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Pre-Discharge Urinary Albumin-Creatinine Ratio as a Predictor of Post-Hospitalization Major Adverse Cardiovascular Events (MACEs) Due to Acute Heart Failure

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ABSTRACT

Background: Acute heart failure (AHF) is a multifactorial syndrome associated with rehospitalization and higher mortality. Impaired renal function is one of non-cardiac comorbidities which aggravate the progression of heart failure (HF). Increased in urinary albumin-creatinine ratio (UACR) reflects decline of renal function. It also provides useful information for risk stratification and determining prognosis of HF patient. ***Methods:*** Patients with AHF who met inclusion-exclusion criteria were included in a prospective observational cohort study. After achieving decongestion state, we obtained early morning urine samples of these patients to examine pre-discharge UACR. We monitored patients within 60 days post-discharged. Demographic, clinical characteristics, comorbidities, laboratory and echocardiographic data were also collected. The outcomes studied were major cardiovascular events (MACEs), consisted of rehospitalization due to heart failure and/or cardiovascular mortality. Cut-off point of pre-discharge UACR was determined by ROC curves, Kaplan-Meier curve was used to assess survival of MACEs based on pre-discharge UACR values, and multivariate analysis using Cox Regression was performed using SPSS version 24.0.0.0. ***Results:*** A total of 70 samples were involved until the end of the study. The cut-off point of pre-discharge UACR was 46.5 mg/gram creatinine (AUC 0.653, sensitivity of 67.5% specificity of 66.7%). Subjects with pre-discharge UACR ≥46.5 mg/gram creatinine had a survival of 39.40% while those with a value <46.5 mg/gram creatinine had a survival of 73.0% (p = 0.003). Multivariate analysis showed that pre-discharge UACR ≥ 46.5 mg/gram creatinine was independently associated with an increased risk of MACEs within 60 days post-hospitalization due to AHF (adjusted HR 4.76; 95% CI 1,455-15,622; p=0.010). ***Conclusion:*** Pre-discharge UACR ≥ 46.5 mg/gram creatinine was independently associated as a predictor of MACEs within 60 days post-hospitalization due to AHF.

Keywords: urinary albumin-creatinine ratio (UACR); acute heart failure (AHF); major adverse cardiovascular events (MACEs); rehospitalization; cardiovascular mortality

INTRODUCTION

The epidemiologic transition due to lifestyle changes increases the risk factors and prevalence of heart failure (HF) in Asian populations, including Indonesia. An epidemiologic study by Reyes, et al (2016) showed that the prevalence of HF in Indonesia is around 5%, with obesity, diabetes mellitus (DM) and hypertension as the main risk factors [1]. The results of the Basic Health Research of the Republic of Indonesia in 2018 showed that more than one million Indonesians suffered from cardiovascular disease, and 20% of them were diagnosed with HF [2]. HF is the leading cause of hospitalization in patients aged over 65 years. In hospital mortality ranges from 4-10%. Mortality within one-year post-hospitalization reaches 25-30%, with a rehospitalization rate of more than 45% [3].

This makes HF a health burden as well as an economic burden that significantly increases health expenditure [1,4].

The natural course of HF is characterized by the presence of an AHF episode, which is defined as worsening signs and symptoms of heart failure that occurs gradually or suddenly and leads to unplanned office visits, emergency department visits or even hospitalization [5]. During their lifetime, HF patients may experience multiple episodes of AHF, leading to repeated hospitalizations. Approximately 30% of re-hospitalizations occur in the "vulnerable phase", within 60 to 90 days post-hospitalization for heart failure [6,7].

Frequent rehospitalization will lead to a progressive decline in cardiac function and quality of life and increase the risk of mortality [8].

Impaired renal function is one of the causes of heart failure progression, which increases the risk of hospitalization and mortality [9,10]. Acute kidney injury can impair cardiac function and trigger AHF through several pathways known as cardiorenal connectors, such as activation of the systemic immune system, release of inflammatory mediators, oxidative stress, cell apoptosis and neurohormonal activation including the sympathetic nervous system and renin angiotensin aldosterone system (RAAS). The activation of these various pathways will directly cause vascular endothelial injury and dysfunction, ventricular remodeling, hypertrophy to cardiomyocyte apoptosis which leads to a progressive decrease in myocardial contractility. On the other hand, the conditions of volume overload, electrolyte balance disorders, acidemia and uremic toxin accumulation that accompany acute kidney injury will also indirectly trigger the progression of heart failure [11].

Albuminuria, assessed by the 24-hour or baseline UACR, is one of the markers for filtration function and glomerular integrity [10]. Increased albuminuria is the earliest marker of glomerular damage, preceding the decline in glomerular filtration rate [9]. Albuminuria is also a marker of a complex pathophysiologic process involving systemic inflammatory conditions, endothelial and microvascular dysfunction, and tubular damage [12]. Renal venous congestion leads to dysfunction of the glomerular filtration barrier and renal tubules. There is an increase in glomerular permeability to macromolecules such as albumin. Neurohormonal activation, systemic inflammation, as well as oxidative stress lead to glomerular endothelial dysfunction and injury to the podocyte layer that aggravates glomerular filtration barrier dysfunction. On the other hand, tubular injury leads to decreased albumin reabsorption, thereby increasing urinary albumin excretion [9].

