr (BUN / Cr) has been supported as a metric of neurohormonal activity, which may promote prognostic values.[2]

Takaya et al (2015) in their study stated that AHF patients with Acute Kidney Injury (AKI) who had the initial BUN/Cr ratio above 22.1 had a poor prognosis compared to those who had below 22.1. They also say that the single value of initial BUN/Cr alone will not affect the prognosis of AKI in AHF patients.[3] Researchers classify the ratio of BUN/Cr to studying the neurohormonal system which can help improve performance in AHF patients with a lower BUN/Cr ratio rather than increased Cr levels, and to improve additional strategies in patients with

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higher BUN/Cr ratios.[4] The purpose of this study was to determine the ability of initial BUN/Cr ratio in predicting the onset of major adverse cardiovascular events (MACEs) within 30 days in patients with AHF.

Method

This study was a prospective cohort study that conducted at H. Adam Malik General Hospital Medan in the period of July 2018 until January 2019. The inclusion criteria of this study were patients over 18 years with a diagnosis of acute heart failure based on ESC Guideline for the diagnosis and treatment of acute and chronic heart Failure 2016, had no history of acute myocardial infarction, congenital heart disease, advanced stage malignancy, and chronic kidney disease, Creatinine clearance results below 15 cc/min/m2, and there are no comorbid shock except cardiogenic shock. The clinical course of the patient is examined starting at the emergency department for the next 30 days, this includes intensive care and wards until the patient returns home or dies. Systematic records were carried out to determine MACEs (death, readmission, arrhythmia, and stroke).

All patients who met the inclusion criteria were asked for approval after an explanation of the study objectives and procedure. This study has received the approval of the Health Ethics Committee from the Medical Faculty of the University of Sumatera Utara and the Health Ethics Committee of the Haji Adam Malik General Hospital Medan.

Data obtained from history taking, physical examination, electrocardiography (EKG), echocardiography, and the first laboratory examination when the patient comes to the emergency unit including creatinine and BUN were collected. Examination of blood creatinine and BUN is carried out using the Architech C4000 and C8000 devices. Electrocardiographic examination using a Bionet Cardio touch 3000 device speed 25mm/s and a scale of 10 mV/mm. Echocardiography checks using a GE Vivid S6 heart probe 3.25 MHz or Medison Accuvix 10 device with a 3.50MHz sector heart probe.

Nominal data were presented in frequency and percentage. Numerical data were presented in mean with standard deviation for normally distributed data and median with minimum and maximum value for skewed data. Bivariate analysis were done to test nominal-numerical data using independent T-test for normally distributed and Mann-Whitney for not normally distributed data. Nominal-nominal data were analyzed using Chi-square test. We performed receiver operating characteristic (ROC) curve analysis to define the optimum cut-off value for BUN/Cr ratio. After that, all of the variables with p value< 0.25 will be included into the multivariate analysis. Multivariate analysis were done using logistic regression analysis with p value<0.05 means statistically significant. All of the statistical analysis were done using Statistical Package for Social Sciences (SPSS) version 23.0 (Armonk, NY: IBM Corp).

Result

This study involved 96 patients with acute heart failure (AHF) that met the inclusion criteria. From our study, males were found to be more common than females with 76 patients (79.2%), and the mean of age was 58.2 ± 8.84 years old. The risk factors obtained in this study were smoking in 64 people (66.7%), hypertension in 58 people (60.4%), diabetes in 32 people (33.3%), with a median of ejection fraction is 35.5 (16-67). Almost all of the patients were given diuretic, 96 out of 100 (96%), and most of them using ACE-i, 72 samples (75%), ß-blockers in 84 samples (87.5%), nitrate in 64 samples (66.7%), and aspirin in 78 samples (81.3%). Laboratory results show a median of BUN 22.5 (5-97), Cr 1.2 (0.55-4.48), BUN-Cr ratio 16.7 (6.17-44.87), and CrCl 55.4 (15.34-155.07). Major adverse cardio vascular events (MACEs) including death, rehospitalization, arrhytmia and stroke were occurred in 27 (28.1%), 32 (33.3%), 6 (6,3%) and 3 (3.1%) respectively. We present the data in table 1.

