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Value of plasma Cystatin C in the diagnosis of cardiorenal syndrome type 1

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Abstract---Background: The presence of acute kidney injury in the setting of acute heart failure is very common occurrence and was termed cardiorenal syndrome 1 (CRS1). In CRS1 the diagnosis of acute kidney damage is often delayed by creatinine and urine output following KDIGO standards (Kidney Disease Improving Global Outcomes). Cystatin C is one of the earliest markers of worsening renal function. We studied the value of plasma Cystatin C in the diagnosis of cardiorenal syndrome type 1. Purpose: This study was aimed: (1) to describe clinical, subclinical characteristics, prevalence of CRS1; (2) to evaluate the diagnostic efficacy of Cystatin C in diagnosis of CRS1. Materials and Method: there were 139 patients with acute heart failure or acute decompensated heart failure (ADHF) in the Department of cardiovascular resuscitation and Interventional cardiology at 115 Ho Chi Minh City People's Hospital from September 2018 to June 2019. This research was a prospective cohort study. Results: there were 48 cases (rate 34.5%) with CRS1, medium age 66.12 ± 15.77 , men accounted for 50.4%. The optimal cut-off Cystatin C for diagnosing CRS1 is > 1.81 mg/dl, AUC is 0.787 (95% CI 0.71-0.85, $p < 0.001$), sensitivity 75%, specificity 83.52%, positive predictive value 70.6%, negative predictive value 86.4%. Building the optimal regression model by the BMA (Bayesian Model Average) method with only one variable Cystatin C: Odds Ratio = e^y , while $y = -2.75 + 1.11 \times \text{Cystatin C}$. Moreover, a nomogram with variable Cystatin C was designed to predict the likelihood of CRS1 with AUC 0.842. Ultimately, a confusion matrix was constructed to determine model accuracy 81.82%, sensitivity 78.26%, specificity 100%, positive predictive value 100%, negative predictive value 47.37%. Conclusions: Cystatin C is quite good value in the diagnosis of CRS1 in patients with acute heart failure or ADHF. A predictive model based on Cystatin C may help early diagnose CRS1 in patients with acute heart failure or ADHF.

Keywords---Neutrophil Gelatinase-Associated Lipocalin (NGAL), Cardio-Renal Syndrome (CRS1) Type 1, biomarkers.

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 injury and/or acute renal dysfunction(Claudio Ronco, et al., 2008). The prevalence of cardiorenal syndrome type 1 accordings 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 damage is often delayed because of the creatinine and urine output according to KDIGO (Kidney Disease Improving Global Outcomes). Cystatin C, a 13-kDa non-glycosylated protein, is produced by all nucleated cells (Breidhardt Tobias, et al., 2011). Cystatin C was shown to be a promising biomarker for the early detection of AKI after cardiac surgery (Breidhardt, et al., 2017). However, in AHF or ADHF patients, the diagnostic value of Cystatin C for CRS1 remains poorly understood.

Study Objectives

We aimed to evaluate the diagnostic efficacy of Cystatin C in diagnosis of CRS1 in AHF or ADHF patients.

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 $\geq 0,3\text{mg/dL}$ ($\geq 26.5\mu\text{mol/l}$) 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 was a prospective cohort study

Sample size

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

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

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 needed 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 minimum sample size would be 38 patients

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 (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 laboratory 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 mortality or serious illness. 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 $\pm$ standard deviation (SD) or median and interquartile range [IQR] with a non-normal distribution. Comparison the mean 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 $J = \text{Sensitivity} + \text{Specificity} - 1$. Calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

Evaluating the correlation between two normally distributed continuous variables by Pearson and otherwise Spearman correlations was used. Binary univariate logistic regression analysis between CRS1 and variables. The variables with p value < 0.1 were selected in the multivariate logistic regression model by Wald test with backward-stepwise method to determine predictors.

Optimal regression models were determined by Bayesian Model Average method, the most optimal model was chosen with the smallest BIC (Bayesian Information Criteria) and the highest post probabilities [9]. Forecasting model was built by dividing data into two small data sets: "training set" accounting for 60% of data and "testing set" accounting for 40% of data. Develop a forecasting model in a "training set", then validate the forecasting model on a "testing set" using 10-fold cross-validation to evaluate the model in the "testing set".

Finally, accuracy, sensitivity, specificity, positive predictive value, negative predictive value were calculated by confusion matrix. Forecasting model was represented by: (1) forecasting equation; (2) nomogram; (3) dynamic nomogram posted on the website. 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.

