

Serum neutrophil gelatinase-associated lipocalin and decreased kidney function as predictor of mortality and major adverse cardiac events during acute heart failure hospitalizations



Rani Paramitha Iswari Maliawan^{1*}, I Ketut Badjra Nadha¹, I Gde Raka Widiana²,
I Gusti Ngurah Putra Gunadhi¹, Ida Sri Iswari³, I Wayan Wita¹

ABSTRACT

Introduction: Decreased renal function is associated with a poor prognosis in acute heart failure (AHF). The current standard for assessing the decline in kidney function, creatinine, has several limitations. Serum Neutrophil gelatinase-associated lipocalin (NGAL) is one of the predictive biomarkers that was shown better at indicating an early AKI. Although several studies have examined the role of NGAL as a predictor for poor prognosis in various medical conditions, the result in AHF condition is still inconsistent. This study aimed to determine the role of serum NGAL and decreased renal function (estimated using serum creatinine) in predicting the mortality and major adverse cardiovascular (MACE) events during hospitalization in acute heart failure patients

Methods: Prospective cohort study with consecutive sampling was conducted in AHF patients who were treated at Sanglah General Hospital from July to September 2017. Serum NGAL and creatinine levels were measured at the onset of hospital admission and observed for mortality and MACE during hospitalization.

Results: Seventy-seven patients were involved in this study. We found hazard ratio (HR) serum NGAL to mortality was 7.8 ($p = 0.009$) and increased to 18.9 in multivariate analysis with cox proportional hazards regression model ($p = 0.002$). There were significant differences in survival ($p = 0.002$) between patients with high serum NGAL (424 hours survival rate, 95% CI 296-552) than low serum NGAL (baseline survival 680 hours; 95% CI 584-775) after log rank test. Meanwhile, the effect of serum NGAL on MACE and decreased of kidney function on mortality or MACE did not yield significant result.

Conclusion: High serum NGAL is an independent predictor of in-hospital mortality among AHF patients.

Keywords: Acute heart failure, serum NGAL, decreased renal function, in-hospital mortality, MACE

Cite This Article: Maliawan, R.P.I., Nadha, I.K.B., Widiana, I.G.R., Gunadhi, I.G.N.P., Iswari, I.S., Wita, I.W. 2021. Serum neutrophil gelatinase-associated lipocalin and decreased kidney function as predictor of mortality and major adverse cardiac events during acute heart failure hospitalizations. *Bali Medical Journal* 10(2): 857-862. DOI: 10.15562/bmj.v10i2.2451

¹Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital, Denpasar, Bali Indonesia.

²Department of Internal Medicine- Nephrology Division, Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital, Denpasar, Bali Indonesia.

³Department of Clinical Microbiology, Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital, Denpasar, Bali Indonesia.

*Corresponding to:

Rani Paramitha Iswari Maliawan.
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital, Denpasar, Bali Indonesia.
ranimaliawan@yahoo.com

Received: 2021-04-27

Accepted: 2021-06-19

Published: 2021-07-01

INTRODUCTION

Acute heart failure (AHF) is the most common cause of hospitalization in the population aged 65 years and older. The trends showed that the mortality and morbidity of AHF tends to increase over time. The mortality of AHF during hospitalization was about 6.7%, which increased to 13.5% after 3 months. Recurrent hospitalization is still very high, around 24% after 3 months and reaching 30-50% during treatment.¹⁻³ Data from integrated emergency cardiac care Sanglah General Hospital (RSUP Sanglah) in 2016 showed that there were approximately 446 (27%) AHF patients from a total of

1618 admitted patients. The mortality rate of AHF patients admitted to Sanglah Hospital also higher when compared to the mortality rate of AHF patients worldwide, which about 11% during year 2016 and increased to 15% during January until April 2017.