Table 1. Characteristics of Study Subject

Characteristics	n = 96
Age (years)	58.2 ± 8.84
Gender	
Male	76 (79.2%)
Female	20 (20.8%)
Smoking	64 (66.7%)
Hypertension	58 (60.4%)

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Diabetes	32 (33.3%)
EjectionFraction	35.5 (16 – 67)
Drugs	
ACE-i	72 (75%)
ARB	18 (18.8%)
ß-blockers	84 (87.5%)
Nitrate	64 (66.7%)
Inotropic	19 (19.8%)
Diuretic	96 (100%)
Aspirin	78 (81.3%)
Clopidogrel	40 (41.7%)
LaboratoryResults	
Hemoglobin	13.2 ± 2.69
BUN	22.5 (5 – 97)
Cr	1.2 (0.55 – 4.48)
BUNtoCrRatio	16.7 (6.17 – 44.87)
CrCl	55.4 (15.34 – 155.07)
RandomBloodGlucose	131 (12 – 534)
MajorCardiovascularEvents (MACEs)	
Death	27 (28.1%)
Readmission	32 (33.3%)
Arrhythmia	6 (6.3%)
Stroke	3 (3.1%)

From 96 samples, 47 people having MACEs with the mean of age of 59.0 ± 9.68 years, with the comparison between male and female were 36 patients (47.4%) compared to 11 patients (55%). History of smoking was found in 31 patients (48.4%), while hypertension and diabetes were found in 26 (44.8%) and 15 (46.9%) respectively. From bivariate analysis between samples characteristics with MACEs, a statistical significance was found in ejection fraction (34.4 ± 10.89) with a p-value of 0.024; and inotropic administration in 15 patients (78.9%) with a p-value of 0.008. Other significant results were found in laboratory results of hemoglobin 12.8 ± 2.45 (p= 0.187), BUN 23 (9-97) (p= 0.008), Cr 1.34 (0.55-4.48) (p= 0,118), CrCl 47.08 (15.40-155.07) (p= 0,021). Data were shown in table 2.

Table 2. Bivariate Analysis of Demographic Characteristic and MACEs

Characteristics	MACE		P Value
	Yes (n=47)	No (n=49)	
Age (years)	59.0 ± 9.68	57.4 ± 7.97	0.35*
Gender			
Male	36 (47.4 %)	40 (52.6 %)	0.722**
Female	11 (55 %)	9 (45 %)	
Smoking	31 (48.4 %)	33 (51.6 %)	0.885**
Hypertension	26 (44.8 %)	32 (55.2 %)	0.429**
Diabetes	15 (46.9 %)	17 (53.1 %)	0.942*
EjectionFraction	**34.4 ± 10.89**	**40.0 ± 13.26**	**0.024***
Drugs			
ACE-i	35 (48.6 %)	37 (51.4 %)	0.906**
ARB	7 (38.9 %)	11 (61.1 %)	0.492**
ß-blockers	40 (47.6 %)	44 (52.4 %)	0.700**
Nitrate	**26 (40.6 %)**	**38 (59.4 %)**	**0.036***
Inotropic	**15 (78.9 %)**	**4 (21.1 %)**	**0.008***
Aspirin	38 (48.7 %)	40 (51.3 %)	0.922**
Clopidogrel	19 (47.5 %)	21 (52.5%)	0.972**

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LaboratoryResults			
Hb	**12.8 ± 2.45**	**13.6 ± 2.90**	**0.187***
BUN	**23 (9-97)**	**29 (5-73)**	**0.008#**
Cr	**1.34 (0.55-4.48)**	**1.14 (0.65-2.73)**	**0.118#**
CrCl	**47.08 (15.40-155.07)**	**59.27 (15.34-153.84)**	**0.021#**
RandomBloodGlucose	139 (66 – 337)	130 (12-534)	0.56#

