Acta Cardiologia Indonesiana

pISSN:2460-5700
eISSN:2579-4345

Web page: jurnal.ugm.ac.id/v3/jaci

Creatinine Levels at Admission as Predictors of In-Hospital Major Adverse Cardiovascular Events in Acute Heart Failure Patient

Farida Hanum Margolang*, Refli Hasan, Abdul Halim Raynaldo, Harris Hasan, Ali Nafiah, Andre Pasha Ketaren

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sumatera Utara / Haji Adam Malik General Hospital, Medan, North Sumatera, Indonesia.

ARTICLE INFO

*Corresponding author
Email:
faridahanummargolang@gmail.com
Address:
Jalan Samanhudi Nomor 100 B,
Binjai 20715

Keywords:
Creatinine;
acute heart failure;
major adverse cardiovascular events

Manuscript submitted: Mei 2, 2019
Revised and accepted: June 24, 2019

ABSTRACT

Background: Acute heart failure is a global health problem with high morbidity and mortality. Short term and long term prognosis of these patients is poor. Therefore, early identification of patients at high risk for major adverse cardiovascular events (MACEs) during hospitalization was needed to improve outcome. Creatinine levels at admission could be used as predictors of major adverse cardiovascular events in acute heart failure patients because creatinine is a simple and routine biomarker of renal function examined in patients with acute heart failure. This study aimed to determine whether creatinine can be used as a predictor of major adverse adverse cardiovascular events in patients with acute heart failure.

Methods: This study is a prospective cohort study of 108 acute heart failure patients treated at H. Adam Malik Hospital from July 2018 to January 2019. Creatinine cut-off points were determined using the ROC curve, then bivariate and multivariate analyzes were performed to determine predictors of major adverse cardiovascular events during hospitalization.

Results: From 108 study subjects, 24 (22.2%) subjects experienced major adverse cardiovascular events during hospitalization. The subjects who died were 20 people (83.4%), subjects with arrhythmia were 2 people (8.3%), and those who had stroke were 2 people (8.3 %). Through the ROC curve analysis, we found creatinine cut-off values of ≥1.7 mg / dl (AUC 0.899, 95% CI 0.840-0.957, p <0.05). Creatinine ≥1.7 mg/dl could predict major adverse cardiovascular events with a sensitivity of 87.5% and specificity of 79.5%. Multivariate analysis showed that creatinine ≥1.7 mg / dl was an independent factor to predict MACEs during hospitalization in this study (OR 18,310, p 0.001) as well as creatinine clearance and heart rate.

Conclusion: Creatinine levels at admission is an independent predictor for major adverse cardiovascular events during hospitalization in acute heart failure patients.

INTISARI

Latar belakang: Gagal jantung akut adalah masalah kesehatan global dengan morbiditas dan mortalitas yang tinggi. Prognosis jangka pendek dan jangka panjang pasien ini buruk. Oleh karena itu, identifikasi awal pasien dengan risiko tinggi untuk *major adverse cardiovascular events* (MACE) selama rawat inap diperlukan untuk meningkatkan hasil. Kadar kreatinin saat masuk dapat digunakan sebagai prediktor kejadian kardiovaskular merugikan utama pada pasien gagal jantung akut karena kreatinin adalah biomarker fungsi ginjal yang sederhana dan rutin diperiksa pada pasien dengan gagal jantung akut. Penelitian ini bertujuan untuk menentukan apakah kreatinin dapat digunakan sebagai prediktor *major adverse adverse cardiovascular events* pada pasien dengan gagal jantung akut.

Metode: Penelitian ini adalah studi kohort prospektif dari 108 pasien gagal jantung akut yang dirawat di Rumah Sakit H. Adam Malik dari Juli 2018 hingga Januari 2019. Poin batas kreatinin ditentukan menggunakan kurva ROC, kemudian analisis bivariat dan multivariat dilakukan untuk menentukan prediktor *major adverse cardiovascular events* selama rawat inap.