Decreased of kidney function occurs in approximately 25-40% of AHF patients and is associated with poor prognosis, such as increased mortality, recurrent hospitalization rate and longer duration of hospitalization. Sudden deterioration in cardiac function that results in acute kidney injury (AKI) is known as cardio renal syndrome (CRS).⁴⁻⁶ Estimated

glomerular filtration rate (eGFR) and serial measurements of serum creatinine (Cr) are standard methods for assessing worsening renal function. However, decreased eGFR and increased of serum Cr usually occur in the advanced phase of AKI. Therefore, a new method/biomarker that can detect AKI at early phase are needed so that early intervention can be done to prevent further deterioration of renal function and improve the prognosis of AHF patients.

Neutrophil gelatinase-associated lipocalin (NGAL) is a small molecule belonging to the lipocalin protein class. NGAL is found on the brush-border side

of renal tubular cells whose concentration increases during the acute phase of renal injury due to toxic and ischemic insult. The serum and urine concentrations have been shown to increased approximately 24 hours prior to the increase in creatinine and show a strong correlation with changes in serum creatinine levels.^{1,7,8} In addition to its correlation with markers of renal function, NGAL was also thought to play a role in inflammation, apoptosis and remodeling of the cardiomyocyte's extracellular matrix, thus potentially influenced the prognosis of AHF.⁸

Serum NGAL has a predictive value for early detection of AKI in several conditions, including cardiac surgery, contrast-induced nephropathy (CIN) and critically-ill patients.⁴ However, studies on the role of NGAL in predicting decreased or deteriorating renal function and mortality in patients with AHF yield conflicting result. A prospective single center cohort study concluded that an initial serum NGAL of 140 ng/mL in acute decompensated heart failure (ADHF) patients worsen the renal function by 7.4-fold with a sensitivity of 86% and a specificity of 54%.^{4,9} Another prospective study with an observation time of about 3 months suggested that serum NGAL was a predictor of short-term mortality in patients with AHF where high serum NGAL was associated with an increased risk of death up to 2.7 times.¹⁰ However, recent multicenter studies in the United States and Europe showed different results. The study concluded that NGAL plasma was not superior than the creatinine in predicting worsening of renal function and complications during hospitalization. Thus, the use of NGAL plasma in diagnosing acute renal injury in patients with AHF is not yet recommended.^{4,9,11,12} Meanwhile, studies assessing the role of NGAL in patients with AHF in Asia are scarce and no similar study have been conducted in Indonesia. This study aimed to determine the role of serum NGAL and decreased renal function (estimated from serum creatinine) in predicting mortality and major adverse cardiovascular events (MACE) during AHF hospitalization.

METHODS

This was a single-center prospective cohort

study aimed to investigate the role of high serum level of NGAL and the worsening kidney function as predictor of in-hospital mortality and MACE in AHF patients admitted to emergency ward of integrated cardiac care unit (PJT) RSUP Sanglah during July to September 2017. AHF Patients were observed for progression of MACE or occurrence of mortality during hospitalization. Event counted as MACE were cardiogenic shock and malignant arrhythmias (supraventricular, ventricular arrhythmias or atrioventricular block that caused hemodynamic disturbance). All patients were managed with standard therapy based on the clinical pathways of RSUP Sanglah. Exclusion criteria were patients with acute stroke/TIA within previous year, malignancy, history of thoracic or abdominal surgery within previous month, pregnancy and admitted with ungoing cardiogenic shock. Patients data were obtained from history taking, physical, and laboratory examinations during hospitalization. Blood serum NGAL and Creatinine was taken at initial admission.

