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Value of plasma NGAL in the 12-month all-cause mortality prognosis of acute heart failure or acute decompensated heart failure

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ABSTRACT

Background: The presence of acute kidney injury in the setting of acute heart failure (AHF) or acute decompensated heart failure (ADHF) is very popular and was called cardiorenal syndrome 1 (CRS1). CRS1 is associated with significant morbidity and mortality.

Neutrophil gelatinase-associated lipocalin (NGAL) is an early predictor of acute kidney injury and poor outcomes in various diseases; though, in AHF or ADHF patients, its significance remains poorly understood. This study was aimed to evaluate the 12 month prognostic value of plasma NGAL in AHF or ADHF patients. *Methods*: There were 139 patients with AHF or ADHF in the department of cardiovascular resuscitation and Interventional cardiology at Ho Chi Minh City 115 People Hospital from September 2018 to March 2019 and 12 months follow-up. A prospective cohort study was carried out. *Results*: There were 46 all-cause mortality cases (rate 33.1%) 12 months follow up after discharge. There were 11 cases (rate 7.9%) lost to follow-up; mean age 66.12 ± 15.77, men accounted for 50.4%. The optimal cut-off of NGAL for 12-month all-cause mortality prognosis was> 383.74 ng/ml, AUC 0.632 (95% CI 0.53-0.74, p = 0.011), sensitivity 58.7 %, specificity 68.29 %, negative predictive value74.7%, positive predictive value 50.9%. Kaplan-Meier analysis revealed that the high plasma NGAL (≥ 400 ng/ml) group exhibited a worse prognosis than the low plasma NGAL (< 400 ng/ml) group in 12-month all-cause death (Hazard Ratio 2.56; 95%CI 1.35-4.84, P=0.0039. Independent predictors of 12-month all-cause-mortality were identified using multivariable Cox proportional-hazards regression models with backward-stepwise selection method consisted of two variables: level of NGAL, mechanical ventilation at admission. *Conclusions:* Plasma NGAL and mechanical ventilation at admissions were independent predictors of 12-month all-cause mortality in patients with AHF or ADHF. The survival probability 12-month follow-up of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml), difference was statistically significant $\chi 2 = 8.31$; p = 0.0047 by Kaplan-Meier curve.

Keywords: Neutrophil Gelatinase-Associated Lipocalin (NGAL), Cardio-Renal Syndrome (CRS1) Type 1, biomarkers, 12-month mortality prognosis

1. INTRODUCTION

Acute kidney injury (AKI) in the setting of acute heart failure (AHF) or acute decompensated heart failure (ADHF) is very common occurrence and was termed cardiorenal syndrome type 1 (CRS1) (Kurt W. Prins et al., 2015). CRS is a disorder of the heart and kidneys that can cause acute or chronic dysfunction of one organ to cause another. CRS was divided into 5 types, of which the first type is called acute cardiorenal syndrome, which is an acute cardiac dysfunction leading to damage and/or acute renal dysfunction (Claudio Ronco et al., 2008). The prevalence of cardiorenal syndrome type 1according to studies varies from 32% to 40% in patients hospitalized for episodes of ADHF (Johan P.E. Lassus et al., 2010). It is estimated that in the United States, there will be 320,000 to 400,000 hospitalizations with CRS type 1 every year. Moreover, with the increasing number of heart failure patients, the rate of CRS type 1 will be an important issue in the future.

Neutrophil gelatinase-associated lipocalin (NGAL) in the blood and urine is one of the earliest indicators of acute kidney injury due to ischemia or nephrotoxicity. One study showed that using NGAL in urine to diagnose acute kidney injury with 90% sensitivity and 99% specificity (Yasuki Nakada et al., 2017). Neutrophil gelatinase-associated lipocalin (NGAL), synthesized abundantly in kidney tubules, is a protein of the lipocalin superfamily. Its expression is rapidly upregulated by ischemia-reperfusion injury in renal tubular epithelial cells, and NGAL is released into urine in an experimental model. In human, NGAL has been recognized as a surrogate marker of AKI complicated with various diseases, including sepsis, post–cardiac surgery, and admission to the intensive care unit. In particular, a few studies reported an association between the elevation of serum NGAL levels on admission and consequent AKI in patients with chronic heart failure (Yasuki Nakada et al., 2017). However, in AHF or ADHF patients, the prognostic value of plasma NGAL for 12-month all-cause mortality remains poorly understood.