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, $n = 91$). In the CRS1 group, there were 04 cases without EF evaluation, 01 case without cell blood count; Non-CRS1 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 interquartiles 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 medical history of diabetes 36.7%, heart failure 32.6% and chronic kidney disease 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 Hx chronic kidney disease between the two groups, statistically significant $p < 0.05$.

There were 60 cases (43.2%) were diagnosed with acute pulmonary edema; 38.8% were ADHF; 16.5% were cardiogenic shock; 56 patients (40.9%) acute myocardial infarction. There were 65 cases (50.8%) of heart failure with preserved EF $\geq 50\%$; 26.6% heart failure reduced EF $< 40\%$; 22.7% heart failure mid-range EF 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 values 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 the groups. However, the concentration of Urea, CreatininD1 and D3, plasm NGAL and NT-proBNP in the CRS1group were higher than the Non-CRS1group, the differences were statistically significant $p < 0.05$. eGFR by creatinine on first day (eGFR_{CKDEPID1}) and third day (eGFR_{CKDEPID3}) in CRS1group lower than Non-CRS1group, $p < 0.05$.

The majority of patients using furosemide diuretics 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% received noradrenaline. There were 2 patients (1.4%) indicated continuous renal replacement therapy in the CRS1 group, but the differences between two groups were 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 interquartile 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 mortality or serious illness was 21 cases, accounting for 15.1%. In-hospital mortality/serious illness were higher in the CRS1 group compared with the Non-CRS1 group, $p < 0.05$.

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*	23.44 [21.56 - 25.05]	24.29 [22.5 - 26.0]	23.44[21.33 - 25.55]	0.037

(kg/m ²)	25.05]	25.82]	24.38]	
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	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				
Cardiogenic shock	60 (43.2)	15 (31.3)	45 (49.5)	} 0.11
ADHF	23 (16.5)	9 (18.8)	14 (15.4)	
Others	54 (38.8)	24 (50)	30 (32.9)	
Acute MI	2 (1.4)	0 (0)	2 (2.2)	
Laboratory values	56 (40.9)	18 (37.5)	38 (41.8)	0.66
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#	7.84 [5.50 -10.71]	8.5 [5.37 -11.96]	7.73 [5.50-10.32]	0.39
(K/ μ L)	11.60 [9.98 – 13.53]	10.8 [9.13 – 13.38]	12.15 [10.4-13.60]	0.087
Hb (g/dl)#	47.49 [28.98-104.83]	48.2 [30.2-106.33]	46.9 [28.58-104.83]	0.41
AST (UI/l)##	33.11[17.78-85.64]	28.02 [18.08-69.20]		0.94
ALT (UI/l)##	12.67 [8.51-19.27]	8.09 [5.45-11.67]		< 0.01
Ure (mmol/l)###	29.7 [17.86-79.04]	2.44 [1.47-4.09]	1.08 [0.83-1.47]	< 0.01
CreatininD1(mg/dl)	9.82 [6.20 – 14.53]	22 [13– 44]	64 [38.25-84.05]	< 0.01
eGFR _{CKD-EPID1}	1.31 [0.99 – 2.24]	2.84 [1.38-4.8]	1.07 [0.8 -1.44]	< 0.01
Creatinin D3	47 [23 – 75.75]	19.5 [11 – 47.5]	67 [38-86.50]	< 0.01
eGFR _{CKD-EPID3}	1.29 [0.87- 2.32]	136.8 [130.55-138.8]	138.4[135.03-141.05]	0.49
Na ⁺ (mmol/l)	50 [23.25 – 79]	4.15 [3.58-4.59]	3.96 [3.52-4.44]	<
	137.4 [133.48-140.48]	511.63 [338.27-	262.59[193.07-	0.001