AHF refers to rapid onset or worsening of symptoms and/or signs of heart failure. These symptoms and sign include shortness of breath during activity, rhonchi in both lung fields, S3 gallop in auscultation of the heart, jugular venous distention, orthopneu, paroxysmal nocturnal dyspnea, using more than two pillows at rest, fatigue, edema, increased frequency of dry cough especially when lying supine, and coughing with thick sputum or accompanied by blood spots.¹² Patients should have at least one of the above symptoms and signs of heart failure and one criteria for echocardiography examination that consist of: 1) Left ventricular ejection fraction less than 40%; 2) Left ventricular ejection fraction 40% or more with at least one of the relevant structural heart disease (left ventricular hypertrophy and/ left atrial dilatation) or diastolic dysfunction.^{13,14} AHF may present as a first occurrence (de novo) or, more frequently, as a consequence of acute decompensation in previously chronic heart failure (CHF). Decreased kidney function characterized by serum creatinine levels more than 1.2 mg/dl at the onset of admission. The specimen taken from

the peripheral vein and examined in the clinical pathology laboratory of Sanglah Hospital with enzymatic colorimetric test using Roche Cobas 6000 immediately after the specimen was taken. NGAL serum are taken from the peripheral vein at the onset of admission and immediately processed, aliquoted, and stored at 80 °F. Serum NGAL was examined at the clinical laboratory of Sanglah hospital using immunosorbent enzyme-linked immunosorbent assay (ELISA). The reagent used is the Human NGAL ELISA kit produced by Elabscience (Cat No. E-EL-H0096) with detection range 0.156-10 ng/mL. It was assumed that all diluted samples fall within the range of the calibration curve.⁴

Cut off value of NGAL for in-hospital mortality and MACE obtained through Receiver Operating Characteristic curve (ROC) analysis. Characteristics of study participants was carried out using univariate analysis. Data were presented using a table that divided the study participants into three groups based on the cut of point: serum NGAL according to mortality, MACE, and decreased kidney function. Numerical data were presented by mean \pm standard deviation and categorical data were presented by percentage and frequency distribution. The association between serum NGAL and decreased kidney function to in-hospital mortality and MACE was analyzed using Cox's proportional hazard model to obtain its hazard ratios (HR) with 95% CI and *p*-value. The survival difference was presented by Kaplan–Meier curve and analyzed using log-rank test. Statistical significance was assumed if the null hypothesis could be rejected at the level of *p* = 0.05. All analyses were performed using SPSS software version 23.

RESULTS

A total of 77 patients were retrospectively studied. The mean age of the study participants was 58 \pm 12 years. Based on the latest WHO criteria, there were 56 (63.6%) young people, 18 (20.5%) young-old, and 3 (3.4%) old-old. Among 77 patients, 21 (27.3%) de novo AHF patients and 56 (72.7%) of ADHF patients. The most common etiology were acute coronary syndromes (ACS) experienced by 33 (42.9%) patients followed by coronary

artery disease (CAD) (23 patients, 29.9%), 6 (7,8%) hypertensive heart disease (HHD), 6 (7,8%) rheumatic heart disease (RHD), and cardiomyopathy (5 patients, 6.5%). Other AHF etiologies such as valvular heart disease (VHD), ventricular septal defect (VSD), thyroid heart disease or Cor pulmonale experienced by 4 patients (5.1%). In terms of ejection fraction, 32 patients (41.6%) had left ventricular (LVEF) less than 40% and 45 patients had LVEF at least 40%.

The demographic, clinical and laboratory characteristics of the study subjects based on serum NGAL levels and decreased renal function for mortality and KKM were presented in

Table 1. Patients with high NGAL level were more commonly accompanied by comorbid such as sepsis and anemia, more often had reperfusion therapy, and came with lower systolic blood pressure and lower serum albumin levels. While patients with reduced kidney function have older age, more often male, have a history of hypertension, anemia, and decreased LVEF compared with patients whose kidney function still normal. The patients also had lower serum albumin and eGFR levels. In addition, patients with high NGAL level as well as decreased renal function have longer duration of hospitalization. During in-hospital follow up, cardiovascular mortality occurred in 12

(15.6%) patients and MACE experienced by 41 (53.2%) patients in which each patient could experience one or more type of MACE such as cardiogenic shock (25 patients, 32.5%) and/or arrhythmias (30 patients, 39%).