In the context of cardiorenal interactions, albuminuria is an independent predictor of worsening heart failure condition and increased risk of mortality in heart failure patients [9] This is supported by the findings in a number of studies proving that albuminuria has a strong prognostic value for death from all causes, death from cardiovascular disease, as well as rehospitalization due to heart failure [10]. In the 2009 CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) sub-study, 30% of patients had microalbuminuria and 11% had macroalbuminuria. Increased albuminuria is associated with an increased risk of composite outcomes (including death from cardiovascular causes and hospitalization due to heart failure) [13]. The 2010 Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza Cardiaca (GISSI-HF) sub-study, showed that elevated albuminuria is a strong prognostic sign in patients with chronic heart failure, irrespective of the presence of comorbidities such as diabetes, hypertension, and renal disease [14]. The TOPCAT (Aldosterone Antagonist Therapy for Heart Failure with Preserved Ejection Fraction) sub-study of 2019, showed that increased albuminuria was independently associated with worse cardiovascular outcomes, whereas a 50% reduction in albuminuria was associated with decreased hospitalization for heart failure and all-cause mortality [12].

Most studies examine the relationship between albuminuria and long-term clinical outcomes of chronic heart failure patients, while studies assessing the prognostic benefits of albuminuria in the AHF population are limited. An observational study by Koyama, et al (2013) examining changes in urinary albumin creatinine ratio during the treatment of patients with AHF found an increasing trend in albuminuria at the time of admission and a significant decrease within 7 days of treatment. This decrease correlates with serum concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) and bilirubin which are markers of congestion as well as prognostic indicators in AHF patients [15]. However, this study did not assess the relationship between elevated albuminuria and the clinical outcomes of patients either during or post-hospitalization.

The study by Matsumoto, et al (2022) was the first study to report the prognostic role of assessment of UACR ratio at the time of admission due to AHF, on the risk of early rehospitalization. This study showed that increased albuminuria was significantly associated with a higher incidence of rehospitalization within 1 year. Elevated albuminuria and serum BNP are independent risk factors for rehospitalization due to heart failure [16]. This study has a limitation because it uses a retrospective design and UACR examination was only carried out at the time of admission. Analysis of the pre-discharge UACR might predict prognosis more precisely.

Because of these limitations, the authors consider that it is necessary to conduct further research to determine the prognostic benefits of albuminuria assessment based on predischarge UACR on short-term outcomes after hospitalization due to AHF, in the form of major cardiovascular events (MACE), which include rehospitalization and death from cardiovascular disease. If the hypothesis is proven, this examination can potentially become an affordable additional non-invasive supporting examination, that can further guide us in providing therapy and monitoring for patients with heart failure.

METHODS

This study was conducted with a prospective observational cohort design to see the relationship between predischarge UACR and MACE in the form of rehospitalization and or death from cardiovascular disease within 60 days post-hospitalization in patients with AHF. The target population in this study were patients with AHF who underwent hospitalization at Prof. Ngoerah General Hospital.

The Inclusion Criteria are: 1) Patients with AHF who are aged ≥ 18 years; 2) Willing to participate by signing an informed consent sheet after getting an explanation; 3) Patients with de novo or recurrent AHF; 4) Patients with HFrEF, HFmrEF, or HFpEF. Exclusion Criteria: 1) Patients with CKD (based on diagnosis in medical records, or a history of eLFG < 60 ml/min/1.73m^2 in the last 3 months based on laboratory data of Clinical Pathology of Prof. Ngoerah General Hospital that persisted during treatment; 3) AHF patients with nephrotic syndrome; 4) AHF patients with urinary tract infection, and high output state conditions (fever, hyperthyroidism, severe infection, sepsis) that have not been resolved; 5) AHF patients with pregnancy; 6) AHF patients with malignancy; 7) AHF patients with chronic liver disease (CLD).

The sampling technique in this study was non-probability sampling using consecutive sampling. Samples were taken sequentially from all subjects observed and met the sample selection criteria until the required sample size was met. Samples were taken by including the entire affordable population who met the inclusion criteria and excluding samples that fell within the exclusion criteria.

The predischarge UACR examination was performed by taking the first urine sample in the morning after clinical improvement of congestion, or at least the morning before the patient was discharged.

The samples were then sent to Prodia Clinical Laboratory, Denpasar to be analyzed using the Nephelometry method with the Cobas 6000 device. All data collected in each group were then analyzed with the SPSS program. Data analysis was performed with Descriptive analysis. Receiver Operating Characteristic (ROC) Curve analysis was used to determine the cut off for UACR value. Kaplan-Meier Curve was used to assess survival, cox regression analysis was performed to identify independently associated risk factors as predictors of MACE. The confidence level in this study was 95%. H0 was rejected if the p value was <0.05.

RESULTS

A total of 70 patients with AHF who underwent hospitalization at Prof. Dr. I G. N. G. Ngoerah, hospital was involved in this study. The basic characteristics of the study subjects are shown in Table 1. The average age of the subjects was 56.18 ± 12.76 years and was dominated by male gender (71.4%). A total of 32% of subjects were obese, majority did not suffer from type 2 DM (72.9%), 50% of subjects suffered from hypertension, and more than half of the subjects were smokers (55.7%). A history of COPD and asthma was found in 10% and 4.3% of subjects, respectively. All subjects had never received SGLT2-i therapy before.

TABLE 1: Basic Characteristics of Study Subjects.