Study Objectives

Aim to evaluate the value of plasma NGAL biomarkers in the prognosis 12-month all-cause mortality in AHF or ADHF patients.

2. MATERIALS AND METHODS

Selection of participants

Study Population

All patients with AHF or ADHF admitted to Cardiovascular Resuscitation and Interventional Cardiology Department of 115 People Hospital in Ho Chi Minh City from September 2018 to March 2019. Inclusion criteria for this study were adult inpatients (≥18 years old) with AHF or ADHF with or without CRS type 1 Criteria for diagnosing AHF or ADHF according to Canadian Cardiovascular Society guidelines for the management of heart failure 2017 (Justin A. Ezekowitz et al., 2017). Criteria for diagnosing AKI: according to KDIGO clinical practice guideline for acute kidney injury 2012 (John A Kellum et al., 2012): increase in serum creatinine ≥ 0.3mg/dL (≥26.5µmol/l) within 48 hours or a 50% increase in serum creatinine from the level on admission during hospitalization.

Urine criteria (0.5 mL/kg per hour for 6 hours) were not utilized for AKI diagnosis because of the potential alterations in urine volume induced by therapeutic medication. Criteria for diagnosing CRS type 1: patients suffered from AHF or ADHF developed AKI within 48 hours (Claudio Ronco and Luca Di Lullo, 2016). Exclusion criteria were not agree to participation; hospitalization period <2 days; multiple organ failure or septic shock; AKI caused by contrast; renal dialysis; kidney transplant; progressive hepatitis; acute pancreatitis; long-term use of high steroids; cyclosporin; malignancy.

Study design

This was a prospective cohort study

Sample size

This was a diagnostic study, the sample size is calculated by the Buderer formula(Buderer, 1996):

$$nse = \frac{Z^2\alpha \times Pse \times (1-Pse)}{w^2 \times Pdis} \quad \text{and} \quad nsp = \frac{Z^2\alpha \times Psp \times (1-Psp)}{w^2 \times (1-Pdis)}$$

where:

n_{se}: estimated sample size to estimate for sensitivity

n_{sp}: estimated sample size to estimate for specificity

P_{se} : the reference sensitivity according to the literature. For NGAL, this sensitivity is 100% (Anahita Izadi, et al., 2016)

P_{sp}: the reference specificity according to the literature. For NGAL, this specificity is equal to 86.7% (Anahita Izadi, et al., 2016)

P_{dis}: the rate of CRS type 1 according to F.Fabbian et al is 48.2% (F. Fabbian, et al., 2011)

Z : the constant of the normal distribution, with a type I error of 5%, we have $Z^2_{\alpha} = 1.96$

W^2 : the true positive and true negative error of the 95% confidence interval, we choose W = 0.15.

The required sample size n only needs to be larger than n_{se} and n_{sp}

For NGAL, calculate $n_{se} = 31.9$ and $n_{sp} = 38$

So $n \geq 38$ patients. Therefore we will proceed with sampling of at least 38

Clinical Evaluation and Biomarker Measurements

All patients were taken medical history, meticulous physical examination, assessment of vital signs: pulse, systolic and diastolic blood pressure; jugular venous distention, S3, murmurs, rales, edema. It was then tested: first day serum creatinine (creatininD1) and third day (creatinine D3) with Alinity c Creatinine Reagent running on Abbott's Alinity machine; plasma NGAL with Human NGAL ELISA kit 036RUO of BioPorto Diagnostics A/S Copenhagen, Denmark; NT-proBNP with the Elecsys® proBNP II reagent kit from Roche Diagnostics, Bromma, Sweden, running on Cobas e411 analyzer, these tests were performed at the laboratory department of Medic Medical Center, Vietnam. Addition tests: cell blood counts, urea, AST, ALT, troponin I, electrolytes panel, arterial blood gas were performed at the laborartory department of People's Hospital 115. Electrocardiography, chest X-ray, echocardiography, medications on admission and follow-up during hospital stay: hospital stays length and in-hospital all-cause mortality and 12-month follow-up. Estimated glomerular filtration rate was determined by using the 2009 CKD-EPI creatinine formula ($eGFR_{CKDEPI}$).

