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Original Research

Acute Kidney Injury as Predictor of Major Adverse Cardiac Event (MACE) in 3 Months after Admission of Acute Heart Failure Patients in Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: Acute heart failure is a condition with high morbidity and mortality. Decreased renal function after hospitalization is a predictor of longer hospitalization and increased mortality. Patients with acute renal failure, especially injury or failure grade, have a worse long-term prognosis compared to patients without acute renal failure, which will lead to MACE. Major adverse cardiovascular events are a combination of non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death. **Material and Methods:** This study was a retrospective cohort study of 159 patients with acute heart failure at HAM General Hospital from April 1, 2023 to December 31, 2023. Electrocardiographic, laboratory, and echocardiographic data were collected. Patients were categorized according to RIFLE classification and monitored to see MACE in the samples. Bivariate tests were performed to see the correlation between samples. Furthermore, Kaplan-Meier curves were analyzed to see the survival rate. **Results:** Total subjects were 159 patients consisting of 98 acute heart failure patients with AKI and 61 heart failure patients without AKI. There was a correlation between heart failure patients who developed acute renal failure and the number of days of hospitalization (p = 0.000), in hospital mortality (p = 0.002), rehospitalization in less than 3 months (p = 0.000), and mortality in less than 3 months (p = 0.001). **Conclusion:** Acute kidney injury has a correlation with MACE so that it can be a predictor of major cardiovascular events in patients with acute heart failure.

Highlights:

1. This study provides novel evidence that acute kidney injury (AKI) is a strong predictor of major adverse cardiovascular events (MACE) in patients with acute heart failure, highlighting the critical need for early detection and intervention to improve outcomes.
2. This research underscores the importance of incorporating kidney function assessment into the comprehensive management of acute heart failure patients.

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Introduction

Acute heart failure is a condition with high morbidity and mortality. The interaction between the heart and kidney, otherwise known as cardiorenal syndrome (CRS), has become a concern for cardiologists and nephrologists due to its association with poorer prognosis. Worsening of renal function after hospitalization for heart failure is characteristic of cardiorenal syndrome type-1. Deterioration of renal function after hospitalization is a predictor for longer length of stay and increased mortality.[1]

Renal dysfunction in patients with acute heart failure involves complex and multifactorial hemodynamic mechanisms (renal artery hypoperfusion and renal vein congestion) and non-hemodynamic factors with unknown mechanisms. Evaluation of renal dysfunction criteria in patients with acute heart failure generally uses the RIFLE classification with the parameter used is creatinine.[2]

Major cardiovascular events (MACE) include all-cause mortality, non-fatal acute myocardial infarction, non-fatal ischemic stroke, and unplanned coronary revascularization at 30 days after diagnosis[3]. The risk of death in patients with acute decompensated heart failure after discharge from hospital with an average 1-year mortality ranges from 25-40% and mortality at 2 years of 22-52.9%. One study with a total sample size of 478 showed a 1-year mortality of 41.7% and a 2-year mortality of 56%[4]. A study in 168 patients with acute pulmonary edema without acute coronary artery disease showed an in-hospital mortality of 31.5% with a recurrence rate of 6.5%.[5]

Short-term prognosis of acute kidney injury in patients with acute heart failure includes ICU length of stay, length of hospitalization, and hospital mortality as well as the long-term prognosis of KKVM[2]. Considering that the incidence of decompensated heart failure and acute renal failure is quite high and has a poor prognosis, an early prognostic assessment of patients is needed since hospital admission, so this study aims to assess the relationship between the occurrence of KKVM and acute renal failure in patients with early phase acute heart failure.

Material and Methods

This study design is a retrospective cohort study, with the sampling technique being total sampling. The samples in this study were heart failure patients at Haji Adam Malik General Hospital, Medan from April 2023 to December 2023. Based on the sample size calculation, the minimum sample required in this study was 32 samples.

The inclusion criteria in this study were:

(1) Acute heart failure patients who are admitted to the ICU and ward;
(2) Heart failure patients with any ejection fraction;

(3) Patients with acute heart failure classification in chronic heart failure;
(4) Male and female patients with an age range of 18 years and over.