Basic Characteristics	Total (N=70)
Gender	
Male, n (%)	50 (71.4)
Female, n (%)	20 (28.6)
Age, years, mean ± SB	56,18±12,76
BMI, kg/m^2, mean ± S.D.	24,38±3,60
Underweight (BMI <18.9 kg/m2), n (%)	3 (4,3)
Normal (BMI ≥18.9-22.9 kg/m2), n (%)	19 (27,1)
Overweight (BMI ≥23-24.9 kg/m2), n (%)	25 (35,7)
Obesity (BMI ≥25 kg/m2), n (%)	23 (32,9)
Risk factors and comorbidities	
Smoking, n (%)	39 (55,7)
Hypertension, n (%)	35 (50,0)
Diabetes mellitus, n (%)	19 (27,1)
CHD, n (%)	28 (40,0)
Asthma, n (%)	3 (4,3)
COPD, n (%)	7 (10,0)

The clinical characteristics of the study subjects as presented in Table 2 show that most of the causes of AHF in this study were acute myocardial infarction (IMA) (45.71%). In terms of HF phenotype, most of the study subjects belonged to the heart failure reduced ejection fraction (HFrEF) phenotype (70%). Majority of the study subjects had *de novo* AHF (61.2%). The incidence of cardiogenic shock occurred in 25.7% of the study subjects. The median length of stay (LOS) is 5 days.

TABLE 2 : Clinical Characteristics of Study Subjects.

Characteristics	Total (N=70)
Heart failure	
De novo heart failure, n (%)	41 (61.2)
ADHF, n (%)	26 (38.8)
Heart failure phenotype	
HFrEF (LVEF ≤ 40%), n (%)	49 (70,0)
HFmrEF (LVEF 41- 49%), n (%)	5 (7,1)
HFpEF (LVEF ≥50%), n (%)	16 (22,9)
Etiology of heart failure	
Acute myocardial infarction (IMA), n (%)	32 (45.71)
Coronary artery disease (CAD), n (%)	21 (30,00)
Emergency hypertension, n (%)	6 (8,57)
Valvular heart disease (VHD), n (%)	4 (5,71)
Rheumatic heart disease (RHD), n (%)	3 (4,28)
Adults with Congenital Heart Disease (ACHD), n (%)	3 (4,28)
Cardiogenic shock during treatment, n (%)	18 (25,7)
Length of stay (days), median (IQR)	5 (2-15)

Laboratory and echocardiographic characteristics are presented in Table 3. The mean pre-discharge BUN and creatinine were 19.16± 9.4 mg/dL and 1.01± 0.185 mg/dL, respectively, while the median eLFG and pre-discharge UACR were 69.84 (27.51) (mL/min/1.73 m^2) and 36,52 (1,43-3.920,74) mg/gram creatinine, respectively. The mean LV systolic function (LVEF) was 38.29± 14.91%, while the mean RV contractility (TAPSE) was 1.97± 0.37 cm.

TABLE 3 : Characteristics of laboratory and echocardiography.

Parameters	Total (N=70)
Laboratory pre-discharge	
UACR, mg/gram creatinine, median (IQR)	36,52 (1,43-3920,74)
BUN, mg/dL, mean± SB	19.16± 9.4
Creatinine, mg/dL, mean± SB	1.01± 0.185
eGFR, (mL/min/1.73 m^2), median (IQR)	69,84 (59,94-126,00)
Na, mmol/L, mean± SB	137.50± 4.31
K, mmol/L, mean± SB	3.90± 0.46
Cl, mmol/L, median (IQR)	103 (84,20-120,00)
Echocardiography during hospitalizarion	
LVEF, %, mean± SB	38.29± 14.91
TAPSE, cm, average± SB	1.97± 0.37
CI, l/min/m^2, mean ± SB	2.31± 0.94
SVR, dynes/second/cm^{-5}, mean ± S.D.	1,743, 63± 783

Table 4 shows the characteristics of cardiovascular outcomes in this study. A total of 42.8% of subjects experienced MACEs, consisting of rehospitalization due to heart failure as much as 41.4% and death from cardiovascular causes as much as 10%.

TABLE 4: Cardiovascular Outcome Characteristics.

Outputs	Total (N=70)
Total MACE, n (%)	30 (42.8)
MACE rehospitalization, n (%)	29 (41,4)
MACE cardiovascular death, n (%)	7 (10,0)

ROC curve analysis and depiction were used to obtain the best cut-off value of pre-discharge UACR, as a predictor of MACEs within 60 days post-hospitalization due to AHF. Based on this analysis, the best pre-discharge UACR cut-off value was 46.5 mg/gram creatinine, with a sensitivity of 67.5%, specificity of 66.7%, and AUC value of 0.653 (95%CI 0.552-0.783; p = 0.03) as presented in Figure 1.