Hasil: Dari 108 subjek penelitian, 24 (22,2%) subjek mengalami peristiwa kardiovaskular merugikan utama selama rawat inap. Subjek yang meninggal adalah 20 orang (83,4%), subjek dengan aritmia adalah 2 orang (8,3%), dan mereka yang mengalami stroke adalah 2 orang (8,3%). Melalui analisis kurva ROC, kami menemukan nilai cut-off kreatinin ≥1,7 mg / dl (AUC 0,899, 95% CI 0,840-0,957, p <0,05). Kreatinin ≥1,7 mg / dl dapat memprediksi kejadian kardiovaskular yang merugikan dengan sensitivitas 87,5% dan spesifisitas 79,5%. Analisis multivariat menunjukkan bahwa kreatinin ≥1,7 mg / dl merupakan faktor independen untuk memprediksi MACE selama rawat inap dalam penelitian ini (OR 18,310, p 0,001) serta pembersihan kreatinin dan denyut jantung.

Kesimpulan: Kadar kreatinin saat masuk adalah prediktor independen untuk *major adverse cardiovascular events* selama rawat inap pada pasien gagal jantung akut.

Introduction

Acute heart failure is a global health problem that causes high rates of hospitalization in people over 65 years old.[1,2,3] The prevalence of acute heart failure is about 1-2% and increases more than 10% at the age above 70 years old.4 In the United States, around 3 million patients were treated every year while in Europe higher number of patients with heart failure were treated.[2]

Acute heart failure has a poor prognosis, both short, medium and long term. Data from the United Kingdom National Heart Failure Audit showed mortality rates during hospitalization were about 10% with 30 days mortality and 1 year mortality after hospitalization of 6.5% and 30%, respectively.[1,4] Data from ADHERE registry showed mortality from acute heart failure during maintenance is about 4%.[3]

Because of the poor prognosis of acute heart failure, early identification of patients at high risk of major adverse cardiovascular events such as death, arrhythmias and strokes, is needed to help with immediate treatment to improve outcome. Several prediction models have been developed for acute heart failure. Many parameters and variables could be used to predict outcomes of patients with acute heart failure. Based on the European Society of Cardiology 2016 Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure, variables that could be used to predict heart failure prognosis include age, functional class, left ventricular systolic function, blood sugar levels, sodium levels, potassium levels and others.[5] The 2017 American Heart Association Guidelines for Management of Heart Failure prioritized the use of biomarkers as parameters, such as natriuretic peptide, galactein-3, ST2 soluble receptors and troponin, to predict the prognosis of acute heart failure patients.[6]

Biomarkers used as predictors of the prognosis of heart failure vary, but not all biomarkers are available and routinely examined because of the health cost burden. Therefore, simple and routine biomarkers which could be used as predictors of prognosis for acute heart failure are needed. One example of simple and routine biomarker is creatinine. From several studies, it was known that creatinine is a strong predictor for death in acute heart failure patients. Studies that have proven the role of creatinine as a predictor of death during treatment of acute heart failure patients include ADHERE Registry,[3] OPTIMIZE-HF Registry[7] and meta-analysis conducted by Rahimi.[8]

The interaction between heart and kidneys is very complex. Acute heart failure causes kidney dysfunction through several mechanisms, including increased renal and intra-abdominal pressure, renal hypoperfusion, neurohormonal and inflammatory activation, release of adenosine[9,10,11] and the drug used in the treatment of acute heart failure such as diuretics, Angiotensin Converting Enzyme Inhibitors (ACE-i) and Angiotensin Receptor Blocker (ARB). This deterioration of kidney function is called cardiorenal syndrome.[9,12,13] In more severe heart failure, more severe kidney dysfunction could occur indicated by high levels of biomarkers of kidney function (creatinine). Because heart failure is closely related to kidney function, the presence of abnormal kidney function could predict outcomes of acute heart failure patients.[9,14] The aim of this study was to evaluate creatinine as predictor of major cardiovascular events during hospitalization in patients with acute heart failure at H. Adam Malik Hospital Medan.