Data Analysis

Data were processed using IBM SPSS Statistics Version 25 software, MedCalc @ version 19.0.5 software. A p-value less than 0.05 were statistically significant. Two-sided hypothesis testing was used. Categorical variables were presented as counts (percentage) and continuous variables as means ± standard deviation (SD) or median and interquartile range [IQR] with non-normally distributed data. Comparison the means of the two groups by the t-test; comparison two rates by the chi-square test; using a ROC curve and calculate the AUC. The cut-off value was chosen at the highest score of Youden (J) with J = Sensitivity + Specificity - 1. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) was determined.

Evaluating the correlation between two normal distributed continuous variables by Pearson and Spearman correlations if those not in normal distribution. Survival analysis is by using univariate Cox proportional-hazard regression between 12-month mortality and some variables. The variables which p value < 0.1 were selected in the multivariate Cox proportional-hazard regression model by Wald test with backward-stepwise method. The associations of plasma NGAL levels with 12-month mortality were assessed by

Kaplan-Meier curves which compared by log-rank test. The study was executed according to the principles of the Declaration of Helsinki. Ethical approval was received from Hue University of Medicine and Pharmacy. All participants got informed consent forms.

3. RESULTS

From September 2018 to March 2019, 172 AHF or ADHF patients were initially diagnosed. After follow-up, 33 cases were excluded from the study because they did not meet the inclusion criteria; we eventually collected 139 cases of AHF or ADHF met our criteria. Among 139 cases, there were 48 cases of diagnosis of CRS type 1 accounting for 34.5%. Data were divided into two groups with CRS type 1 (CRS1, n = 48) and no CRS type 1 (Non-CRS1, n = 91). Among the group with CRS type 1, there were 04 cases without EF evaluation, 01 case without cell blood count; group without CRS type 1 had 07 cases without evaluation of EF, 01 case without cell blood count. After 12 months follow-up there were 11 cases (rate 7.9%) lost to follow-up.

Demographic and clinical characteristics

Detailed baseline characteristics of the study population are summarized in Table 1. Mean age was 66.12 ± 15.77; minimum 20 years old and maximum 96 years old. Male/female ratio: 1.01; BMI, median and quartiles of the two groups were 23.44 [21.56 - 25.05], statistically significant difference $p < 0.05$. The majority of patients with a history of arterial hypertension accounted for 63.3%, followed by diabetes accounting for 36.7%, heart failure accounted for 32.6% and chronic kidney disease accounted for 15.8%. There were no differences in medical history between 2 groups with CRS1 and Non-CRS1, $p > 0.05$. However, there was a difference in the patients with medical history of chronic kidney disease between the two groups, statistically significant $p < 0.05$. There were 60 cases (rate 43.2%) diagnosed with acute pulmonary edema; 38.8% of cases diagnosed with acute decompensated heart failure; 16.5% of cases were diagnosed with cardiogenic shock; 56 patients (40.9%) were diagnosed with acute myocardial infarction. There were 65 cases (50.8%) of preserved EF heart failure ≥ 50%; 26.6% of cases of reduced EF heart failure <40%; 22.7% of cases of mid-range EF heart failure 40-49%. There was no difference in vital signs at admission, diagnosis, type of EF based-heart failure between two groups, $p > 0.05$.

There were similarities in laboratory results at admission: Neutrophil, hemoglobin, liver enzymes (AST, ALT), troponin I, arterial blood gases (pH, HCO_3^-, pCO_2, pO_2), Na^+, K^+ concentration between two groups. However, the concentration of Urea, CreatininD1 and creatinine D3, NGAL and NT-proBNP in the CRS1group is higher than the Non-CRS1 group, the differences were statistically significant $p < 0.05$. eGFR by creatinine on day 1 and 3 $eGFR_{CKDEPID1}$, $eGFR_{CKDEPID3}$ in CRS1group lower than Non-CRS1group, $p < 0.05$. The majority of patients using diuretics furosemide accounted for 77.7%, the mean dose 40 mg. Nitrates were used in 85 patients (61.2%). Only one patient (0.7%) used beta-blockers, up to 18.7% of patients received nor adrenaline. There were 2 patients (1.4%) indicated continuous renal replacement therapy (CRRT) in CRS1 group, but the difference between the two groups was not statistically significant $p > 0.05$. There were similarities in treatment at admission between two groups.