K ⁺ (mmol/l)	4.05 [3.54-4.49]	587.94]	401.11]	0.005
NGAL (ng/ml)	327.13 [205.38-	20131[6350-	6378[2935.25-	0.79
NT-proBNP	516.76]	35000]	17177.50]	0.08
(pg/ml)	8814 [3860-26419]	6575.08	5941.86 ± 13080.16	0.25
Troponin I ^{\$}	6156.18±13176.59	±13505.34	7.42 ± 0.079	0.67
(pg/ml)	7.40 ± 0.087	7.39 ± 0.099	22.6 [19.1-25.98]	0.77
pH ^{\$\$}	21.8 [17.85-24.98]	20.03 [16.4-23.7]	35 [29.98-39.48]	
HCO ₃ ^{\$\$\$} (mmol/l)	35 [29.08-40.03]	35 [27.85-40.95]	77 [62.75-111]	
pCO ₂ ^{\$\$\$} (mmHg)	76 [61.75-111]	75 [60-110.5]		
pO ₂ ^{\$\$\$} (mmHg)				
Therapy at admission				
Furosemide				
Furosemide dose (mg)	108 (77.7)	36 (75)	72 (79.1)	0.58
ACEIs/ARBs use	40 (20-40)	40 (20-40)	40 (20-40)	0.50
Beta blockers	14 (10.1)	4 (8.3)	10 (10.98)	0.62
Dobutamin	1 (0.7)	0 (0)	1 (1.1)	0.66
Dopamin	19 (13.8)	7 (14.6)	12 (13.2)	0.84
Noradrenaline	7 (5)	3 (6.3)	4 (4.4)	0.64
Nitrates	26 (18.7)	9 (18.8)	17 (18.7)	0.99
Conventional oxygen	85 (61.2)	28 (58.3)	57 (62.6)	0.62
Ventilation	110 (79.1)	41(85.4)	69 (75.8)	0.19
Invasive Mechanicalventilation	12 (8.6)	5 (10.4)	7 (7.7)	0.59
CRRT	13 (9.4)	5 (10.4)	8 (8.8)	0.75
Length of Hospital stay (days)	2 (1.4)	2 (4.2)	0 (0)	0.051
In-hospital mortality/serious illness				
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

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: Continous Renal Replacement Therapy. ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; 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 diagnosing CRS1

The diagnostic accuracy of the NGAL was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off point of NGAL to diagnose CRS1 was > 353.23 ng/ml, the area under the AUC curve is 0.732 (95% CI 0.65-0.80, p<0.001), sensitivity 74.47%, specificity 68.48%, positive predictive value 54.7%, negative predictive value 84%. The result was displayed in **Table 2** and **Figure 1**.

Table 2
Cut-off point, sensitivity, specificity, AUC of NGAL diagnosing CRS1

Variable	Cut-off point	Sensitivity Se (%)	Specificity Sp (%)	Area Under Curve (AUC)	Confident Interval (CI) 95%	P value
NGAL (ng/ml)	> 353.23	74.47	68.48	0.73	0.65 - 0.80	< 0.001

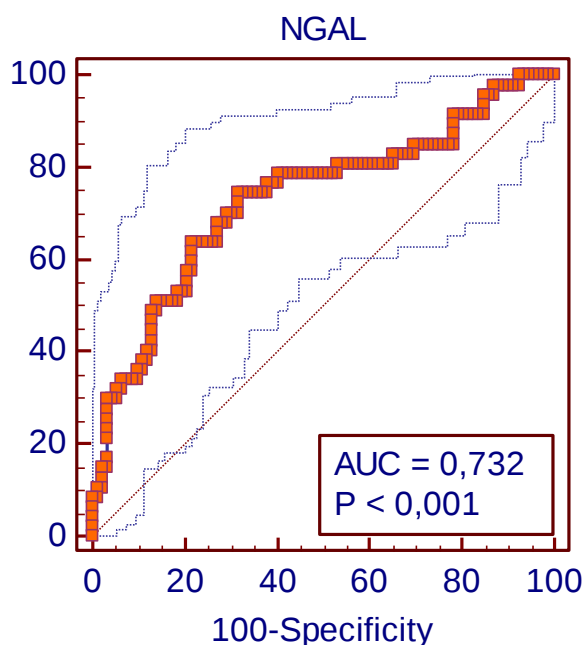


Figure 1. Cut-off point, sensitivity, specificity of plasma NGAL on first day for diagnosing CRS1

The correlation between CRS1 and some factors

To investigate the correlation between CRS1 and several factors, we conducted Pearson correlation analysis if variables was normal distribution and otherwise Spearman rank was used. As a result, there were six variables correlating to CRS1 as in Table 3.

