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

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ABSTRACT

Background: Renal dysfunction is common in patients with AHF or ADHF and is associated with significant early and late morbidity and mortality. Neutrophil gelatinase-associated lipocalin (NGAL) is an early predictor of acute kidney injury and adverse events in various diseases; however, in AHF or ADHF patients, its significance remains poorly understood. This study was aimed to evaluate the in-hospital all-cause mortality prognostic value of 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 November 2018 to May 2019. This research was a prospective cohort study. *Results:* there were 21 cases (rate 15.1%) in-hospital all-cause mortality or serious illness, mean age 66.12 ± 15.77, men accounted for 50.4%. The optimal cut-off of NGAL for in-hospital all-cause mortality prognosis is > 399.58 ng/ml, AUC is 0.668 (95% CI 0.58-0.75, p = 0.0163), sensitivity 71.43 %, specificity 66.95 %, positive predictive value 27.8%, negative predictive value 92.9%. Patients were divided into two groups according to their plasma NGAL levels: high level (≥ 400 ng/ml) and low level (< 400 ng/ml). Kaplan-Meier analysis revealed that the high level plasma NGAL group exhibited a worse prognosis than the low level plasma NGAL group in all-cause death/serious illness (Hazard Ratio 2.56; 95%CI 1.35-4.84, P=0.0039.Independent predictors of in-hospital-all-cause-mortality/serious illness were identified using multivariable Cox proportional-hazards regression models with backward-stepwise selection method consisted of two variables: level of NGAL ≥ 400ng/ml, mean blood pressure at admission. *Conclusions:* Plasma NGAL ≥ 400ng/ml and mean blood pressure on admission were independent predictors of in-hospital all-cause mortality/serious illness in patients with AHF or ADHF. The survival probability in hospital of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml,), difference was statistically significant $\chi 2 = 7.99$; p = 0.0047 by Kaplan-Meier curve.

Key words: Neutrophil Gelatinase-Associated Lipocalin (NGAL); Cardio-Renal Syndrome (CRS1) Type 1; biomarkers; in-hospital all-cause mortality prognosis

1. INTRODUCTION

Background

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. The prevalence of cardiorenal syndrome type 1 according 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.

In the CRS type 1, the diagnosis of acute kidney injury is often delayed because of the creatinine and urine output according to KDIGO (Kidney Disease Improving Global Outcomes). 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), a protein of the lipocalin superfamily, is synthesized abundantly in kidney tubules. 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 humans, 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 in-hospital all-cause mortality remains poorly understood.

Study Objectives

We studied the value of plasma NGAL biomarkers with aim to evaluate the in-hospital all-cause mortality prognostic value of NGAL 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 November 2018 to May 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): serum creatinine increased ≥ 0,3mg/dL (≥ 26.5µmol/l) within 48 hours 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 dose steroids; cyclosporin; malignancy

Study design

This research was a prospective cohort study.

Sample size

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

$$n_{sen} = \frac{Z^2_{\alpha} x\ P_{sen} x\ (1-P_{sen})}{w^2 x\ P_{dis}} \quad \text{and} \quad n_{spe} = \frac{Z^2_{\alpha} x\ P_{sp} x\ (1-P_{spe})}{w^2 x\ (1-P_{dis})}$$

where:

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

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

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

P_{spe}: 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_{sen} and n_{spe}

For NGAL, calculate $n_{sen} = 31.9$ and $n_{spe} = 38$

Therefore n ≥ 38 patients. Minimum sample size would be 38 patients

Clinical Evaluation and Biomarker Measurements

All patients were taken their 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 (creatininD3) 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 254 Hoa Hao street, district 10, Ho Chi Minh City, Vietnam. Addition tests: cell blood counts, urea, AST, ALT, electrolytes panel, arterial blood gas were performed at the laborartory department of 115 People Hospital. Electrocardiography, chest X-ray, echocardiography, medications on admission and follow-up during hospital stay: length of hospital stay and in-hospital all-cause mortality. We calculated the estimated glomerular filtration rate by using the 2009 CKD-EPI creatinine formula ($eGFR_{CKDEPI}$).