The median of length of hospital stay of the two groups was 9 days; the interval quartile was 7-12 days. Length of hospital stay in CRS1 group was longer than in the Non-CRS1 group, but this difference was not statistically significant $p > 0.05$. In-hospital mortality or serious illness was 21 cases (15.1%); in-hospital mortality/serious illness were higher in CRS1 group compared with the Non-CRS1 group, $p<0.05$. There were 46 cases (33.1%) death after 12 months follow-up, the rate of 12-month mortality between two groups were similar.

Table 1 Demographic and clinical characteristics

Variables	Total (n=139)	CRS1 (n=48)	Non-CRS1 (n=91)	P value
Age (years)	66.12 ± 15.77	64.06 ± 15.29	67.19 ± 15.98	0.27
Male	70(50.4)	24(51.4)	46(50)	0.95
Body Mass Index* (kg/m^2)	23.44 [21.56 – 25.05]	24.29 [22.5 –25.82]	23.44[21.33 – 24.38]	0.037
Medical History				
Arterial Hypertension	88 (63.3)	34 (70.8)	54 (59.3)	0.18
Diabetes mellitus	51 (36.7)	20 (42.6)	31 (33.7)	0.38
Dyslipidemia	9 (6.5)	4 (8.5)	5 (5.4)	0.49
Smoking	14 (10.1)	5 (10.4)	9 (9.9)	0.92
Alcohol drink	1 (0.7)	1 (2.1)	0 (0)	0.17
IHD/old MI	42 (30.2)	15 (31.3)	27 (29.7)	0.85

DCM	5 (3.6)	2 (4.2)	3 (3.3)	0.56
Valve heart diseases	25 (18)	5 (10.4)	20 (21.9)	0.092
Heart Failure	45 (32.6)	17 (35.4)	28 (30.8)	0.61
CKD	22 (15.8)	12 (25)	10 (10.9)	0.031
Stroke	10 (7.2)	4 (8.3)	6 (6.6)	0.74
Vital signs at admission				
Heart rate (beats/min)	102 [88 – 114]	98 [84 -115]	104 [90 – 114]	0.89
BP (mmHg)				
Systolic	120 [90 – 140]	120 [90 – 140]	110 [100 – 140]	0.79
Diastolic	70 [60 – 80]	70 [60 – 80]	70 [60 – 80]	0.29
Mean	86.67 [70-100]	86.67 [70-100]	86.67 [73.33-100]	0.58
Oxygen saturation (%)**	90 [86-95]	90 [87-96]	90 [86-94]	0.53
Diagnosis				
APE	60 (43.2)	15 (31.3)	45 (49.5)	
Cardiogenic shock	23 (16.5)	9 (18.8)	14 (15.4)	0.11
ADHF	54 (38.8)	24 (50)	30 (32.9)	
Others	2 (1.4)	0 (0)	2 (2.2)	0.66
Acute MI	56 (40.9)	18 (37.5)	38 (41.8)	
Laboratory values				
EF*** based-HF				
EF reduced	34 (26.6)	9 (20.9)	25 (29.4)	
EF mid-range	29 (22.7)	13 (30.2)	16 (18.8)	0.29
EF preserved	65 (50.8)	21 (48.8)	44 (51.8)	
Neutrophil# (K/µL)	7.84 [5.50 -10.71]	8.5 [5.37 -11.96]	7.73 [5.50–10.32]	0.39
Hb (g/dl)#	11.60 [9.98 – 13.53]	10.8 [9.13 – 13.38]	12.15 [10.4–13.60]	0.087
AST (UI/l)##	47.49 [28.98-104.83]	48.2 [30.2-106.33]	46.9 [28.58-104.83]	0.41
ALT (UI/l)##	29.7 [17.86-79.04]	33.11[17.78-85.64]	28.02 [18.08-69.20]	0.94
Ure (mmol/l)###	9.82 [6.20 – 14.53]	12.67 [8.51–19.27]	8.09 [5.45–11.67]	< 0.01
CreatininD1(mg/dl)	1.31 [0.99 – 2.24]	2.44 [1.47–4.09]	1.08 [0.83–1.47]	< 0.01
$eGFR_{CKD-EPID1}$	47 [23 – 75.75]	22 [13– 44]	64 [38.25–84.05]	< 0.01
Creatinin D3	1.29 [0.87- 2.32]	2.84 [1.38-4.8]	1.07 [0.8 -1.44]	< 0.01
$eGFR_{CKD-EPID3}$	50 [23.25 – 79]	19.5 [11 – 47.5]	67 [38–86.50]	< 0.01
Na^+ (mmol/l)	137.4[133.48-140.48]	136.8[130.55-138.8]	138.4[135.03-141.05]	0.49
K^+ (mmol/l)	4.05 [3.54-4.49]	4.15 [3.58-4.59]	3.96 [3.52-4.44]	0.54
NGAL (ng/ml)	327.13[205.38-516.76]	511.63[338.27-587.94]	262.59[193.07-401.11]	< 0.001
NT-proBNP (pg/ml)	8814[3860-26419]	20131[6350-35000]	6378[2935.25-17177.50]	0.005
Troponin I$ (pg/ml)	6156.18±13176.59	6575.08 ±13505.34	5941.86 ± 13080.16	0.79
pH$$	7.40 ± 0.087	7.39 ± 0.099	7.42 ± 0.079	0.08
$HCO_3^{-}$$$ (mmol/l)	21.8 [17.85-24.98]	20.03 [16.4-23.7]	22.6 [19.1-25.98]	0.25
$pCO_2$$$ (mmHg)	35 [29.08-40.03]	35 [27.85-40.95]	35 [29.98-39.48]	0.67
$pO_2$$$ (mmHg)	76 [61.75-111]	75 [60-110.5]	77 [62.75-111]	0.77
Therapy at admission				
Furosemide	108 (77.7)	36 (75)	72 (79.1)	0.58
Furosemide dose (mg)	40 (20-40)	40 (20-40)	40 (20-40)	0.50
ACEIs/ARBs use	14 (10.1)	4 (8.3)	10 (10.98)	0.62
Beta blockers	1 (0.7)	0 (0)	1 (1.1)	0.66
Dobutamin	19 (13.8)	7 (14.6)	12 (13.2)	0.84
Dopamin	7 (5)	3 (6.3)	4 (4.4)	0.64
Noradrenaline	26 (18.7)	9 (18.8)	17 (18.7)	0.99
Nitrates	85 (61.2)	28 (58.3)	57 (62.6)	0.62
Conventional oxygen	110 (79.1)	41(85.4)	69 (75.8)	0.19