Methods

Study Design

This study was a prospective cohort study conducted at Haji Adam Malik Hospital Medan (RSHAM) with permission from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara-RSHAM. Subjects enrolled from July 2018 to January 2019 were patients with diagnosis of

acute heart failure based on diagnostic criteria of the ESC Guidelines in 2016. The inclusion criteria were acute heart failure patient ≥18 years old and diagnosed based on 2016 ESC Guidelines about acute heart failure. While the exclusion criteria were heart failure patients with comorbidities, such as shock except cardiogenic shock, congenital heart failure, heart failure due to organic valve abnormalities, acute heart failure secondary to advanced stage malignancy, acute heart failure documented with chronic renal failure or creatinine clearance <15 ml/minute/1.72m2. The number of subjects that met the inclusion and exclusion criteria in the study were 108

Study Procedure

The data of anamnesis, physical examination, electrocardiography (ECG), echocardiography, laboratory examination at admission were recorded in the medical record. Examination of blood creatinine levels was carried out when the patient was admitted to the hospital through the Clinical Pathology Laboratory of Haji Adam Malik Hospital using the Architech C4000 and C8000 devices. Electrocardiographic examination using Bionet Cardiotouch 3000 device with 25mm/s speed and 10 mV/mm for voltage scale were also carried out at admission at the Emergency Unit. Echocardiography were carried out in the Emergency Room or at intensive care unit with GE Vivid S6 heartprobe 3.25 MHz or Medison Accuvix 10 devices with a 3.50MHz sector heart probe.

The clinical course of the patient were examined since in the Emergency Unit, intensive care and wards until discharge or death and were systematically recorded to determine major adverse cardiovascular events (death, arrhythmia and stroke) during hospitalization.

The data obtained was analyzed with SPSS 20, to evaluate whether creatinine values at admission could predict in-hospital major adverse cardiovascular events in patients with acute heart failure.

Statistical Analysis

All the data were processed and analyzed using SPSS software. Categorical variables were presented as number or frequency (n) and percentage (%). Numerical variables were presented as mean values with standard deviations for data that were normally distributed and median for non-normally distributed data. We used Kolmogorov-Smirnov test to test the normality of numerical variables in all subjects with n> 50.

We performed bivariate analysis for comparisons between two groups on categorical independent variables and categorical dependent variables using Chi Square test. When the Chi Square test conditions were not met, Fisher or Kolmogorov Smirnov test was used. Major adverse cardiovascular events to determine the optimal cut off value of creatinine levels at admission were determined using the Receiving Operating Curve (ROC). Then Area Under Curve (AUC) was used to assess the prognostic strength of the tested variable. Variables with p <0.25 was included in the multivariate analysis.

Multivariate analysis of categorical independent variables with categorical dependent variables was tested by logistic regression with backward stepwise method. Variables found to have significance values p <0.05 in multivariate analysis were shown in the form of Odds Ratio (OR) with 95% confidence intervals. Variables were considered significant if the value is p <0.05.

Result

Baseline Characteristics

The total subjects in this study were 108 people. They were divided into two groups, group that experienced major adverse cardiovascular events (MACEs) and group that did not experience major adverse cardiovascular events. In this study, there were 24 people who experienced a cardiovascular event (22.2%) and 84 subjects (78.8%) did not experience a major adverse cardiovascular event. The age of subjects with MACEs was higher (61 years old) than those without MACEs (58 years old) but was not statistically significant. Men were 86 people (79.6%) and women numbered 22 subjects (20.4%). The average systolic and diastolic blood pressure in the group with MACEs was lower than the group without MACEs and was statistically significant. The frequency of heart rate is higher in the group with MACEs. Respiratory rate was not different in the two groups. Body mass index in the group with MACEs was lower than the group without MACEs.