Statistical Analysis

Data were processed using IBM SPSS Statistics Version 25 software, MedCalc @ version 19.0.5 software. The statistical significance level was 0.05. All hypothesis testing was two-tailed. Categorical variables were presented as counts (percentage) and continuous variables as means ± standard deviation (SD) or median and interquartile range [IQR]with a non-normal distribution. Ccomparison the mean of 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. Calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

Evaluating the correlation between two normal distributed continuous variables by Pearson and Spearman correlations if those not in normal distribution. Survival analysis by using univariate Cox proportional-hazard regression between in-hospital mortality/serious illness and some variables. The variables with 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 in-hospital all-cause mortality were assessed by Kaplan-Meier curves. Comparisons between Kaplan-Meier curves were performed by log-rank test.

The study was performed according to the principles of the Declaration of Helsinki. This study was approved by the ethical committee of Hue University of medicine and Pharmacy. All participants wrote informed consent.

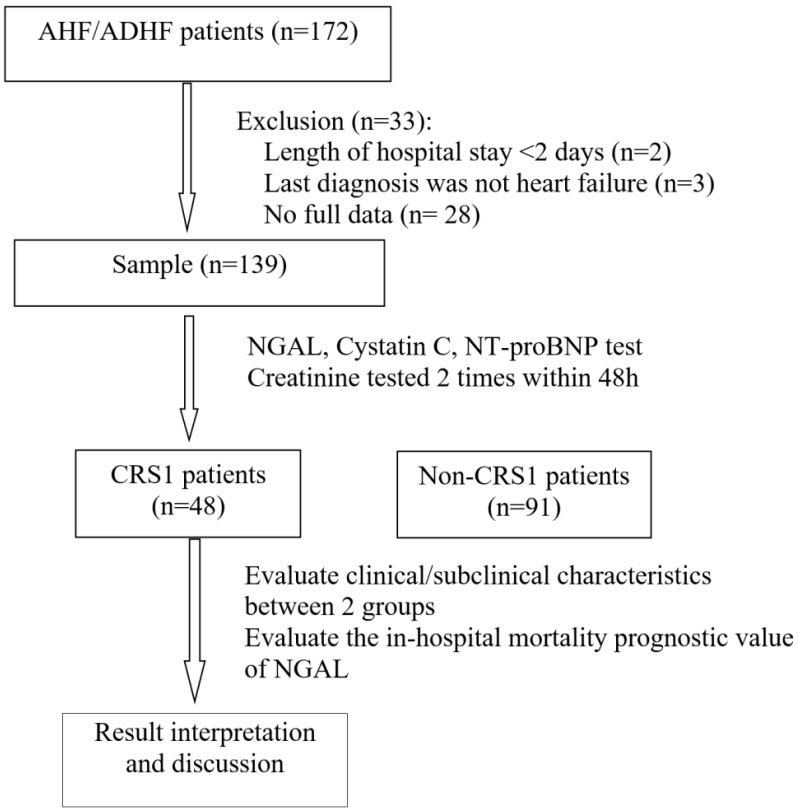

Figure 1 Flow chart for methodology of the study

3. RESULTS

During November 2018 and May 2019, 172 patients were initially diagnosed with AHF or ADHF. 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 inclusion criteria and no exclusion 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). Between the CRS1 group, there were 04 cases without EF evaluation, 01 case without cell blood count; Non-CRS group had 07 cases without evaluation of EF, 01 case without cell blood count.

Demographic and clinical characteristics

Detailed baseline characteristics of the study population were 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 two 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 (43.2%) diagnosed with acute pulmonary edema; 38.8% of cases were diagnosed with ADHF; 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 failure40-49%. 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 creatininD3, NGAL and NT-proBNP in the Non-CRS1group were lower than the CRS1group, 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 noradrenaline. 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 length of hospital stay of the two groups with the median was 9 days, the quartile interval was 7-12 days. Length of hospital stay in the CRS1 group was longer than in the Non-CRS1 group, but this difference was not statistically significant $p > 0.05$. In-hospital all-cause mortality or serious illness was 21 cases, accounting for 15.1%. In-hospital all-cause mortality/serious illness were higher in the CRS1 group compared with the Non-CRS1 group, $p < 0.05$.