Non-Invasive ventilation	12 (8.6)	5 (10.4)	7 (7.7)	0.59
Mechanical ventilation	13 (9.4)	5 (10.4)	8 (8.8)	0.75
CRRT	2 (1.4)	2 (4.2)	0 (0)	0.051
Length of hospital stay(days)	9 [7 – 12]	10 [7 – 12]	8 [7 – 12.75]	0.33
In-hospital mortality/serious illness	21 (15.1)	12 (25)	9 (9.9)	0.018
12-month mortality	46 (33.1)	20 (43.48)	26 (56.52)	0.15

Data are presented as n (%); medium± SD; median [interquartile range]
*n=113; **n= 131; *** n=128; # n=137; ##n=115; ###n=134; $n=130; $$n=117; reduced EF< 40%; mid-range 40-49 % EF; preserved EF ≥ 50%. APE: Acute Pulmonary Edema; BP: blood Pressure; MI: Myocardial Infraction; IHD: Ischemic Heart Disease; DCM: Dilated cardiomyopathy CCRT: Continuous Renal Replacement Treatment. ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers. Hx: history. Bold words indicated statistically significant. Serious illness: high risk of mortality patients were resuscitated but their families asked to be discharged before death in hospital.

The value of plasma NGAL in predicting 12-month all-cause mortality after discharge

The prognostic accuracy of the plasma NGAL was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off of NGAL for 12-month all-cause mortality prognosis is > 383.74 ng/ml, AUC is 0.651 (95% CI 0.56-0.74, p = 0.005), sensitivity 62.8 %, specificity 68.4 %, positive predictive value 27.8%, negative predictive value 92.9%. The result was displayed in Table 2 and Figure 1.