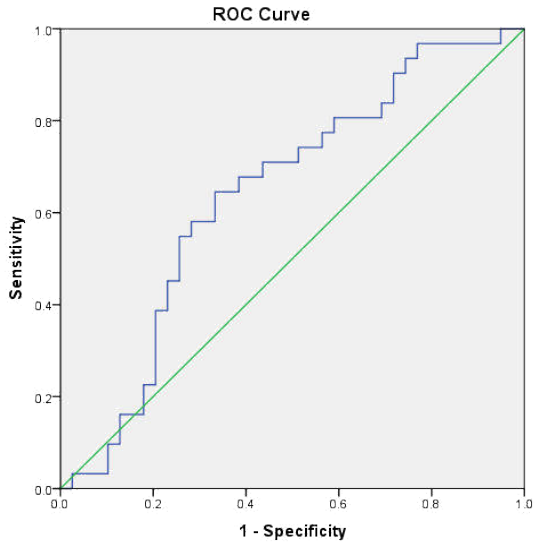

FIGURE 1 : ROC curve, sensitivity and specificity of pre-discharge UACR as a predictor of MACEs within 60 days post hospitalization due to AHF.

The bivariate analysis between pre-discharge UACR and MACEs is presented in Table 5. This table shows that during the 60 days post hospitalization monitoring period, subjects who had higher pre-discharge UACR values (≥ 46.5 mg/gram creatinine) experienced MACEs at a rate of 60.6% (p=0.007).

TABLE 5: Relationship between pre-discharge UACR and MACEs.

Pre-Discharge Urinary Albumin Creatinine Ratio	MACE		P-value
	Yes.	No	
≥ 46.5 mg/gram creatinine	20 (60,6)	13 (39,4)	0,007*
<46.5 mg/gram creatinine	10 (27,0)	27 (73,0)	

The subject characteristics based on MACE are presented in Table 6. The table shows some characteristic differences between subjects who experienced MACEs and those who did not experience MACEs. Subjects with ADHF presentation had more MACEs than subjects with de novo AHF. Subjects who experienced MACEs also had higher systemic vascular resistance (SVR) values than those who did not experience MACEs. In addition, the incidence of MACEs was significantly higher in subjects with pre-admission oral loop diuretic therapy, pre-admission beta blocker therapy, and subjects who did not receive ACE-i/ARB/ARNI therapy at discharge.

TABLE 6: Characteristics of study subjects based on MACEs.

Variables	MACE		P-value
	Yes (N=30)	No (N=40)	
Age, years, mean ± SB	55,60 ± 12,78	56,62 ± 12,88	0,742
BMI, kg/m2, mean ± SB	23.76± 3.20	24.84± 3.85	0,219
Gender			
Male, n (%)	20 (40)	30 (60)	0,594
Female, n (%)	10 (50)	10 (50)	
AHF Presentation			
ADHF, n (%)	16 (66,7)	8 (33,3)	0,005*
De novo AHF, n (%)	14 (30,4)	32 (69,6)	
Cardiogenic shock			
Yes, n (%)	8 (44,4)	10 (55,6)	1,000
No, n (%)	22 (42,3)	30 (57,7)	
Length of stay, days, median (IQR)	6 (2-15)	5 (2-13)	0,246

Variables	MACE		P-value
	Yes (N=30)	No (N=40)	
Comorbidities			
Smoking			
Yes, n (%)	15 (38,5)	24 (61,5)	0,470
No, n (%)	15 (48,5)	16 (51,6)	
Hypertension			
Yes, n (%)	14 (40,0)	21 (60,0)	0,809
No, n (%)	16 (45.5)	19 (54,3)	
DM			
Yes, n (%)	9 (47,4)	10 (52,6)	0,787
No, n (%)	21 (41,2)	30 (58,8)	
CAD			
Yes, n (%)	15 (53,6)	13 (46,4)	0.806
No, n (%)	17 (40,5)	25 (59,5)	
Pre-admission routine medication			
ACEi/ARB/ARNI			
Yes, n (%)	11 (55,0)	9 (45,0)	0,285
No, n (%)	19 (38,0)	31 (62,0)	
Beta blockers			
Yes, n (%)	15 (60,0)	10 (40,0)	0,044*
No, n (%)	15 (33,0)	30 (66,7)	
MRA			
Yes, n (%)	9 (52,9)	8 (47,1)	0,404
No, n (%)	21 (39,6)	32 (60,4)	
Digitalis			
Yes, n (%)	4 (80,0)	1 (20,0)	0,157
No, n (%)	26 (40,0)	39 (60,0)	
Oral loop diuretic, n (%)			
Yes, n (%)	15 (75,0)	5 (25,0)	0,001*
No, n (%)	15 (30,0)	35 (70,0)	
Pre-discharge vital signs			
SBP, mmHg, mean ± SD	110.83± 18.27	112.83± 17.15	0,642
DBP, mmHg, mean ± SD	70.00± 10.37	71.15± 11.31	0,664
HR, beats per minute, mean ± SD	77.63± 11.17	76.85± 12.83	0,790
Discharge medications			
ACE-i/ARB/ARNI			
Yes, n (%)	26 (39,4)	40 (0,0)	0,03 *#
No, n (%)	4 (100,0)	0 (0,0)	
Beta blockers, n (%)			
Yes, n (%)	26 (40,0)	39 (60,0)	0,302
No, n (%)	3 (75,0)	1 (25,0)	
MRA, n (%)			
Yes, n (%)	22 (40,0)	33 (60,0)	0,391
No, n (%)	8 (53,3)	7 (46,7)	
Digitalis, n (%)			
Yes, n (%)	4 (57,1)	3 (42,9)	0,690
No, n (%)	26 (41,3)	37 (58,7)	
Ivabradine, n (%)			
Yes, n (%)	5 (50,0)	5 (50,0)	0,735
No, n (%)	25 (41,7)	35 (58,3)	
Oral loop diuretic, n (%)			
Yes, n (%)	27 (40,3)	40 (57,1)	0,074
No, n (%)	3 (100,0)	0 (0,0)	