Based on the results, we perform the ratio of BUN-Cr to predict the prognosis of MACEs using ROC methods (Figure 1).
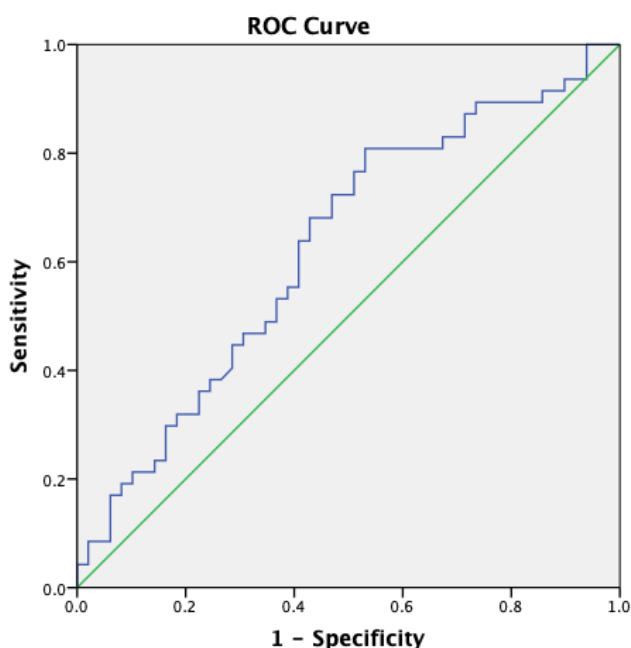

Diagonal segments are produced by ties.

Figure 1. ROC Curveof BUN/Cr toMACEs

Table 3. Area Under the Curve of Prognostic Model

Parameters	AUC	P	Sens	Spec
BUN/Cr	62.7 %	0.032	63.8 %	56.9 %

An area under the curve (AUC) of 62.7% was found with a cut-off point 16.05 together with 63.8% sensitivity and 56.9% specificity (Table 3). From bivariate analysis on high BUN/Cr ratio ($\geq$16.05) and low ($<$16.05) to MACEs, we found 50 patients in high BUN/Cr ratio with 30 patient shaving MACEs (60%) while in 46 low BUN/Cr ratio patients, MACEs occurred in 17 patients (37%) with p-value of 0.024 (Table 4).

Table 4. Bivariate Analysis of BUN/Cr Ratio to MACEs

BUN/Crratio	MACEs		P Value
	Yes	No	
High ($\geq$ 16,05)	30 (60 %)	20 (40 %)	0.024
Low ($<$ 16,05)	17 (37 %)	29 (63 %)	

We performed multi variate analysis, and BUN/Cr ratio has successfully maintained its significant result to MACEs in 30 days with a p-value of 0.001. Moreover, the OR was 2.47 (95% CI = 1.011-6.012) showing a high

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BUN/Cr ratio (≥16.05) increase the risk of major cardio vascular events within 30 days 2.47 times more likely than patients with low BUN/Cr ratio (<16.05) (Table 5).

Table 5. Multivariate Analysis of Factors Associated with MACEs within 30 Days

Variable	OR (95% CI)	Nilai p
EF	0.97 (0.937 – 1.012)	0.181
Drugs		
Nitrate	0.48 (0.181 – 1.317)	0.156
Inotropic	3.16 (0.878 – 11.345)	0.078
LaboratoryResults		
Hemoglobin	0.86 (0.716 – 1.043)	0.129
BUN	0.97 (0.915 – 1.018)	0.188
Cr	1.74 (0.928 – 3.243)	0.084
BUN-Cr ratio≥16.05	**2.47 (1.011 – 6.012)**	**0.001**
CrCl	1.00 (0.981 – 1.026)	0.763