Table 1. Baseline 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				
Aterial 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)	0.29
EF mid-range	29 (22.7)	13 (30.2)	16 (18.8)	
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
Urea (mmol/l)###	**9.82 [6.20 – 14.53]**	**12.67 [8.51–19.27]**	**8.09 [5.45–11.67]**	**< 0.01**
Creatinine D1(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**
Creatinine 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
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 all-cause mortality/serious illness	**21 (15.1)**	**12 (25)**	**9 (9.9)**	**0.018**

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; EF reduced < 40%; EF mid-range 40-49%; EF preserved ≥ 50%.
APE: Acute Pulmonary Edema; BP: blood Pressure; MI: Myocardial Infraction; IHD: Ischemic Heart Disease; DCM: Dilated cardiomyopathy
CCRT: Continuous Renal Replacement Therapy. ACEIs: Angiotensionogen Converting Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers. Bold indicated statistically significant. Serious illness: high risk of mortality patients were resusciated but their families asked to be discharged before death in hospital.

The value of plasma NGAL in prognosing in-hospital all-cause mortality or serious illness

The prognostic accuracy of the plasma NGAL was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off of NGAL for in-hospital all-cause mortality prognosis is > 399.58 ng/ml, AUC is 0.668 (95% CI 0.58-0.75, p = 0.0163), sensitivity 71.43 %, specificity 66.95 %, positive predictive value 27.8%, negative predictive value 92.9%. The result was displayed in Table 2 and Figure 2.

Table 2. Cut-off point, sensitivity, specificity, AUC of NGAL prognosing in-hospital all-cause mortality or serious illness.

Variable	Cut-off point	Sensitivity Se (%)	Specificity Sp (%)	Area Under Curve (AUC)	Confident Interval (CI) 95%	P value
NGAL (ng/ml)	>399.68	71.43	66.95	0.67	0.53 -0.80	0.0163

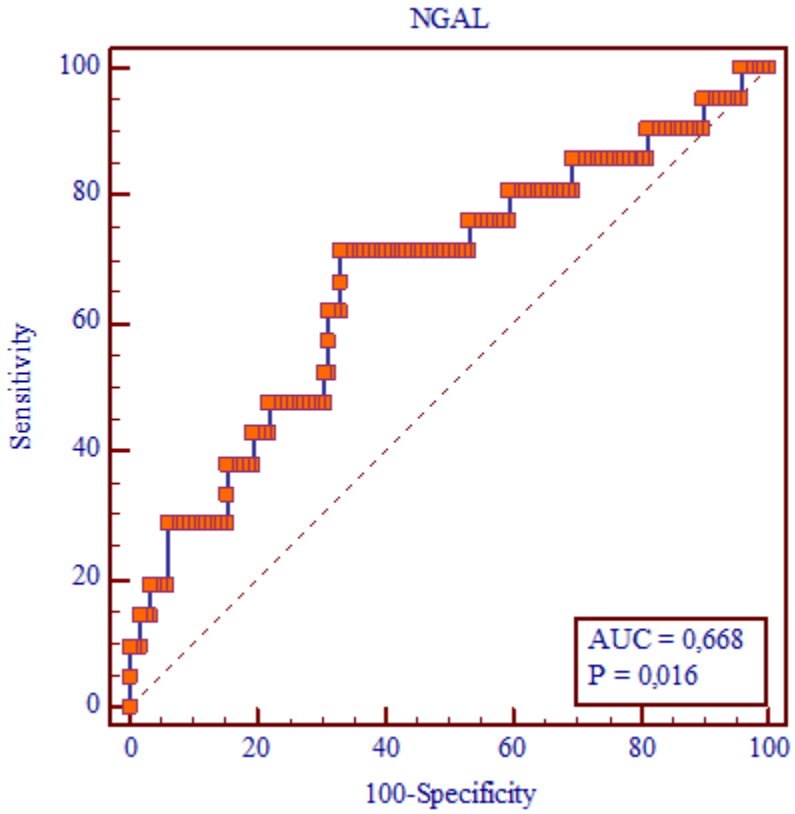

Figure 2. Cut-off point, sensitivity, specificity of plasma NGAL for prognosing in-hospital all-cause mortality/serious illness

The correlation between in-hospital all-cause mortality/serious illness and some factors

To investigate the correlation between in-hospital all-cause mortality/serious illness and several factors, we conducted Pearson correlation analysis if variables was normal distribution and otherwise Spearman rank was used. As a result, there were 7 variables correlating to CRS1 as in Table 3.