Variables	MACE		P-value
	Yes (N=30)	No (N=40)	
Pre-discharge laboratory results			
BUN, mg/dL, mean± SB	21,22± 11,54	17.61± 7.21	0,113
Creatinine, mg/dL, mean± SB	1.02± 0.18	1.01± 0.18	0,702
eGFR, (mL/min/1.73 m^2), median (IQR)	69,71 (27,90)	73,28 (29,04)	0,794
Declining (<90 mL/min/1.73 m)^2	24 (41,4)	34 (58,6)	0,750
Normal (≥ 90 mL/min/1.73 m)^2	6 (50,0)	6 (50,0)	
Na, mmol/L, mean± SB	137.16± 4.89	137.75± 3.86	0,439
K, mmol/L, mean± SB	3.83± 0.43	3.95± 0.47	0,204
Cl, mmol/L, median (IQR)	101.96± 6.10	103, 12 (3,93)	0,293
Echocardiographic parameters			
LVEF, %			
LVEF <40	22 (47,8)	24 (52,2)	0,312
LVEF ≥ 40%	8 (33,3)	16 (66,7)	
TAPSE, cm			
TAPSE ≥ 1.7 cm	23 (39,0)	36 (61,0)	0,186
TAPSE < 1.7 cm	7 (63,6)	4 (36,4)	
SVR, dynes/second/cm^{-5}, mean ± S.D.	2.019,38 ± 951,34	1.528, 38 ± 543,26	0,008*
CI, l/min/m2, mean ± S.D.	2,18 ± 0,85	2,4 ± 0,93	0,203

- Normally distributed numerical data are presented as mean ± standard deviation (S.D.), while non-normally distributed data are presented as median (interquartile range (IQR)).
- Analysis of normally distributed numerical data was performed using the Independent Student T-test.
- Analysis of non-normally distributed numerical data was performed using the Mann-Whitney test.
- Categorical data were displayed in frequency (n) and percentage (%), and was analyzed using the Chi-square test.
- # = categorical data which was analyzed using Fisher's Exact Test.
- * = there was a statistical difference between the two groups (p<0.05) and was included in the multivariate analysis.

The interaction of pre-discharge UACR as a predictor of MACEs was performed using a survival analysis. The survival analysis was first performed by checking the proportional hazard (PH) assumption using Kaplan-Meier curves for the independent variable (pre-discharge UACR) and the dependent variable (MACEs) (Figure 2). Based on the survival analysis, subjects with higher pre-discharge UACR values (≥ 46.5 mg/gram creatinine) had significantly lower 60-day survival rates than those with lower pre-discharge UACR values (73.0% versus 39.4%; p=0.003).

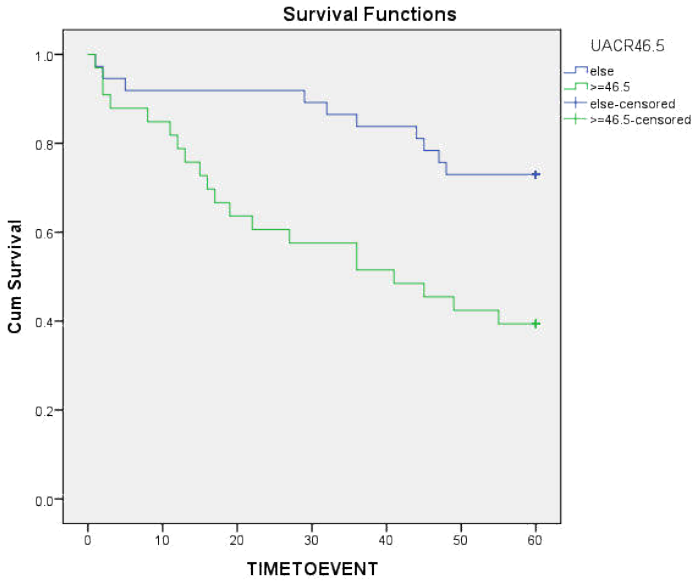

FIGURE 2: Kaplan-Meier survival curve of pre-discharge UACR as a predictor of MACEs within 60 days post-hospitalization due to AHF.

The Kaplan-Meier curve in Figure 2 shows that the pre-discharge urinary creatinine albumin ratio value fulfills the PH assumption, so the analysis was performed using Independent Cox regression. Through Independent Cox regression analysis, it was found that subjects with higher pre-discharge urinary creatinine albumin ratio values had a 3.006 times higher risk of experiencing MACE within 60 days (unadjusted HR 3.006; 95%CI 1.402-6.443; p=0.005).

To identify risk factors that independently associated as predictors of short-term MACEs in patients with AHF, all variables that did not have a multicollinearity relationship and had a p value <0.05 in the bivariate analysis (Table 6), namely: pre-discharge UACR, pre-admission routine oral loop diuretic therapy, pre-admission routine beta blocker therapy, discharge ACE-i/ ARB/ ARNI therapy, and SVR were included in the multivariate analysis using Cox Regression with the backward method.

TABLE 7: Multivariate analysis using cox regression.