Table 2 Cut-off point, sensitivity, specificity, AUC of NGAL prognosing 12-month all-cause mortality

Variable	Cut-off point	Sensitivity Se (%)	Specificity Sp (%)	Area Under Curve (AUC)	Confident Interval (CI) 95%	P value
NGAL (ng/ml)	>383.74	62.8	68.4	0.651	0.56 -0.74	0.005

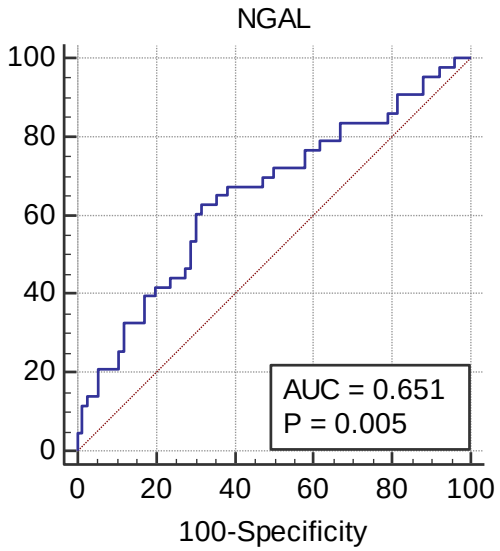

Figure 1. Cut-off point, sensivity, specificity of plasma NGAL for prognosing 12-month all-cause mortality after discharge

To investigate the correlation between 12-month all-cause mortality after discharge and several factors according to Khibar Salah et al. (Salah, et al., 2015) a total of 15 clinically relevant prognostic variables, we conducted Pearson correlation analysis if variables was distributed normal and otherwise Spearman rank was done. As a result, there was only one variable-mechanical ventilation correlating to 12-month all-cause mortality after discharge as in Table 3.

Table 3 The correlation between 12-month all-cause mortality after discharge and some variables

Variables	Coefficients Pearson r or Spearman rho	P value
Age (years)	0.059	0.49
Sex (Male/Female)	0.096	0.26
Heart rate (beats/min)	0.082	0.34
Systolic blood pressure (mmHg)	-0.13	0.13
Diastolic blood pressure (mmHg)	-0.097	0.25
Mean blood pressure (mmHg)	-0,13	0.14
Hb (g/dl)	-0.099	0.25
Urea (mmol/l)	0.094	0.28
Creatinine D1(mg/dl)	0.083	0.33
$eGFR_{CKD-EPID1}$	-0.15	0.074
NGAL (ng/ml)	0.062	0.055
NT-proBNP (pg/ml)	0.21	0.47
Hx Chronic Kidney Disease	0.16	0.057
Hx Hypertension	0.046	0.59
Hx Diabetes mellitus	0.095	0.27
Hx Heart failure	0.12	0.17
Atrial fibrillation	0.083	0.33
Mechanical ventilation	0.26	0.0023
ACEIs/ARBs at admission	0.12	0.17
CRS1	0.15	0.069

Bold indicated statistically significant

Univariable and multivariable Cox regression between 12 month all-cause mortality after discharge and some variables

One variable correlated with 12 month mortality after discharge and 15 clinically relevant prognostic variables according to Khibar Salah were analysed by univariable Cox proportional-hazard regression. The variables with p value < 0.1 amd/or clinically relevant prognostic variables (inspite of p > 0.1) were selected in the multivariate Cox proportional-hazard regression model by Wald test with backward-stepwise method. During multivariable Cox proportional-hazard regression analysis mechanical ventilation and plasma NGAL remained the strongest independent predictors of 12-month all-cause mortality after discharge (HR 0.36 95%CI (0.16-0.81); p=0.0140 and HR 1.002 95% CI (1.0000-1.0003); p=0.03) (Figure 2). The result was displayed in Table 4.