TABLE 3. The correlation between in-hospital all-cause mortality/serious illness and some factors

Variables	Coefficients Pearson r or Spearman rho	P value
Age (years)	-0.01	0.89
Sex (Male/Female)	-0.097	0.25
Heart rate (beats/min)	0.025	0.77
Systolic blood pressure (mmHg)	-0.13	0.13
Diastolic blood pressure (mmHg)	**-0.19**	**0.022**
Mean blood pressure (mmHg)	**-0,18**	**0.032**
Hb (g/dl)	0.038	0.66
Urea (mmol/l)	0.14	0.1
Creatinine D1(mg/dl)	0.068	0.43
$eGFR_{CKD-EPID1}$	-0.096	0.26
NGAL (ng/ml)	**0.24**	**0.0046**
NT-proBNP (pg/ml)	**0.21**	**0.013**
Hx Chronic Kidney Disease	-0,018	0.84
Hx Hypertension	0.10	0.73
Hx Diabetes mellitus	0.054	0.53
Hx Heart failure	-0.036	0.67
Atrial fibrillation	0.028	0.74
Mechanical ventilation	**0.28**	**0.0009**
ACEIs/ARBs at admission	**0.19**	**0.023**
CRS1	**0.20**	**0.018**

Bold indicated statistically significant. Hx: history.

Univariable and multivariable Cox regression between in-hospital all-cause mortality/serious illness and some variables

Seven variables correlated with in-hospital all-cause mortality/serious illness were analysed by univariable Cox proportional-hazard regression. The variables with p value < 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 mean blood pressure and NGAL ≥ 400 ng/ml remained the strongest independent predictors of in-hospital all-cause mortality/serious illness (HR 4.55 (1.70-12.17); p=0.0025 and HR 0.97; 95%CI 0.96-0.99; p =0.0209). The result was presented in Table 4.

TABLE 4. Univariable and multivariable Cox proportional-hazard regression between in-hospital all-cause mortality/serious illness and some variables

Univariable Cox proportional-hazard regression				
Predictors	**β**	**SE**	**Hazard Ratio (CI 95%)**	**P value**
Diastolic Blood Pressure	-0.022	0.011	0.98 (0.96-0.99)	0.039*
Mean Blood Pressure	-0.018	0.011	0.98 (0.96-1.00)	0.093
NGAL (ng/ml)	0.0024	0.0012	1.0024 (1.0000-1.0048)	0.051
NGAL ≥ 400 ng/ml	1.62	0.52	5.06 (1.82-14.07)	0.0019*
NT-proBNP (pg/ml)	0.000	0.000	1.00	0.16
Mechanical ventilation	1.024	0.51	2.78 (1.02-7.59)	0.046*
ACEIs/ARBs at admission	0.57	0.54	1.77 (0.61-5.09)	0.29
CRS1	0.74	0.44	2.10 (0.88-7.11)	0.029*
Multivariable Cox proportional-hazard regression				
Predictors	**β**	**SE**	**Hazard Ratio (CI 95%)**	**P value**
Mean Blood Pressure	-0.024	0.011	0.97 (0.96-0.99)	0.0209*
NGAL ≥ 400 ng/ml	1.52	0.50	4.55 (1.70-12.17)	0.0025*

Multivariable analysis included all significant candidate variables (p < 0.1) identified in univariate analysis.
NGAL was dichotomized at the cut-off point 400ng/ml: high level ≥ 400 ng/ml; low level < 400 ng/ml.
* p<0.05

Survival analysis in hospital by using Kaplan-Meier curves

The survival probability in hospital of high level NGAL (≥ 400 ng/ml) group was lower than that of low level NGAL (< 400 ng/ml,), difference was statistically significant $\chi 2 = 7.99$; Logrank test, p = 0.0047. Result was presented in Figure 3 and 4.

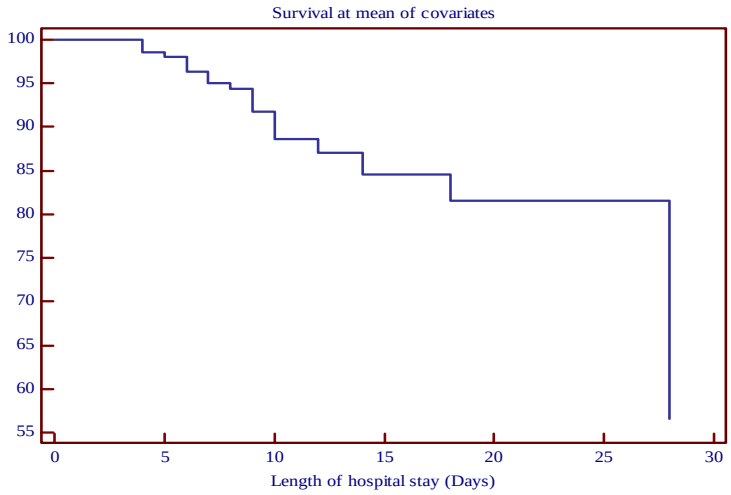

Figure 3. Survival probability from admission to discharge

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 T 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 A et al., (2010) which percentage of women was 43%. The male rate was similar to that of Margarida et al., (2011) was 47.9% by Nakada et al., (Yasuki Nakada, et al., 2017), 59.6% by Alan S. Maisel et al., (2011), 61% ($p > 0.05$); however, the male rate was lower than that of Aghel et al., (2010) 68% ($p < 0.05$).