Based on ROC analysis, the best cut off point for serum NGAL to predict mortality was 7.145 ng/mL with area under curve (AUC) 0.830 ($p < 0,0001$), sensitivity 91,7% and specificity 72,3%. Meanwhile, the best cut off point for serum NGAL to predict MACE was 6,476 ng/mL with an AUC 0,692 ($p = 0,004$), sensitivity 65,9% and specificity 66,7%. The ROC curve of serum NGAL as a predictor of in-hospital mortality and MACE were

Table 1. The demographic, clinical and laboratory characteristics of patients according to serum NGAL levels and decreased renal function on mortality and MACE.

Variable	Patient characteristics according to serum NGAL level on mortality		Patient characteristics according to serum NGAL level on MACE		Patient characteristics according to decreased renal function on mortality and MACE	
	High NGAL $\geq 7,145$ ng/mL (n=26)	Low NGAL $< 7,145$ ng/mL (n=51)	High NGAL $\geq 6,476$ ng/mL (n=40)	Low NGAL $< 6,476$ ng/mL (n=37)	Decreased Sc $> 1,2$ ng/mL (n=45)	Normal Sc $\leq 1,2$ ng/mL (n=32)
Age	58 \pm 11	57 \pm 12	58 \pm 11	57 \pm 13	58 \pm 10	56 \pm 14
Gender						
Male	17 (65)	35 (69)	28 (70)	24 (65)	35 (78)	17 (53)
Female	9 (35)	16 (31)	12 (30)	13 (35)	10 (22)	15 (47)
Hypertension	11 (42)	27 (53)	16 (40)	22 (56)	27 (60)	11 (34)
Sepsis	5 (19)	4 (8)	5 (13)	4 (11)	5 (11)	4 (13)
Anemia	8 (31)	9 (18)	9 (23)	8 (22)	13 (29)	4 (13)
Diabetes mellitus	5 (19)	15 (29)	10 (25)	10 (27)	11 (24)	9 (28)
Smoking	11 (42)	19 (43)	14 (58)	22 (43)	20 (44)	13 (41)
Reperfusion therapy	9 (35)	12 (24)	15 (38)	6 (16)	12 (27)	9 (28)
Obesity	3 (12)	8 (16)	3 (8)	8 (22)	7 (16)	4 (13)
AHF de novo	7 (27)	14 (28)	14 (35)	7 (19)	35 (78)	21 (66)
ADHF	19 (73)	37 (73)	26 (65)	30 (81)	35 (78)	21 (66)
LVEF						
< 40	9 (35)	23 (45)	15 (38)	17 (46)	20 (44)	12 (38)
≥ 40	17 (65)	28 (55)	25 (63)	20 (54)	25 (56)	20 (63)
Systolic BP	11 \pm 627	127 \pm 34	116 \pm 29	131 \pm 55	128 \pm 33	116 \pm 31
eGFR	62 \pm 30	52 \pm 39	59 \pm 30	51 \pm 42	39 \pm 21	78 \pm 41
Albumin (mg/dL)	3,4 \pm 0,7	3,8 \pm 0,6	3,6 \pm 0,7	3,7 \pm 0,7	3,6 \pm 0,7	3,8 \pm 0,7
Serum Creatinine (mg/dL)	1,8 \pm 1,8	2,5 \pm 2,8	1,8 \pm 1,5	2,8 \pm 3,2	2,9 \pm 2,7	1,3 \pm 1,8
Duration of hospitalization (hours)	216 \pm 162	175 \pm 134	201 \pm 150	176 \pm 138	210 \pm 156	160 \pm 122

Categorical data in n (%),

Numerical data in mean \pm SD

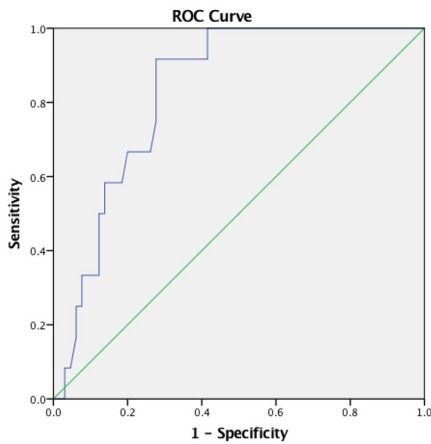


Figure 1. The ROC curve in determining the cut-off point of serum NGAL as a predictor of mortality.