While the exclusion criteria in this study include:

(1) Patients who have been diagnosed with chronic kidney failure or who are routinely hemodialyzed;
(2) Patients with acute heart failure due to heart valve abnormalities;
(3) Patients with acute heart failure due to congenital heart disease;
(4) Patients with acute heart failure accompanied by sepsis;
(5) Patients with acute heart failure due to cardiac tamponade.

Patients with acute heart failure on admission at H. Adam Malik Hospital Medan will be examined to assess the presence or absence of acute renal failure based on creatinine levels according to the RIFLE classification. The RIFLE classification is based on the serum creatinine ratio. Patients were then classified into not acute renal failure, R (Risk), I (Injury), or F (Failure).

Occurrence of acute renal failure was assessed using the RIFLE classification at the time of hospitalization. Based on the RIFLE classification, samples were classified into acute renal failure and not acute renal failure groups (acute renal failure at admission). Clinical outcomes during follow-up were defined as major adverse cardiovascular events (MACE) in the form of in-hospital mortality, rehospitalization within 3 months, and mortality within 3 months.

Categorical variables were analyzed using the chi-square test or Fisher's exact test. All collected data will be analyzed using the SPSS data application. All numerical data will be presented as mean + SD. Comparisons between all proportions were made using chi-square analysis. Significant factors are determined based on the logistic regression model with a p value <0.05 considered as statistically significant. Kaplan-Meier curves will be performed to assess the survival of heart failure patients with or without acute renal failure to KKVM.

This study has received approval from the Ethics Committee of the University of Sumatera Utara and Haji Adam Malik Hospital Medan.

Result

In this study, 159 respondents met the criteria as research subjects. This number exceeds the minimum number required for data significance in the study according to the calculations in the research methods section. Description of the subjects' characteristics was presented in table 1.

Table 1. Subject Characteristics

Characteristics	AKI			Non-AKI (%)
	Risk (%)	Injury (%)	Failure (%)	
Age	57,60 ± 7,17	57,07 ± 12,28	56,10 ± 10,56	56,46 ± 10,60
Gender				
Male	23 (14,5)	32 (20,1)	21 (13,2)	50 (31,4)
Female	7 (4,4)	7 (4,4)	8 (5,0)	11 (6,9)
Ejection Fraction <50%	29,36 ± 7,63	27,51 ± 7,64	26,93 ± 8,16	28,57 ± 7,03
OMI				
(+)	15 (9,4)	24(15,1)	18 (11,3)	39(24,5)
(-)	15 (9,4)	15(9,4)	6(6,9)	22(13,8)
DM type-2				
(+)	14 (8,8)	21(13,2)	18 (11,3)	24(15,1)
(-)	16 (10,1)	18(11,3)	11(6,9)	37(23,3)
Hypertension				
(+)	18 (11,3)	26(16,4)	26 (16,4)	28(17,6)
(-)	12 (7,5)	13(8,2)	3(1,9)	33(20,8)
Dyslipidemia				
(+)	14 (8,8)	11(6,9)	8(5,0)	9(5,7)
(-)	16 (10,1)	28(17,6)	21 (13,2)	52(32,7)
Smoking				
(+)	16 (10,1)	12(7,5)	8(5,0)	24(15,1)
(-)	14 (8,8)	27(17.0)	2 (13,2)	37(23,3)

In this study, 159 samples collected, 126 were male and the remaining 33 were female. There were 98 samples in the AKI group, with details of 30 samples in the risk group consisting of 23 men and 7 women, 39 samples in the injury group consisting of 32 men and 7 women, and 29 samples in the failure group consisting of 21 men and 8 women. Meanwhile, in the non-AKI group there were a total of 61 samples consisting of 50 men and 11 women.