Variables		HR	95%CI		P-value
			Lower Limit	Upper Limit	
Step 1	Pre-discharge UACR	4,996	1,491	16,746	0,009
	SVR	1,001	1,000	1,002	0,093
	Pre-admission routine beta blockers therapy	0,481	0,055	4,177	0,507
	Pre-admission routine oral loop diuretic therapy	4,312	0.702	26,498	0,115
	Discharge ACE-i/ARB/ARNI therapy	0,000	0,000	NA	0,999
	ADHF vs de-novo AHF	3,064	0,472	18,875	0,241
Step 3	Pre-discharge UACR	4,767	1,455	15,622	0,010*
	SVR	1,001	1,000	1,002	0,08
	Pre-admission routine oral loop diuretic therapy	4,527	1,198	17,107	0,026*

Through backward analysis, after adjusting some confounding factors (SVR, and pre-admission routine oral loop diuretic therapy), it was found that higher pre-discharge UACR (≥ 46.5 mg/gram creatinine) is independently associated as a predictor of MACEs within 60 days post-hospitalization due to AHF (adjusted HR 4.767; 95% CI 1.455-15.622; p=0.010).

DISCUSSION

AHF is a multifactorial syndrome associated with high rates of in hospital and long-term mortality, as well as recurrent hospitalization. Hospitalization due to HF illustrates the dynamics clinical course of the disease. The severity of AHF is largely determined by the complex interactions between precipitating factors, the underlying substrate of cardiac disorders, and the presence or absence of cardiac and non-cardiac comorbidities. Several studies have found that short-term rehospitalization is most often caused by residual congestion or recurrent congestion. Meanwhile, long-term rehospitalization is a consequence of worsening cardiac substrate, worsening cardiac and non-cardiac comorbidities, and because of the difficulty in implementing the guideline-directed medical therapy (GDMT) [17].

In a recent European Society of Cardiology-Heart Failure Association (ESC-HFA), EURObservational Research Programme Heart Failure Long Term Registry (EORP-HF-LT) study involving 25,621 patients with AHF, it was found that 80% of patients admitted for AHF had at least one non-cardiac comorbidity which was associated with rehospitalization and higher post-discharge cardiovascular mortality.

Renal impairment is one of the three major non-cardiac comorbidities (in addition to anemia and COPD), that increased risk of rehospitalization due to HF as well as cardiovascular mortality, post-hospitalization due to AHF [17,18].

Albuminuria assessed by UACR is one of the markers of filtration function and glomerular integrity. An increased in albuminuria may reflect a decline in renal function even before a decreased in eGFR. In the context of cardiorenal interactions, albuminuria is an independent predictor of worsening HF and increased risk of mortality in HF patients [9,10]. One study by Matsumoto, et al (2022) proved the the prognostic role of UACR assessment at the time of admission due to AHF, on patient outcomes. This study found that elevated UACR and serum BNP predict early rehospitalization due to HF [16].

Our study is aimed to determine the potential role of pre-discharge UACR in predicting short-term outcomes of patients with AHF. The subjects in this study were dominated by male gender (71.4%). This finding is in accordance with the finding of the Saiful Anwar Hospital Heart Failure Registry (SAHEFAR) registry study (2020). This study found that the majority of hospitalized AHF patients involved in their registry were male (58.1%) (Santoso et al., 2020). The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry (2020) also found that most symptomatic heart failure patients in Asia were male (83%) [19].

The mean age of the subjects in this study was 56.18± 12.76 years. These results are not much different from the HF registry in Southeast Asia by Reyes, et al (2016) which found that the mean age at admission due to AHF in Indonesia was 57.8 years [1]. The mean age of the subjects in this study was younger than the results of the ASIAN-HF registry which found that the mean age of patients with symptomatic heart failure was 61.6± 13.3 years old [19].

Majority of subjects in this study experienced de novo AHF (65.7%), with the most risk factors/comorbidities are smoking (55.7%), hypertension (50.0%), CHD (40%) and DM (27.1%). These results are in accordance with the findings of Acute Decompensated Heart Failure Registry (ADHERE) registry by Siswanto, B.B, et al (2010). This study also found that most of the patients had de novo AHF (66.7%), with smoking (74.0%), hypertension (54.8%), CHD (49.9%), DM (31.2%) as the main risk factors/comorbidities [21].

The proportion of de novo AHF in this study was higher than the results of studies in western countries. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) study in 2017, the proportion of de novo AHF was only 26.7%. (Greene et al., 2017). In the Danish Nationwide Registries observational cohort study, although most of patients had de novo AHF clinical presentation (approximately 51.6%) [22], however the percentage was not as large as the results of our study or study by Siswanto, B.B, et al [21].

The ASIAN-HF registry (2020) highlights significant differences in the age and comorbidities of HF patients in Asia compared to patients in the western countries [3]. HF patients in Asia are relatively younger and have more comorbidities. Socio-cultural constraints, low education levels, lack of health knowledge (especially in the elderly population), weak primary health care systems and high health costs are some of the obstacles that make cardiovascular disease prevention programs not running well, as well as access to health services more limited. These factors are likely to influence the onset of HF at a relatively younger age, as well as the clinical presentation of predominantly de-novo AHF [23].