For risk factors, this study found more subjects who had history of diabetes mellitus, history of hypertension, smoking history, percutaneous coronary intervention history and a history of heart failure in the group without MACEs. The prevalence of comorbidities, such as chronic obstructive pulmonary disease (COPD), did not differ in the two groups statistically. From the electrocardiographic parameters, it was found that the average duration of the QRS complex was 0.08 seconds, in the MACEs group 0.080 seconds and the group without MACEs 0.08 seconds.

From the laboratory parameters there were no statistical differences in hemoglobin levels, sodium levels, potassium levels and blood sugar levels. Osmolality in MACEs group was 296 mOsm/L and in group without MACEs was 291 mOsm/L.

In terms of kidney function parameters, the average creatinine level of the group with MACEs were higher (2.44 mg/dl) than the group without MACEs (1.35 mg/dl). These creatinine levels differed significantly in the two groups. Creatinine clearance in the group with MACEs were lower than the group without MACEs and was statistically different between the two groups. Blood urea nitrogen levels were 23

mg/dl in averaged, in MACEs group were mg/dl and group without MACEs were 22 mg/dl and difference statistically.

From the echocardiographic parameters there were no statistically significant difference between the two groups. Based on the clinical subset of acute heart failure, the highest was acute decompensated heart failure, 81 people (75%), followed by cardiogenic shock 12 people (11.1%), Acute Hypertensive Heart Failure 9 people (8.3%), Acute Lung edema 5 people (4.6%) and acute right heart failure 1 people (0.9%). The duration of treatment was not statistically different in both groups. Demographics and basic characteristics of research subjects can be seen in table 1.

Major Adverse Cardiovascular Events Percentage

From 108 study subjects, there were 24 subjects (22.2%) with major adverse cardiovascular events (MACEs) during hospitalization in patients with acute heart failure. On the other hand, 84 subjects (78.8%) did not experience MACEs during hospitalization. From 24 subjects with MACEs during hospitalization, subjects who died were 20 people (83.4%), those with arrhythmias were 2 people (8.3%), and 2 people had stroke (8.3%). Percentage of MACE was shown in table 2.

Cut off value of blood creatinine levels at admission for predicting major cardiovascular event during hospitalization

Using the Receiving Operating Curve (ROC), Area under the Curve (AUC) could be assessed from creatinine level, which showed creatinine ability as predictor of major cardiovascular events during hospitalization in patients with acute heart failure. In this study, AUC of 0.899 were found with p value <0.05. This showed that creatinine is clinically significant as a predictor of MACEs. The cut off value of >1.7mg/dl predicted MACEs with 87.5% sensitivity and 79.5% specificity (Figure 1).

In 108 study subjects, 39 people have creatinine levels ≥ 1.7 mg/dl and 69 people have creatinine levels <1.7 mg/dl. In the group with creatinine ≥ 1.7 mg/dl, MACEs were higher at 21 people compared to 18 people without MACEs. Whereas in the group with creatinine <1.7 mg/dl, there were fewer subject with MACEs, 3 people compared to 66 people without MACEs.

Multivariate Analysis with the Backward Stepwise Method

Multivariate analysis was performed to determine the prognostic variables that most affected MACEs in patients with acute heart failure. The results of multivariate analysis are shown in table 4.

Discussion

From 108 subjects, there were 24 (22.2%) subjects who experienced major adverse cardiovascular events during hospitalization including death, arrhythmia and stroke acute heart failure patients. MACEs, especially deaths, in this study were higher than previous studies. The incidence of death during hospitalization for acute heart failure patients was found to be lower in the OPTIMIZE-HF study (3.8%),7 ADHERE (4%),3 EHFS II (6.7%),15 FINN-AKVA (7.1%) 16 and AHEAD (12.7%).17 This was because of the different population characteristics and percentage of cardiogenic shock was also relatively lower in the studies mention above. The prevalence of cardiogenic shock in the EFHS II study population is 4%, in the FIN-AKVA population of 2.3%. While in this study, the prevalence of cardiogenic shock was 11.1%.