Table 2. Patient's clinical characteristics

Characteristics	AKI			Non-AKI(%)
	Risk (%)	Injury(%)	Failure(%)	
Electrocardiogram				
Sinus	28(17,6)	37(23,3)	29(18,2)	54(34,0)
AF	2(1,3)	2(1,3)	0(0)	6(3,8)
BBB	3(1,9)	5(3,1)	4(2,5)	(1,9)
Peripheral Edema				
(+)	20(12,6)	23(14,5)	13(8,2)	27(17,0)
(-)	10(6,3)	16(10,1)	16(10,1)	34(21,4)
Symptoms				
Dyspnea At Rest	15(9,4)	19(11,9)	16(10,1)	28(17,6)
Dyspnea On Exertion (DOE)	30(18,9)	39(24,5)	29(18,2)	61(38,4)
PND	15 (9,4)	15(9,4)	10(6,3)	18(11,3)
Orthopnea	24(15,1)	30(18,9)	22(13,8)	41(25,8)
Pulmonary Rhales	24(15,1)	31(19,5)	23(14,5)	38(23,9)
JVP	8(5,0)	5(3,1)	4(2,5)	2(1,3)
Acute Heart Failure				
ADHF	22(13,8)	30(18,9)	16(10,1)	41(25,8)
ALO	8(5,0)	9(5,7)	13(8,2)	20(12,6)
Medicine				
ACE/ARB	12 (7,5)	23 (14,5)	16 (10,1)	33 (20,8)
ARNI	15 (9,4)	18 (11,3)	8 (5,0)	24 (15,1)
BB	26 (16,4)	34 (21,4)	23 (14,5)	52 (32,7)
MRA	25 (15,7)	35 (22,0)	21 (13,2)	51 (32,1)
Furosemide	19 (11,9)	28 (17,6)	17 (10,7)	40 (25,2)
SGLT-i	15 (9,4)	14 (8,8)	11 (6,9)	31 (19,5)

All subjects in this study reported dyspnea on exertion (DOE). Dyspnea at rest was found in 78 subjects with 50 of them in the AKI group. Paroxysmal Nocturnal Dyspnea (PND) was found in 58 subjects with 40 of them in the AKI group. Orthopnea was found in 117 subjects with 76 of them in the AKI group. Increasement of jugular venous pressure was found in 19 subjects with 17 of them in the AKI group. Pulmonary rales were found in 116 subjects with 78 of them in the AKI group.

Electrocardiographic features of sinus rhythm were shown in 148 subjects. Atrial fibrillation was found in 4 subjects in the AKI group and 6 subjects in the non-AKI group. Bundle branch block was found in

12 subjects of the AKI group and 3 subjects of the non-AKI group. The ejection fraction in all groups showed results that were not significantly different with the highest mean ejection fraction in the AKI-risk group at 29.36 + 7.63 and the lowest ejection fraction in the AKI-failure group at 26.93 + 8.16.

Peripheral edema was found in 83 subjects with 60 of them in the AKI group. Old myocardial infarction (OMI) was found in 96 samples with 57 of them belonging to the AKI group. Diabetes Mellitus (DM) was found in 77 subjects with 53 of them in the AKI group. Hypertension was found in 98 subjects with 70 of them belonging to the AKI group. Dyslipidemia was found in 42 subjects with 33 of them belonging to the AKI group. Smoking variables were found in 60 subjects with 36 of them belonging to the AKI group.

Hypertension was found in 98 samples with 70 of them belonging to the AKI group. Dyslipidemia was found in 42 samples with 33 of them belonging to the AKI group. ADHF was found in 99 samples with 61 of them belonging to the AKI group. Acute pulmonary edema was found in 50 samples with 30 of them belonging to the AKI group. Cardiogenic shock was found in 10 samples, 7 of which were in the AKI group.

The use of Angiotensin Converting Enzyme Inhibitor (ACE-i) or Angiotensin Receptor Blocker (ARB) was found in 84 samples with 51 of them belonging to the AKI group. Angiotensin Receptor Neprilysin-Inhibitor (ARNI) medicine were found in 65 samples with 41 of them belonging to the AKI group. Beta blockers were found in 135 samples with 83 of them belonging to the AKI group. The use of Mineralocorticoid Receptor Antagonist (MRA) drugs was found in 132 samples with 81 of them belonging to the AKI group. The use of furosemide was found in 104 samples with 64 of them belonging to the AKI group. The use of Sodium-Glucose-Cotransporter (SGLT-i) drugs was found in 71 samples with 40 of them belonging to the AKI group.