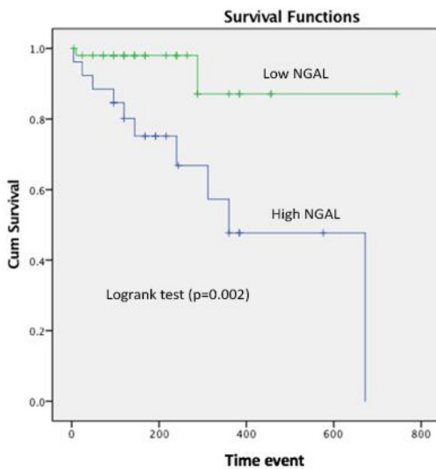


Figure 2. The ROC curve in determining the cut-off point of serum NGAL as a predictor of MACE.

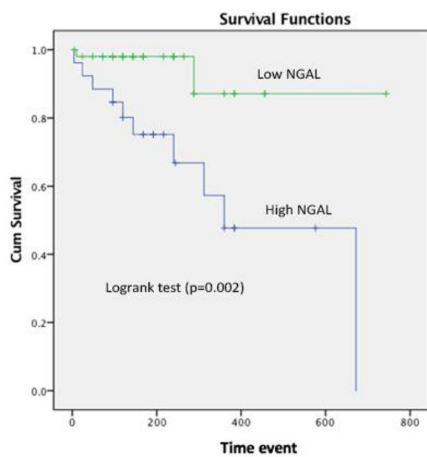


Figure 3. Kaplan-Meier estimated survival curve of AHF patients based on the level of serum NGAL.

shown in **Figure 1** and **2**. High serum NGAL level increased the hazard for in-hospital mortality occurrence both in bivariate analysis (crude hazard ratio [HR] 7.8; $p = 0.009$) and multivariate analysis after adjusting for age, male gender, hypertension, anemia, sepsis, and diabetes mellitus (adjusted HR 18.9; 95% CI 2.959-121.3, $p = 0.002$) as shown in **Table 2**.

There were significant differences in survival ($p = 0.002$) between patients with high serum NGAL (mean survival 424 hours, 95% CI 296-552) than low serum NGAL (mean survival 680 hours; 95% CI 584-775) after log rank test as shown in **Figure 3**. Nevertheless, the effect of serum NGAL on MACE (HR 1.6; $p=0.169$) and decreased of kidney function both on mortality (HR 0.4; $p=0.131$) and MACE (HR 0.8; $p=0.835$) did not give significant result.

DISCUSSION

Majority of patients in this study were admitted due to ADHF (72.7%). Median age of the patients was 58 ± 12 years and more than half of them were men. This was similar to prospective study in Europe which the highest percentage of acute heart failure is ADHF (72%) while the rest is AHF de novo (28%). Most of the subjects were men (56%) but the mean age of patients in those study tended to be older (73 years). Age of AHF patients in large-scale studies such as ADHERE and OPTIMIZE-HF conducted in the United States, EHFS I and II and ESC-HF Pilot registry in Europe also tend to be older (> 70 years). However, some findings are

similar compared to our study. About half of the patients were men and most are ADHF patients. Meanwhile, AHF de novo patients were present in about a quarter to one-third of cases. As with other studies, around 50% patients have good LVEF and coronary heart disease is the most common cause of heart failure.¹⁵ The mortality rates in our study were higher compared with other studies. In most studies, in-hospital mortality rate of AHF patients was 4-7%, except in ALARM-HF study which showed a higher mortality rate (11%). It might explained by the higher proportion of patients with cardiogenic shock in ALARM-HF (12%) when compared with other studies (4%).¹⁵