The mean age of subjects in this study was 58 years old. This was similar to the study by Al-Lawati JA which showed that the mean age of the subjects were 59 years old.18 However, it was different from other studies which have an average age of population >70 years old. The average age in the OPTIMZE-HF registry population is 73 years old and in the FIN- AKVA study 75 years old. From the ADHERE registry the average age of the population is 72 years old. This difference was based on differences in population characteristics in which in this study, there were more risk factors for heart failure, such as history of diabetes (33%), history of hypertension (51.9%) and smoking (72.2%). From OPTIMIZE-HF registry, 23% have hypertension, 11% have type 2 diabetes mellitus and 17% have smoking history. Whereas from the ADHERE registry, smoking history was found in 48%. From the FIN-AKVA study, 32% of patients with diabetes mellitus and hypertension were 54%.

From this study it was known that creatinine levels could be used as predictors of MACEs during hospitalization in patients with acute heart failure. In addition to creatinine, other predictors of MACEs during hospitalization of acute heart failure patients were creatinine clearance and heart rate. This is in accordance with the previous ADHERE registry study that obtained creatinine, blood urea nitrogen and systolic blood pressure at admission as predictor of mortality in acute heart failure. The results of this study were also in accordance with OPTIMIZE-HF registry that found that creatinine levels at admission, older age, low systolic blood pressure and low serum levels as predictors of MACEs in patients with acute heart failure.7 Even data from a meta-analysis conducted by Rahimi et al. found renal dysfunction as a strong predictor of MACEs during hospital care.8 From a study conducted by Blois Jd et al., it was also known about creatinine predictive value in regard to the incidence of cardiovascular events in acute heart failure patients.19From 108 study subjects, 50 (46%) had creatinine levels above normal with average creatinine level of 1.32 mg/dl. In the group with MACEs, creatinine levels were found to be higher (2.44 mg/dl) than in the group without MACEs (1.35 mg/dl). This was closely related to the kidney mechanism in the pathophysiology of acute heart failure. Severe heart failure would be followed by more severe renal dysfunction and increasing creatinine as biomarker of kidney function.14