Table 3. Hospitalization and Outcome

Characteristic	AKI	Non-AKI	*p-value*
Length of Hospitalization			
ICCU	3,21 ± 1,11	1,85±0,68	**0,000****
Ward	2,81±1,45	2,31±0,67	**0,001****
Total	6,02±1,99	4,16±0,95	**0,000****
Outcome			
Inhospital mortality	15 (9,4)	1 (0,6)	**0,005***
Rehospitalization within 3 months	65 (40,9)	10 (6,3)	**0,000***
Mortality within 3 months	23 (14,5)	4 (2,5)	**0,008***

*Chi-Square Test

**Kruskal-Wallis Test

The mean total length of hospitalization in the AKI group was 6.02 + 1.99 days. Mean ICCU care in the AKI group was 3.21 + 1.11 days. Mean hospitalization of the ward in the AKI group was 2.81 + 1.45 days. Results of statistical tests of ICCU hospitalization, regular ward, and total hospitalization showed p value <0.05, which means that the number of days of hospitalization is associated with acute heart failure patients who experience AKI or non-AKI.

In-hospital mortality was found in 16 people with details of 15 people in the AKI group and 1 person in the non-AKI group. Rehospitalization within 3 months were found in 75 subjects with 65 people in the AKI group and 10 people in the non-AKI group. Mortality within 3 months were found in 27 samples with 23 in the AKI group and 4 in the non-AKI group. Statistical analysis of the outcome of in-hospital mortality, rehospitalization within 3 months, and mortality within 3 months showed p value <0.05, which means that the outcome is associated with acute heart failure patients who experience AKI or non-AKI.

Statistical analysis of AKI subgroups (Table 4) showed that the AKI-risk was 6.171 times (p = 0.115) more likely to experience in-hospital mortality. AKI-injury was 6.483 times (p = 0.095) more likely to experience in-hospital mortality compared to the non-AKI group, while the AKI-failure was 19.313 times more likely to experience in-hospital morality than the non-AKI group (p = 0.005), AKI-failure was statistically significant associated with in-hospital mortality while AKI-risk and AKI-injury were not statistically associated significantly.

Table 4. Outcome of Acute Kidney Injury to MACE based on RIFLE Classification

Acute Kidney Injury	In-hospital Mortality			Rehospitalization within 3 months			Mortality within 3 months		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
No AKI	1,000			1,000			1,000		
AKI-Risk	6,171	0,642-59,322	0,115	5,126	2,451-10,719	**0,000**	2,062	0,516-8,244	0,306
AKI-Injury	6,483	0,725-58,004	0,095	3,629	1,709-7,705	**0,001**	2,902	0,849-9,914	0,089
AKI-Failure	19,313	2,413-154,544	**0,005**	6,888	3,221-14,728	**0,000**	8,215	2,646-25,507	**0,000**

AKI-risk, AKI-injury, and AKI-failure were 5.126 times (p = 0.000); 3.629 times (p = 0.001); and 6.888 times (p = 0.000) more likely to experience rehospitalization within 3 months than the non-AKI group, respectively. Statistical tests showed that AKI-risk, AKI-injury, and AKI-failure were statistically associated significantly.

AKI-risk was 2.062 times (p = 0.306) more likely to experience mortality within 3 months than the non-AKI group. AKI-injury was 2.902 times (p = 0.089) more likely to experience mortality within 3 months compared to the non-AKI group. AKI-failure was 8.215 times (p = 0.000) to experience mortality within 3 months. Statistical tests showed that the AKI-failure was significantly associated, while the AKI-risk and AKI-injury were not significantly associated.