The cut-off values of serum NGAL in our study were lower than most of the previous studies.^{3,12,16,17} This may be due to sampling time that relatively earlier. Our study measured serum NGAL at the onset of hospital admission thus the measured serum NGAL levels may not as large as other studies in which the sample is taken the next day, when the patient allowed to move from the cardiac intensive ward or before discharge. In addition, the reagents used in our study have not been used in previous studies so it might be another source of difference.

Our study showed that AHF patients with high baseline serum NGAL level had worse survival than AHF patients with low serum NGAL during hospitalization. High serum NGAL increases the risk of mortality during hospitalization, both occurring in bivariate and multivariate analysis. Similar results are shown by several other studies.^{10,12,16} Although

Table 2. Multivariate analysis between high serum NGAL level on mortality using cox proportional hazards regression.

Variable	Adjusted HR	95% CI	P Value
High Serum NGAL	18.946	2.959-121.3	0.002
Aged ≥ 65 years	9.188	1.930-43.745	0.005
Male gender	0.544	0.123-2.406	0.422
Hypertension	0.553	0.096-3.188	0.507
Anemia	0.640	0.140-2.930	0.565
Sepsis	0.637	0.122-3.338	0.594
Diabetes mellitus	3.191	0.503-20.230	0.218

different results are presented by the multicenter Akinesis study in which states that NGAL plasma is not superior to serum creatinine in predicting worsening of renal function and poor prognosis during hospitalization. This difference perhaps because Akinesis study exclusively aims to assess the worsening of early-stage renal function associated with diuretic therapy while the deterioration of renal function is caused by various factors, including: AHF therapy, other diseases comorbidities, cardiorenal syndrome, and complex critical patient conditions involving many pathophysiological processes. The study was unable to adequately assess the prognosis of increase in serum NGAL from other causes other than diuretic therapy.¹²

Rapid deterioration in kidney function, also known as acute kidney injury (AKI), is a common comorbid in AHF patients and is associated with a poor prognosis such as increased mortality during hospitalization, increased frequency of recurrent hospitalization and longer duration of hospitalization.^{18,19} NGAL is a biochemical marker that indicates an injury to renal tubular cells. The production and secretion of NGAL increased significantly in renal tubular cells followed by elevated levels of NGAL in urine and serum after acute renal injury. NGAL levels in urine and serum begin to rise at two hours and reach a maximum level of about eight hours after the onset of AKI so that it can be used to predict the early phase of cardio renal syndrome type 1 in AHF patients. In pediatric patients undergoing cardiac surgery, NGAL levels increased significantly in plasma and urine 2-6 hours after surgery in patients who developed AKI later while serum creatinine had not increased for 48-72 hours afterwards.¹² Besides being an early marker of AKI, NGAL also thought to have a direct influence on the heart that is play a role in the pathogenesis and progression of heart failure, such as its effect on iron transport regulation into the cardiomyocyte. This mechanism underlies the pathogenesis of heart failure that primarily caused by cardiomyopathy. NGAL receptors (NGAL-R / megalin) can bind and form complexes with siderophore possessed by bacteria or mammals that can bind

iron from the extracellular environment. Internalization of these iron-siderophore complex into cardiomyocytes leads to increased uptake and accumulation of iron in cytoplasm and induces mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress that trigger autophagy and apoptosis of cardiomyocytes.²

NGAL also considered a pro-inflammatory cytokine because of its role in the immune response during bacterial infection and is thought to contribute to the pathogenesis of heart failure depending on the inflammatory response. NGAL can stimulate cardiac inflammation by polarization of the proinflammatory macrophage M1 phenotype. As a result, a vicious circle forms where NGAL can increase inflammation by inducing expression of TNF- α and other pro-inflammatory mediators. One study showed that prevention of NGAL clearance from the circulation promotes vascular inflammation and endothelial dysfunction. In advanced heart failure, increased systemic and local inflammation with elevated circulating TNF- α has an important role in the pathogenesis of disease.² Further studies need to be done to explore it.