Table 1
Baseline Characteristics

Characteristics	All patients N = 108 (100%)	MACEs N= 24 (22.2%)	Without MACEs N=84 (77.8%)	P Value
Age (mean) (years old)	58.58±9.568	61.3±8.761	57.8±9.693	0.11#
Gender (%)				
Male	86 (79.6%)	15 (75%)	73(79.3%)	0.569 b
Systolic Blood Pressure (mmHg)	120(60-220)	100(60-200)	120(70-220)	<.001*
Diastolic Blood Pressure (mmHg)	80(30-120)	60(30-100)	80(30-120)	<0.001*
Heart Rate (times/minute)	101(50-180)	117(50-130)	101(64-180)	<0.001*
Respiratory Rate (times/minute)	26(22-36)	26(23-32)	26(22-36)	0.571*
Body Mass Index (kg/m2)	24.7(16.5-38.6)	23.8(20.0-30.4)	24.8(16.5-38.6)	0.098*
History of Type 2 Diabetes Mellitus	36(33.3%)	7(19.4%)	29(80.6%)	0.807 a
History of Hypertension	56(51.9%)	11(19.6%)	45(80.4%)	0.644 a
History of Smoking	78(72.2%)	18(23%)	60(77%)	0.802 a
History of PCI	12(11.1%)	2(16.6%)	10(83.4%)	1.000 b
History of Heart Failure	51 (47.2%)	8(15.6%)	43(84.4%)	0.165 a
Hemoglobin (gr/dl)	13.1 (7.4-22.4)	120(9.1-18.5)	13.2(7.4-22.4)	0.307*
Blood Glucose (mg/dl)	131(66-534)	139(66-534)	130(66-512)	0.683*
Sodium (mEq/L)	132(105-144)	133(115-141)	134(105-144)	0.914*
Potassium (mEq/L)	4.1(2.5-6.4)	4.15(2.5-5.9)	4.10(2.7-6.4)	0.445*
Osmolality (mOsm/L)	292.5(244-324)	296(262-318)	291(244-324)	0.032*
Creatinine (mg/dl)	1.32(0.55-5.33)	2.44(1.24-5.33)	1.35(0.55-4.48)	<0.001*
Creatinine clearance (ml/minute/1,72m2)	58.96±32.22	29.20±10.64	67.46±31	<0.001#
Blood Urea Nitrogen (mg/dl)	23(8-97)	35.5(12-97)	22(8-92)	0.023*
QRS Duration (second)	0.08(0.06-0.16)	0.080(0.06-0.16)	0,08(0.06-0.14)	0.220*
Ejection Fraction (%)	35(16-67)	33(23-58)	35(26-67)	0.328*
COPD (%)	11(10.2%)	1(9%)	10(91%)	0.569 b
Clinical Subset: ADHF				
Acute Lung Oedema	81 (75%)	11(13.6%)	70(86.4%)	<0.001a
Hypertensive Heart Failure	5(4.6%)	3(60%)	2(40%)	0.072 b
Cardiogenic Shock	9(8.3%)	1(11.1%)	8(88.9%)	0.680 b
Acute Right Heart Failure	12(11.1%)	9(75%)	3(25%)	<0.001b
	1(0.9%)	0(0%)	1(100%)	1.000 b
Drugs during hospitalization: Ace-inhibitor (%)				
ARB (%)	84(74.1%)	14(16.6%)	70(83.4%)	0.046 a
Beta blocker (%)	17(15.7%)	2(11.8%)	15(88.2%)	0.351 b
Diuretic (%)	97(89.8%)	14(14.4%)	83(85.6%)	<0.001b
Nitrate (%)	108(100%)	24(100%)	84(100%)	-
Inotropic (%)	71(65.7%)	12(16.9%)	59(83.1%)	0.065 a
Aspirin (%)	31(28.7%	17(54.8%)	14(45.2%)	<0.001a
Clopidogrel (%)	89(82.4%)	23(25.8%)	66(74.2%)	0.067 b
CCB (%)	51(47.2%)	18(35.3%)	33(64.7%)	0.002 a
	7(65%)	0(0%)	7(100%)	0.345 b
Length of stay	7.5(1-28)	6(1-28)	8(3-22)	0.529*

*Note: p significant <0.05; a: chi square test; b: fisher exact test; #:t-test; *: mann-whitney test; PCI: percutaneous coronary intervention;COP chronic obstructive pulmonary disease; ADHF: acute decompensated heart failure; CCB: calcium channel blocker.*

Table 2
Major Adverse Cardiovascular Events Percentation

Major Adverse Cardiovascular Events	N (%)
Death	20 (83.4%)
Arrythmia	2 (8.3%)
Stroke	2 (8.3%)
Total	24 (100%)

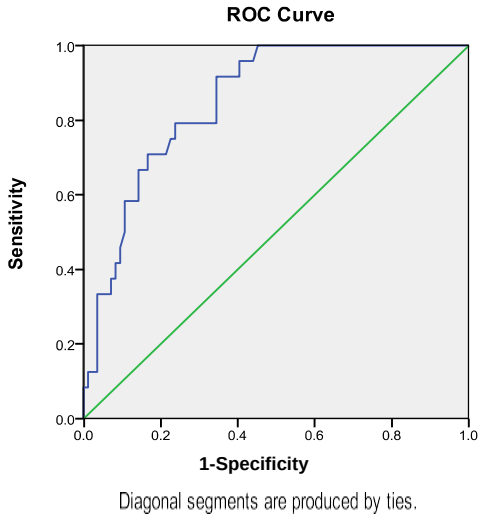

Figure 1. ROC of Optimal Blood Creatinine Level Cut Off Value at Admission for predicting MACEs