Kaplan-Meier curve (Figure 1) shows the survival of acute heart failure patients with or without acute kidney injury to major adverse cardiovascular events including rehospitalization within 3 months or mortality within 3 months. The results show that at month 12, more than 20% of acute heart failure patients with AKI will experience a major cardiovascular event within 3 months, while in the non-AKI group, there are about 10% of patients who experience a major cardiovascular event within 3 months. Statistical test results showed significance association with a p value = 0.00.

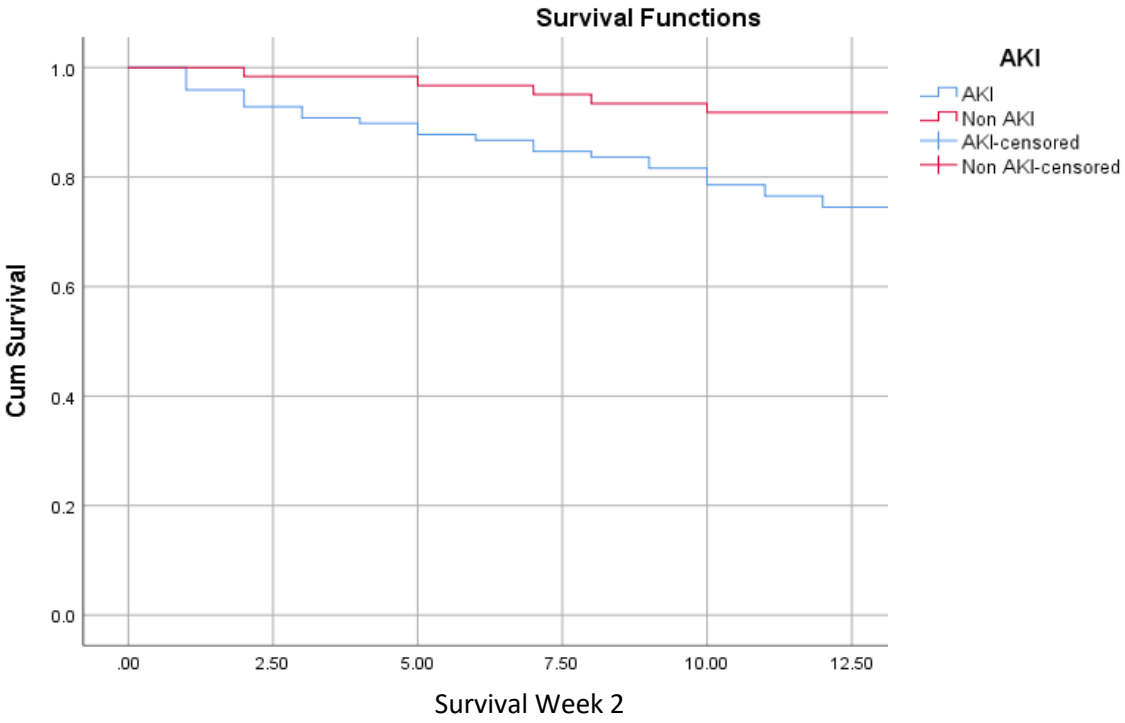

Figure 1. Kaplan Meier Curve in Acute Heart Failure Patients

Discussion

Mechanism of underlying renal dysfunction in patients with acute heart failure is a complex multifactorial process, involving low cardiac output, renal hypoperfusion, fluid overload, renal venous congestion, neurohormonal activation and sympathetic activity, inflammatory response, intrinsic tubular damage, and drugs during heart failure therapy [6]. Persistent stimulation of the Renin-Angiotensin-Aldosteron System (RAAS) induces renal damage through cell hypertrophy, oxidative stress, and inflammatory activation. Neutrophil gelatinase-associated lipocalin levels indicate the presence of renal tubular damage, which is used to identify acute renal failure in acute heart failure patients.[7]

This study showed that MACE occurred in 102 (64.2%) samples. In-hospital mortality occurred in 16 (10.1%) samples, rehospitalization within 3 months occurred in 75 (47.2%) samples, and mortality within 3 months occurred in 27 (17%) samples. One study analyzing HFrEF patients showed that during a median 40-months follow-up period, HFrEF occurred in 49 (35.5%) patients of which 14 (10.1%) experienced mortality and 35 (25.4%) experienced rehospitalization. The median time to onset of MACE in that study was 29 weeks.[8]

Authors analyzed that these results were in line with previous studies that showed an increase in the incidence of KKVM in patients who experienced AKI compared to non-AKI. Another factor that may have caused the higher incidence of MVC in this study is that the sample in this study were patients with acute heart failure accompanied by advanced acute renal failure, which has a worse prognosis.