However, our study failed to show the role of serum NGAL as a predictor of MACE, that consist of cardiogenic shock and lethal arrhythmias. We suggest that MACE in AHF were not merely complications of AKI, but were also caused or aggravated by various factors. These factors include comorbid conditions such as sepsis and anemia that increased risk for myocardial depression, ischemia and cardiac contractility disorders as well as arrhythmias. Furthermore, AHF etiology such as ACS, especially in patients with previously low LVEF, makes it easier for patients to fall into cardiogenic shock and suffered from malignant arrhythmias, and volume overload conditions especially in patients with increased atrial pressure facilitates the onset of atrial fibrillation.

It appears that mortality during hospitalization occurring in patients with high serum NGAL in this study was not only due to the adverse effects of AKI on the progression of cardiogenic shock and malignant arrhythmias. Other factors also affect the mortality, such as acid-base

and electrolyte disturbances, uremia and excessive fluid burden leading to increased microvascular permeability, coagulopathy and hemorrhage, interstitial edema, disturbance of oxygen and metabolites diffusion, increased intra-abdominal pressure, protein catabolism, decreased hepatic blood flow, hemodynamic instability, muscle weakness, paralysis, and severe impairment of consciousness. Comorbid conditions such as sepsis and anemia also increase the risk of mortality.²⁰

Our study also found that decreased renal function, as measured from baseline serum creatinine levels more than 1.2 mg/dL, did not show statistically significant results as a predictor of mortality or MACE in AHF patients. Previous studies consistently showed that decrease or deterioration in renal function is a predictor of poor prognosis in patients with AHF regardless of renal biomarkers used (plasma creatinine, eGFR or cystatin C). Univariate analysis showed that serum NGAL, eGFR and cystatin C were predictors of mortality and recurrent episodes of hospitalization in AHF patients over a 3 month period. However, in multivariate analysis only serum NGAL was shown to be significantly independent predictors of adverse outcomes. Perhaps serum NGAL can indicate the presence of renal injury, that marked an initial stage of AHF deterioration, earlier than other marker such as serum creatinine. This may also indicate the effect of NGAL on the progression of AHF caused by a direct influence on myocardium as described earlier.¹⁰ The use of serum creatinine is even worse in detecting AKI, significant kidney disease can occur with minimal or even non-altered creatinine changes partly due to the ability of kidneys to increase tubular secretion of creatinine.^{21,22} Our study only measured serum creatinine levels at the onset of admission and did not conduct serial measurement. Thus, we could not detect any decline in kidney function during hospitalization. High levels of serum creatinine at the onset of hospitalization may be due to chronic renal injury and may not necessarily reflect acute renal dysfunction as a predictor of mortality and MACE during hospitalization.

Our study also had some limitations.

The standard cut-off value of serum NGAL had not been present. Therefore, the cut-off value that we used may be subjected to bias. We also measured serum NGAL and creatine only once, so we could not be able to assess the changing pattern during hospitalization.

CONCLUSION

High serum NGAL among AHF patients is an independent predictor of in-hospital mortality but not MACE. The survival during hospitalization of patients with high serum NGAL level is worse compared to low serum NGAL. Meanwhile, decreased kidney function, as measured by serum Creatinine at admission, was neither an independent predictor of in-hospital mortality nor MACE.

CONFLICT OF INTEREST

Authors declare no conflict of interest

FUNDING

No funding received from third party sources.

AUTHORS CONTRIBUTION

All authors contributed equally in all phases of the study.