Research on the potential value of pre-discharge UACR as a predictor of MACEs in the AHF population is limited. In our study, the pre-discharge UACR was examined after stabilization of the AHF condition (decongestion) until before the patient was discharged. Based on ROC curve analysis, the best cut-off pre-discharge UACR that could be a predictor of MACEs within 60 days post-hospitalization due to AHF was 46.5 mg/gram creatinine (AUC 0.653 (95%CI 0.552-0.783; p=0.03), sensitivity 67.5% and specificity 66.7%). Our study found lower UACR cut-off value compared with previous study by Matsumoto et al (2022) who found an UACR value of 50 mg/gram creatinine as the best cut-off point in predicting early rehospitalization due to heart failure with (AUC 0.66, sensitivity of 0.909 and specificity of 0.406) [16].

The difference in this cut-off point can be caused by several factors. First, the method chosen in our study was a prospective observational cohort while the study conducted by Matsumoto et al, was a retrospective study. Second, there were differences in the number and characteristics of the study subjects. In his study, Matsumoto et al, used a larger number of samples, excluded only subjects with eGFR values < 15 ml/min/173 m^2, while our study only included subjects with eGFR values ≥ 60 ml/min/1.73 m2 at discharge, without history of previous kidney disease. This may affect the subject's UACR value. Third, Matsumoto et al, assessed the UACR at the time of admission which means that the subjects were examined under congestion condition. Whereas in our study, the UACR was examined after patients achieved decongestion or just before discharge. A study by Koyama, et al (2013), found that there was a significant correlation between congestion and high UACR values [15].

In this study, a higher pre-discharge UACR value showed it potency as predictor of MACEs. Subjects with a pre-discharge UACR value ≥ 46.5 mg/gram creatinine had a 3 times higher risk of experiencing MACEs than subjects with a pre-discharge UACR value < 46.5 mg/gram creatinine (unadjusted HR 3.006; 95%CI, 1.402-6.443; p=0.005). This finding is consistent even after adjustment of another risk factors in multivariate analysis using Cox Regression. We found that higher pre-discharge UACR was independently associated as predictor of MACEs within 60-day post-hospitalization due to AHF (adjusted HR of 4.767, 95% CI 1.455-15.622; p=0.010). This result suggests that a higher pre-discharge UACR is indeed an independent predictor of MACEs with a 4.7-fold increased risk compared to lower pre-discharge UACR value.

The role of UACR in predicting rehospitalization and cardiovascular mortality has been widely proven in various large studies involving chronic heart failure (CHF) patient populations. The cohort study by Shuvy, et al (2022) found that microalbuminuria and macroalbuminuria were directly associated with reduced event free survival for both death and hospitalization due to cardiovascular disease [25]. Although increased albuminuria is more common in patients with comorbidities such as diabetes mellitus, hypertension and obesity, in patients with HF increased albuminuria is a prognostic indicator, even in the absence of all these comorbidities [9]. The TOPCAT (2018) study showed that both microalbuminuria and macroalbuminuria were associated with the primary endpoint of hospitalization for heart failure and all-cause mortality (HR 1.47; 95% CI, 1.15-1.86; HR 1.67; 95% CI, 1.22-2.28). A reduction of 50% albuminuria was associated with a reduction in hospitalization for HF (HR 0.90; p = 0.017) and all-cause mortality (HR 0.90; p = 0.017) [12].

Study by Matsumoto et al (2022) showed that of 140 patients with AHF, only 18% had normal albuminuria, 59% had microalbuminuria, and 23%

had macroalbuminuria. Cutt off UACR ≥ 50 mg/gram creatinine and BNP ≥ 824 pg/ml at the time of admission were independent risk factors for early rehospitalization due to HF (HR 3.32; 95%CI: 1.40-9.77, p = 0.005; HR 2.36; 95%CI: 1.22-4.81, p = 0.011, respectively) [16]. In the 2022 BIOSTAT-CHF study, the prevalence of microalbuminuria was found to be approximately 35.4% and macroalbuminuria 10% respectively. Patients with albuminuria had more severe heart failure symptoms with higher concentrations of congestion biomarkers including: adrenomedullin, cancer antigen 125 and NT-proBNP (all with P<0.0001). The presence of albuminuria is associated with an increased risk of death and hospitalization for HF [26].

The phenomenon of albuminuria is mainly determined by the balance between the filtration function of albumin by the glomerulus and the ability of the proximal tubule to reabsorb albumin that escapes glomerular filtration. Increased albuminuria is generally considered to be associated with impaired renal function.

Subjects included in this study had normal kidney function or improved of kidney function (according to eGFR). Increased albuminuria found in this study supports the hypothesis that in HF patients, especially in acute conditions, the phenomenon of albuminuria is not only a marker of damage to kidney function, but also related to worsening heart failure conditions. When referring to some of the existing literature, the pathophysiological mechanisms linking albuminuria with heart failure may be related to activation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, increased renal venous pressure, and decreased in cardiac output [9,16,26].

Heart failure conditions are associated with chronic RAAS activation with the main product of angiotensin II. Elevated levels of angiotensin II in the heart, blood vessels and kidneys trigger various adverse effects. In the heart, angiotensin II triggers myocardial necrosis, coronary cell death, myocardial fibrosis, peripheral arterial vasoconstriction, vascular remodeling, increased vascular resistance and blood pressure [27,28]. In the kidney, Angiotensin II mediates podocyte injury which has a vital role in glomerular filtration barrier (GFB) structure. Podocyte injury causes changes in GFB permeability to albumin. Angiotensin II also increases the secretion of aldosterone by the adrenal glands. Direct adverse effects of aldosterone on the heart include the development of myocardial hypertrophy, ventricular remodeling, proarrhythmogenic effects, myocardial ischemia, decreased coronary blood flow, and myocardial injury. Effects of aldosterone on the kidney include glomerular hypertrophy, glomerulosclerosis,proteinuria/albuminuria, decreased renal blood flow, and renal injury [26,29].