Discussion

Mortality and readmission rate in this research were high compare to other international researches discussing AHF epidemiology. Mortality and readmission rate in 60-90 days in a study conducted by Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) were 9.8% and 29.9% respectively. While a research piloted by Canadian Enhanced Feedback for Effective Cardiac Treatment (EFFECT) showed a 30 days and 1 year mortality rate of 7.1% and 25.5% respectively and correspondingly the rate of 30 days and 1 year readmission were 4.9% and 16.1%. Acute Decompensated Heart Failure Syndromes (ATTEND) dan Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) Registry studied that the mortality rate within a year were 17% and 8.9% accordingly. The difference may be based on the characteristics of the population in which nearly all patients with MACEs had lower ejection fraction rate 34.4 ± 10.89 compare to those without MACEs, which was 40.0 ± 13.26. The median ejection fraction by OPTIMIZE-HF was 39 ± 18. The use of inotropic was higher in patients with MACEs which was 15 patients (78.9%) compare to those without MACEs which was 4 patients (21.1%), exhibiting that majority of the patients admitted to the ER suffered from cardiogenic shock.

This research of AHF shows a correlation between BUN-Cr ratio at time of admission and incidence of MACEs in 30 days. High BUN-Cr ratio (according to cut of point) in patients with AHF is an independent and significant predictor of MACEs in 30 days OR 2.47 (1.011 – 6.012) (P = 0,001). Individual score of BUN, creatinine, CrCl were not predictors for AHF patients with MACEs in 30 days. Research by Murata et al (2018) has a similar outcome but BUN-Cr ratio was accounted to predict a longer time span of mortality rate which was 1.9 years.[8] Takaya et al (2015) yield a comparable result in which the surge of BUN-Cr rate at time of admission correlates with a higher mortality rate in AHF patients but not the separate value of BUN or ceatinine.

Lindenfeld et al (2011) and Brisco et al (2013) affirmed that lower cardiac output and arterial filling in AHF would activate sympathetic nerve system and renin angiotensin aldosterone system, increase the reabsorption of sodium and water in proximal tubules of kidneys. These in turn will lead to the escalation of ureum concentration in proximal tubules and reduction of urinary flow in collecting duct that cause a further increase of urea reabsorption. Furthermore, lower arterial filling will cause the release of arginine vasopressin (AVP) mediated by baroreceptor, which will increase the regulation of urea transportation in collecting duct of internal medulla. Therefore, the activation of neurohumoral system will inflate the BUN value despite the reduction of the GFR. On the other hand, free creatinine is filtered through glomerulus and not absorbed. The differences shaped the primary hypothesis; BUN-Cr ratio in predicting neurohormonal activity is superior compare to the individual BUN value. Takaya et al (2015) stratified the risk of AKI using BUN-Cr ratio in AHF patients. They discovered that AKI is not always related to mortality in patients with AHF. Several researches presented that increase creatinine serum

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caused by the congestion reduction is not related to permanent kidney damage and poor outcome. Consequently, mechanism of AKI is significant in determining the clinical result in AHF patients. This study shows the rise of BUN-Cr ratio at time of admission suggests neurohormonal activity that could identify the correlation between AKI and mortality in AHF patients. Moreover, risk stratification of AKI done in the ER can help the doctor in charge decide the continuous treatment of decongestion given to patients with lower BUN-Cr ratio even when the creatinine level is high, unlike the additional consideration of higher BUN-Cr ratio in AHF patients.[3]

BUN-Cr cut off point in this study is 16.05 with the sensitivity of 63.8% and specificity of 56.9%. No previous research defining the cut of point of BUN-Cr to date. Preceding research only evaluate the median of BUN-Cr ratio in all samples which was 22.1 and 20.4.[2,3]

Conclusion

Briefly, high BUN-Cr ratio (>16.05) at time of admission in the ER with signs and symptoms of AHF can be the predictor of MACEs incidence in 30 days. This research has its limitations, which is the lack of samples, making it unable to evaluate other confounding factors. MACEs is challenging to be identified especially during the phone follow-up, because patients or the family members were incapable of explaining the disease properly.

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