Table 4 Univariable and multivariable Cox proportional-hazard regression between 12 month all-cause mortality after discharge and some variables

Univariable Cox proportional-hazard regression				
Predictors	**β**	**SE**	**Hazard Ratio (CI 95%)**	**P value**
Urea	0.016	0.029	1.017 (0.96-1.076)	0.57
Mean Blood Pressure	-0.018	0.011	0.98 (0.96-1.00)	0.093
NGAL (ng/ml)	0.002	0.001	1.002 (0.99-1.004)	0.13
$eGFR_{CKDEPID1}$	0.002	0.009	1.002 (0.98-1.02)	0.83
Mechanical ventilation	-0.76	0.45	0.47 (0.19-1.13)	0.091
ACEIs/ARBs at admission	-0.67	0.43	0.51 (0.22-1.19)	0.12
CRS1	-0.31	0.38	0.73 (0.35-1.56)	0.42
Multivariable Cox proportional-hazard regression				
Predictors	**β**	**SE**	**Hazard Ratio (CI 95%)**	**P value**
Mean Blood Pressure	-0.011	0.006	0.99 (0.98-1.002)	0.095
NGAL	0.002	0.001	1.002 (1.0000-1.0003)	0.03
Mechanical ventilation	-1,015	0.41	0.36 (0.16-0.81)	0.014

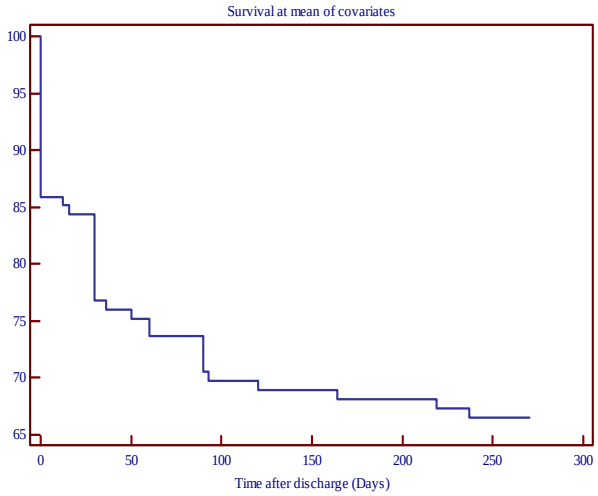

Figure 2 Survival probabilities after discharge

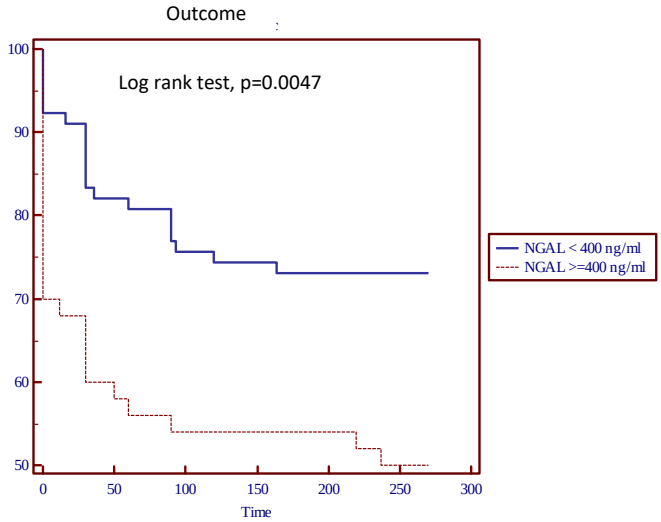

Figure 3 Kaplan-Meier curve for 12-month all-cause mortality after discharge

The survival probability 12-month follow-up after discharge of high level NGAL (≥ 400 ng/ml) group was lower than that of low level NGAL (<400 ng/ml), difference was statistically significant $\chi 2 = 8.31$; $p = 0.0047$ (Figure 3).

4. DISCUSSION

The mean age of patents was 66.12 ± 15.77. The percentage of female patients with AHF or ADHF in our study was 49.6% lower than the study of the author Breidthardt et al. (Breidthardt Tobias et al., 2011) which mean age was 79 [71-85]. When compared with other studies, our results are similar to those of author Belziti César et al. (César A Belziti et al., 2010) which women percentage was 43%. The male rate was similar to that of Margarida et al. (Margarida Alvelos, 2011) was 47.9% by Nakada et al. (Yasuki Nakada et al., 2017), 59.6% by Alan S. Maisel et al. (Alan S. Maisel et al., 2011), 61% (p> 0.05); however, the male rate was lower than that of Aghel et al. (Arash Aghel et al., 2010) 68% (p <0.05).