Table 3.
Creatinine Levels Result based on ROC

Cut Off	Sensitivity	Specificity	AUC	p value	95%CI
≥ 1.7	87.5%	79.5%	0.899	<0.001	0.840-0.957

Table 4.
Multivariate Analysis of Independent Factors as Predictors of In- Hospital Major Cardiovascular Events in Acute Heart Failure Patients

Parameter	Odd Ratio (OR)	P value	95% Confidence Interval	
			Lower	Upper
Creatinine	18.310	0.001	3.313	101.178
Creatinine clearance	8.478	0.031	1.222	58.810
Heart Rate	27.199	<0.001	4.747	155.847

In this study, cut-off of creatinine which that was considered significant was ≥1.7 mg/dl with Odd Ratio about 18.310 times at creatinine level ≥1.7 mg/dl compared to patients with creatinine <1.7 mg/dl. In this study, creatinine clearance also played a role as a predictor of MACEs with Odd Ratio of 8.478 times in creatinine clearance of ≤30 ml/minute/1.72m2 compared to creatinine clearance values >30 ml/minute/1.72m2. This result was similar to the meta-analysis conducted by Smith et al., which reported that creatinine clearance where a predictor for all causes of mortality in acute heart failure patients.20 From the ECSAPE Trial, the proportion of acute heart failure patients with creatinine clearance <60 ml/minute was 31.4%. In patients with heart failure, when compared to the NYHA functional class and ejection fraction, baseline creatinine clearance had been shown to be a better predictor of all cause mortality. Decreased creatinine clearance was associated with high mortality during hospitalization in acute heart failure patients while the mortality rate of acute heart failure patients without kidney dysfunction is 26%. This mortality rate increased to 41% in patients with mild renal dysfunction and 51% in moderate to severe renal dysfunction.21 The ADHERE registry found that in acute heart failure patients with creatinine clearance 15-20 ml/minute/1.72m2, the risk of death during hospitalization was about 7.6%.3

Heart rate was also a predictor of MACEs in patients with acute heart failure during hospitalization with Odd Ratio of 27.199 times with a heart rate of ≥110x/minute compared to heart rate <110x/minute. These results were in accordance with the results of the study by Bui AL et al. that showed high heart rate at admission was related to poor outcomes including death and length of stay. The risk of death was higher in patients with normal ejection fraction with an increase in heart rate >105x/minute compared to reduced ejection fraction with heart rate <105x/minute.22 This was also in accordance with study by Metra which stated that the presence of tachycardia in acute heart failure was associated with the severity of heart failure and short-term outcome.23 The same results were also shown in the study conducted by Aronson et al. which found that there was an increased risk of death with an increase in heart rate.24 The OPTIMIZE-HF registry showed that increased heart rate was also associated with a higher risk of death in patients with acute heart failure. Any increase in heart rate of 10x/minute will increase the risk of death by 1.18x compared with no increase in heart rate.7

There are limitations in this study. First, the number of subjects studied was 108 people. Larger quantities are needed to obtain more representative picture of creatinine levels as a predictor of MACEs during hospitalizationin patients with acute heart failure. Second, monitoring of subjects in this study was carried out only as long as the subject was hospitalized. It was expected that short-term and long-term monitoring of the role of creatinine as a predictor of major adverse cardiovascular events could be carried out in further studies.

Conclusion

We concluded that creatinine levels at admission were independent predictors of major adverse cardiovascular events during hospitalization in patients with acute heart failure with optimal cut-off point ≥1.7 mg/dl. In addition to creatinine levels, heart rate and creatinine clearance were also predictors of major cardiovascular events during hospitalizationin of acute heart failure patients.

Acknowledgement

Authors acknowledged these following persons: dr. Mirhansyah PH, dr. Bertha GN, dr. T. Bob Haykal, Sp.JP(K), dr. Zulfikri Mukhtar, Sp.JP(K).

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