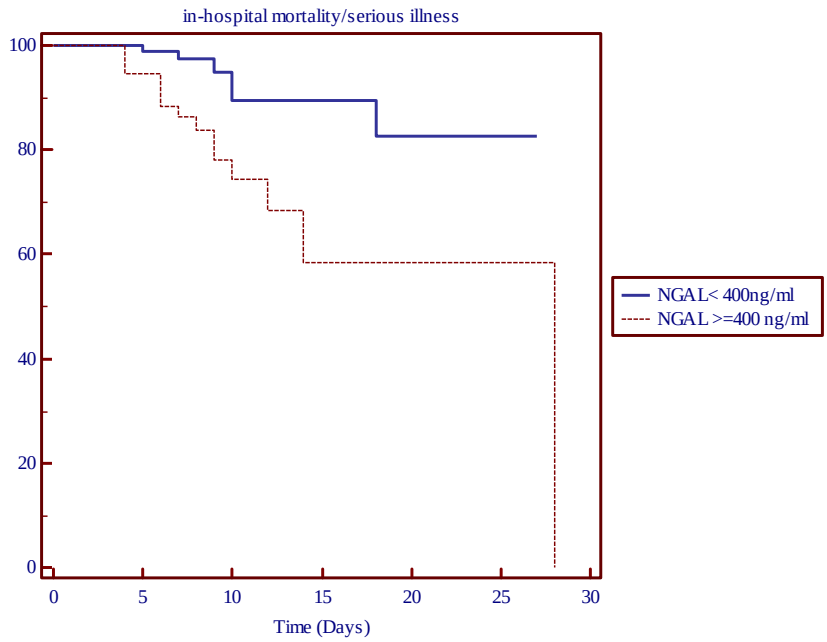

Figure 4. Kaplan-Meier curves for in-hospital all-cause mortality/serious illness between two groups with NGAL

Tachycardia at admission with median was 102 beats/minute and interquartile was [88-114]. This result was higher than the research results of Margarida et al., (2011). Systolic blood pressure 120 [90-140]mmHg, diastolic blood pressure 70 [60-80]mmHg were 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 was 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%) were diagnosed with acute myocardial infarction. There were similarities in vital signs at admission, diagnosis between two groups with CRS1 and Non-CRS1. This was 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, ure 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, $p < 0.001$. Cut-off point for in-hospital all-cause mortality was > 353.23 ng/ml, the area under the AUC curve was 0.732 (95% CI 0.65-0.80, $p < 0.001$), sensitivity 74.47%, specificity 68.48%, positive predictive value 54.7%, negative predicted value 84%.

When entering the variables into a univariate Cox proportional-hazard regression analysis-7 variables predicted in-hospital all-cause mortality/serious illness. During multivariable Cox proportional-hazard regression analysis NGAL ≥ 400 ng/ml and mean blood pressure at admission remained the strongest independent predictors of in-hospital all-cause mortality/serious illness.

The survival probability in hospital of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml,), difference was statistically significant $\chi 2 = 7.99$; $p = 0.0047$ by Kaplan-Meier curves.

Study limitations

There were several limitations to the 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) could 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 kidney condition. Fifth, our sample size was still relatively small and there were some missing data. Sixth, we only evaluate for CRS1 within 48 hours, so we could 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 concentration.

5. CONCLUSION

Plasma NGAL ≥ 400 ng/ml and mean blood pressure at admission were the strongest independent predictors of in-hospital all-cause mortality/serious illness in AHF or ADHF patients. The survival probability in hospital of high level NGAL (≥ 400 ng/ml) groups were lower than that of low level NGAL (<400 ng/ml), difference was statistically significant $\chi^2 = 7.99$; $p = 0.0047$ by Kaplan-Meier curves.

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Author Contributions

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.

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