Endothelial dysfunction is an important contributor of the progression of various cardiovascular, renal, and chronic metabolic diseases (including HF) characterized by decreased endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) bioavailability. High levels of eNOS in the heart can trigger proapoptotic and cytotoxic effects (Fuster et al., 2017). In the kidney, endothelial dysfunction causes a proinflammatory stimulus that increases enzymatic activity to degrade the endothelial glycocalyx, which is the outermost layer of the glomerular and tubular endothelium. Glycocalyx degradation increases the incidence of sheer stress which aggravates endothelial dysfunction that manifests as albuminuria [30,31].

Increased albuminuria in heart failure is also associated with renal congestion. Boorsma, et al (2022) proposed the renal tamponade hypothesis where the presence of congestion (both clinical and hemodynamic) causes an increase in central venous pressure which will be transmitted directly to the renal veins. This leads to an increase in renal interstitial pressure, which compresses renal structures such as tubules, intrarenal veins and glomerulus resulting in decreased GFR, increased renin and aldosterone, and abnormalities in filtration and reabsorption of macromolecules (such as protein/albumin) [26].

Since our kidneys receive approximately 25% of cardiac output (CO), decreased in CO can causes renal hypoperfusion followed by renin release by juxtaglomerular cells, and activation of RAAS which triggers renal vasoconstriction and affects both the glomerular and tubular apparatus. HF with significantly reduced CO (forward failure) leads to renal tubular hypoxia and acute tubular necrosis, due to the sensitivity of renal tubular cells to hypoxic conditions. Furthermore, tubulointerstitial injury in this clinical situation will be aggravated by comorbidities such as DM associated with chronic tubular hypoxia, inflammation and interstitial fibrosis [32].

In this study, it was found that the pre-admission routine oral loop diuretics medication regardless of dose, was also an independent predictor of MACEs (Adjusted HR 4.527; 95%CI 1.198-17.107; p=0.026). A study conducted by Bermejo, Z.B, et al (2022) also found that in patients with AHF, the presence of a history of pre-admission diuretic use > 80 mg/day was associated with a worse disease prognosis (log rank < 0.001). In patients with AHF, pre-admission furosemide dose was independently associated with both mortality and rehospitalization due to HF [33].

The association between a history of pre-admission routine oral loop diuretic use and adverse cardiovascular outcomes may be explained through the phenomenon of diuretic resistance. Diuretic resistance is defined as the failure to adequately increase fluid and sodium (Na+) output to reduce volume overload, edema, or congestion, despite increasing the loop diuretic dose to the maximal limit (80 mg furosemide once or twice daily or greater in patients with reduced eGFR or HF). Diuretic resistance is one of the main causes of rehospitalization due to HF and is associated with worse cardiovascular outcomes [34,35].

HF are often accompanied by intestinal congestion which can reduce the rate of drug absorption and prolong the time to reach the therapeutic threshold. Decreased blood flow to the kidneys in HF patients, coupled with the use of non-steroidal anti-inflammatory drugs (NSAIDs) may also reduce the delivery of diuretics to their site of action at the ascending thick limb of the loop of Henle. The accumulation of endogenous anions may also compete with diuretics at their binding sites, resulting in reduced diuretic secretion. Post-diuretic salt retention is a compensatory mechanism that often occurs after urinary sodium concentrations are reduced following administration of short-acting diuretics. This condition, when accompanied by non-compliance low-salt diet, will eliminate the atmosphere of negative sodium balance. Long-term use of loop diuretics can also weaken their natriuretic effect. This mechanism is known as the braking phenomenon, which is caused by structural changes in the distal cortical tubule, leading to increased sodium reabsorption [22,35].

This study has some limitations. First, this is a single center study with a relatively small sample size. This makes the results of this study cannot be generalized directly to all HF patients. In addition, the monitoring period carried out is short. Second, UACR examination in this study is only carried out at pre-discharge, after the administration of AHF therapies. Previous studies have reported changes in UACR values during treatment of AHF. The magnitude of changes in UACR values may be more appropriate in predicting prognosis of HF patients. Furthermore, this study did not assess standardized prognostic markers of HF, such as natriuretic peptide (NP). Previous studies have shown a correlation between UACR values with NP levels. We recognized that, UACR may be elevated not only in HF conditions but also in other comorbidities such as DM, hypertension, and obesity. Adding NP evaluation may improve UACR accuracy in predicting HF prognosis. Third, that we did not investigate the contribution of other residual confounding variables that may affect MACEs, including pre-admission loop diuretic doses, discharge medication regimens and doses, patient compliance during outpatient care, as well as adherence to low salt and water diet recommendations. Therefore, we could not exclude possible contribution of these factors to the results of our study.

CONCLUSSION

A pre-discharge UACR ≥ 46.5 mg/gram creatinine was independently associated as a predictor of MACEs within 60 days post-hospitalization due to AHF.

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