Tachycardia at admission with median was 102 beats/minute and interquartile was [88-114]. This result is higher than the research results of Margarida et al. (Margarida Alvelos, 2011). Systolic blood pressure 120 [90-140] mmHg, diastolic blood pressure 70 [60-80]mmHg is lower than the research results of Nakada et al. systolic blood pressure 144.1 ± 34.5 and diastolic 81.8 ± 19.4 (Yasuki Nakada et al., 2017). This is explained by the fact that our study included all patients with AHF and ADHF while the study by Nakada et al. only in patients with ADHF. Diagnosed acute pulmonary edema accounts for 43.2%; 38.8% were diagnosed with ADHF;

cardiogenic shock accounted for 16.5%. 56 patients (40.9%) diagnosed with acute myocardial infarction. There are similarities in vital signs at admission, diagnosis between two groups with CRS1 and Non-CRS1. This is also explained by the fact that both groups were patients with AHF or ADHF.

There was a similarity in subclinical features at admission: left ventricular ejection fraction EF neutrophil, hemoglobin between the two groups CRS1 and Non-CRS1. However, urea concentration, creatininD1 and D3, NT-proBNP, NGAL in the CRS1 group were higher than the Non-CRS1 group. Sodium concentration, $eGFR_{CKDEPID1}$, $eGFR_{CKDEPID3}$ in the CRS1 group were lower than the Non-CRS 1 group, p <0.05. This result was similar to the research result of Nakada et al. with Hb 11.6 ± 2.4 g/dl; Na 138.6 ± 4.3mEq/l; eGFR 45.9 ± 24.3ml/min/1.73m^2 (Yasuki Nakada et al., 2017). Plasma NGAL concentrations in the CRS1 group 506.49 [322.51-591.80] ng/ml was higher than in the Non-CRS1 group 1263.89 [193.07-409.46] ng/ml, p <0.001. The optimal cut-off of NGAL for 12-month all-cause mortality prognosis was> 399.58 ng/ml, AUC was 0.668 (95% CI 0.58-0.75, p = 0.0163); sensitivity, specificity, positive predictive value, negative predictive value were 71.43 %, 66.95 %, 27.8%, 92.9%, respectively. The plasma NGAL concentration dichotomized high level (≥ 400 ng/ml) and low level (< 400ng/ml). The associations of plasma NGAL levels with 12-month all-cause mortality were assessed by Kaplan-Meier curves. After that Kaplan-Meier curves were analyzed by log-rank test. The survival probability 12 months follow-up after discharge of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml), difference was statistically significant $\chi 2 = 8.31$; p = 0.0047. During multivariable Cox proportional-hazard regression analysis mechanical ventilation and plasma NGAL at admission remained the strongest independent predictors of 12-month all-cause mortality.

Limitations of study

First, this study was conducted in a single center in Vietnam, limiting the external validity to other centers with different settings. Second, most patients are seriously ill so they have not been fully assessed for hospitalization because ADHF may not be admitted to cardiac resuscitation department. Third, some kidney diseases (such as urinary tract infections or immune diseases) can also lead to an increase in NGAL levels. Although we had tried to eliminate these patients with a history and physical examination, they were still not completely controlled. Fourth, we did not measure hemodynamics or more accurate measurements of glomerular filtration rate to directly link the increased NGAL level to the compensatory ability of kidneys. Fifth, our sample size is still relatively small and there were some missing data. Sixth, we only evaluate for CRS1 within 48 hours, so we can skip cases with CRS1 after 48 hours to 7 days. Lastly, we only tested plasma NGAL once in the first day but did not test after 48 hours and before discharge to assess the variability of plasma NGAL concentration compared with creatinine level.

5. CONCLUSION

The optimal cut-off of NGAL for 12-month all-cause mortality prognosis was > 383.74 ng/ml, AUC was 0.651 (95% CI 0.56-0.74, p = 0.005); sensitivity, specificity, positive predictive value, negative predictive value were 62.8 %, 68.4 %, 27.8%, 92.9%, respectively. Plasma NGAL at admission was the independently predictors of 12-month mortality in AHF or ADHF. The survival probability after 12 months follow up of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml) by Kaplan-Meier curve.

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Details of contribution of each authors regards manuscript work & production.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Hue University of Medicine and Pharmacy, Hue University (ethical approval code: H2018/13).

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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