This study showed rehospitalization within 3 months occurred in 75 (47.2%) samples. This result is different from study in 2019 by Siqi et al. which showed that in the follow-up period of 1 year, MACE occurred in 26 (12.3%) HFrEF patients, 13 (6.5%) HFmrEF patients, 10 (2.9%) HFpEF patients. That study showed that MACE was a statistically significant associated outcome ($p < 0.001$). Multivariate Cox analysis in that study showed NYHA class, increasement of jugular venous pressure, pulse rate, systolic blood pressure, history of heart failure, and previous hospitalization due to cardiac causes were associated with the rate of hospitalization due to heart failure.[9]

In this study, the length of hospitalization in ICCU, ward, and total days of hospitalization showed p value < 0.05 which means statistically related. This result is consistent with the study by Shirakabe et al. which showed an association between total hospitalization with heart failure patients without renal failure worsening in AKI and non-AKI patients (24 and 31 days) and acute heart failure patients with renal worsening in AKI and non-AKI patients (28 and 43 days) with p value < 0.0012. Another study showed that the length of ICU hospitalization and total hospitalization was significantly longer in the failure compared to risk and injury patient groups (24.0 ± 34.0 ; 9.5 ± 16.6 ; 7.1 ± 7.9, $p < 0.001$), (73.9 ± 85.2 ; 48.7 ± 41.4 ; $40.3.9\pm41.1$, p value < 0.001) [10]. Shirakabe et al. showed prognosis, including all-cause death was significantly worse in the injury class compared to the non-injury and risk groups [2]. Study by Lombardi et al on 234 heart failure patients with AKI showed mortality in 35% of patients compared to 21% of patients in the non-AKI group ($p < 0.001$). COX regression analysis also showed persistent acute renal failure was associated with 2.31 times increase in mortality over a 100-day period after furosemide initiation.[11]

Other study show any-cause prognosis is significantly worse in AKI-failure group compared to the non-AKI, AKI-risk, and AKI-injury groups. Cardiovascular event prognosis was significantly worse in AKI-failure group compared to the non-AKI, AKI-risk, and AKI-injury groups [12]. That result was in-line with the results of this study which showed that the failure group had worse survival in terms of in-hospital mortality, rehospitalization within 3 months, and mortality within 3 months.

Study by Cowie et al. also reported higher mortality rate in worsening renal function group compared to those without renal dysfunction (12% vs 2%), increasing to 15% at 30 days, and 28% at 6 months. Compared to those without worsening renal function who had a mortality of 5% at 30 days and 18% at 6 months. The duration of hospitalization was also higher in patients with worsening renal function at 9 days, compared to the group without worsening renal function worsening at only 3 days.[13]

A systematic review study states that acute heart failure patients with AKI have a 3.65 times higher mortality risk than the non-AKI group ($p < 0.001$), Heart failure patients who experience AKI have 1.85 times to experience mortality within 1 year than those who do not experience AKI ($p < 0.001$). In heart failure patients, AKI not only results in a worse in-hospital prognosis, but increases the risk of mortality 3 times greater than the non-AKI group, and the 1-year mortality risk will remain as high as 1.85 times as stated above.[14]

Conclusion

Acute renal failure is a predictor of MACE in patients with acute heart failure. AKI-failure is a predictor of in-hospital mortality, rehospitalization within 3 months, and mortality within 3 months in acute heart failure patients, while AKI-risk and AKI-injury are predictors of rehospitalization within 3 months in acute heart failure patients.

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