REFERENCES

- Bolignano D, Donato V, Coppolino G, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. *Am J Kidney Dis.* 2008;52(3):595-605.
- Chan YK, Sung HK, Sweeney G. Iron metabolism and regulation by neutrophil gelatinase-associated lipocalin in cardiomyopathy. *Clin Sci (Lond).* 2015;129(10):851-862.
- Helanova K, Littnerova S, Kubena P, et al. Prognostic impact of neutrophil gelatinase-associated lipocalin and B-type natriuretic in patients with ST-elevation myocardial infarction treated by primary PCI: a prospective observational cohort study. *BMJ Open.* 2015;5(10):e006872.
- Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. *J Card Fail.* 2010;16(1):49-54.
- Cruz DN, Fard A, Clementi A, Ronco C, Maisel A. Role of biomarkers in the diagnosis and management of cardio-renal syndromes. *Semin Nephrol.* 2012;32(1):79-92.
- De Berardinis B, Gaggin HK, Magrini L, et al. Comparison between admission natriuretic peptides, NGAL and sST2 testing for the prediction of worsening renal function in patients with acutely decompensated heart failure. *Clin Chem Lab Med.* 2015;53(4):613-621.
- Soylu K, Aksan G, Nar G, et al. Serum neutrophil gelatinase-associated lipocalin levels are correlated with the complexity and the severity of atherosclerosis in acute coronary syndrome. *Anatol J Cardiol.* 2015;15(6):450-455.
- Lindberg S, Jensen JS, Hoffmann S, et al. Plasma Neutrophil Gelatinase-Associated Lipocalin Reflects Both Inflammation and Kidney Function in Patients with Myocardial Infarction. *Cardiorenal Med.* 2016;6(3):180-190.
- van Deursen VM, Damman K, Voors AA, et al. Prognostic value of plasma neutrophil gelatinase-associated lipocalin for mortality in patients with heart failure. *Circ Heart Fail.* 2014;7(1):35-42.
- Alvelos M, Lourenço P, Dias C, et al. Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure. *International Journal of Cardiology.* 2013;165(1):51-55.
- Kang SM, Cho MC. Prognostic Factors in Hospitalization for Heart Failure in Asia. *Heart Fail Clin.* 2015;11(4):543-550.
- Maisel AS, Mueller C, Fitzgerald R, et al. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: The NGAL Evaluation Along with B-type Natriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. *European Journal of Heart Failure.* 2011;13(8):846-851.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.
- Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009;119(14):1977-2016.
- Farmakis D, Parisis J, Lekakis J, Filippatos G. Acute heart failure: Epidemiology, risk factors, and prevention. *Rev Esp Cardiol (Engl Ed).* 2015;68(3):245-248.
- Ito M, Doi K, Takahashi M, et al. Plasma neutrophil gelatinase-associated lipocalin predicts major adverse cardiovascular events after cardiac care unit discharge. *J Cardiol.* 2016;67(2):184-191.
- Lahiri A, Alex AG, George PV. Estimating the prevalence of elevated plasma neutrophil gelatinase associated lipocalin (NGAL) level in patients with acute coronary syndromes (ACS), and its association with outcomes. *Indian Heart Journal.* 2017.
- Elsharawy S, Raslan L, Morsy S, Hassan B, Khalifa N. Plasma neutrophil gelatinase-associated lipocalin as a marker for the prediction of worsening renal function in children hospitalized for acute heart failure. *Saudi J Kidney Dis Transpl.* 2016;27(1):49-54.
- Breidhardt T, Socrates T, Drexler B, et al. Plasma neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury in acute heart failure. *Critical Care.* 2012;16(1):R2.
- Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. *Critical Care.* 2016;20(1).
- Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J.* 2013;6(1):8-14.
- Sharifpour F, Hami M, Naghibi M, Zeraati A, Arian S, Azarian AA. RIFLE criteria for acute kidney injury in the intensive care units. *J Res Med Sci.* 2013;18(5):435-437.



This work is licensed under a Creative Commons Attribution