Table 3
The correlation between CRS1 and some variables

Variables	Coefficients Pearson r or Spearman rho	P value
Age (years)	-0.11	0.20
Sex (Male/Female)	-0.01	0.91
Heart rate (beats/min)	-0.09	0.29
Systolic blood pressure (mmHg)	-0.032	0.71
Diastolic blood pressure (mmHg)	0.14	0.11
Mean blood pressure (mmHg)	0.004	0.96

Hb (g/dl)	-0.13	0.14
Ure (mmol/l)	0.32	< 0.001
CreatininD1(mg/dl)	0.38	< 0.001
eGFR _{CKDEPID1}	-0.48	< 0.001
NGAL (ng/ml)	0.40	< 0.001
NT-proBNP (pg/ml)	0.22	0.01
Hx Chronic Kidney Disease	0.19	0.025
Hx Hypertension	0.10	0.23
Hx Diabetes mellitus	0.087	0.31
Hx Heart failure	0.022	0.79
Atrial fibrillation	-0.03	0.71

Bold indicated statistically significant. Hx: history

Univariable and multivariable logistic regression between CRS1 and some variables

Six variables correlated with CRS1 were analysed by univariable logistic regression. The variables with p value < 0.1 were selected in the multivariate logistic regression model by Wald test with backward-stepwise method. During multivariable regression analysis eGFR_{CKDEPID1} remained the strongest independent predictor of CRS1 (OR 0.96; 95%CI 0.94-0.98;p < 0.001). Plasma NGAL failed to predict the occurrence of early CRS1. The result was showed in Table 4.

Table 4.
Univariable and multivariable logistic regression between CRS1 and some variables

Univariable logistic regression				
Predictors	β	SE	Odds Ratio (CI 95%)	P value
Ure (mmol/l)	0.10	0.031	1.11 (1.04-1.18)	0.001*
Creatinin D1(mg/dl)	0.63	0.16	1.87 (1.38-2.54)	< 0.001*
eGFR _{CKD-EPI D1}	-0.045	0.009	0.96 (0.94-0.97)	< 0.001*
NGAL (ng/ml)	0.005	0.001	1.005 (1.0029-1.0074)	< 0.001*
NT-proBNP (pg/ml)	0.000	0.000	1.00	0.016*
Hx CKD	1.034	0.47	2.81 (1.11-7.11)	0.029*
Multivariable logistic regression				
Predictors	β	SE	Odds Ratio (CI 95%)	P value
eGFR _{CKDEPI}	-0.045	0.009	0.96 (0.94-0.98)	< 0.001*

Multivariable analysis included all significant candidate variables (p < 0.1) identified in univariate analysis.

p < 0.05

The optimal multivariate model for correlation between CRS1 and some factors by BMA (Bayesian Model Average) method

According to modern statistical theory, in order to find the optimal model of correlation between CRS1 and some factors, we used the BMA model (Adrian E. Raftery, 1995) using R software to process. Variables likely to predict CRS1 included creatininD1, $eGFR_{CKDEPI}$, Ure, NT-proBNP, NGAL, history of chronic kidney disease, were entered in the regression equation for processing. Because $eGFR_{CKDEPI}$ was calculated by creatinin, we did not enter simultaneously these two variables in regression equation because of according to regression theory: variables must be independent in the multivariate regression equation. The results selected four most optimal models with cumulative posterior probability = 1 (Figure 2) if without $eGFR_{CKDEPI}$ and one model only contained $eGFR_{CKDEPI}$ if with $eGFR_{CKDEPI}$.

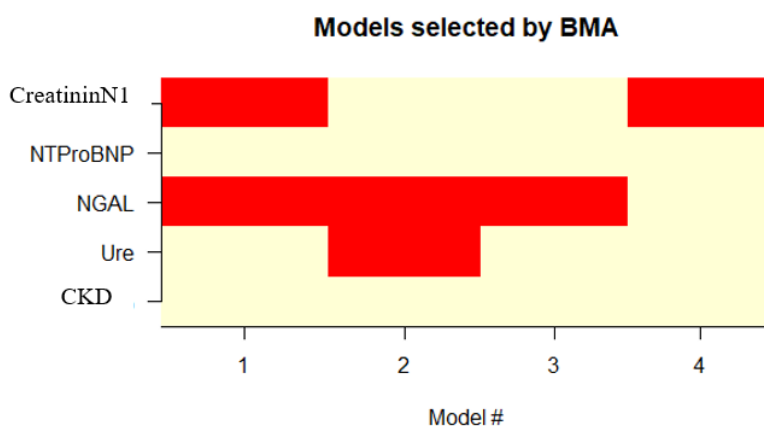


Figure 2. Models were selected by BMA method

Based on the results of selecting the optimal regression models according to BMA method, there are four models in which model 1 with the smallest BIC ($-4.97e^{+02} = -36.72$) and highest post prob ($0.274 = 27.4\%$) was considered the most optimal model with 2 variables: CreatininD1 and plasma NGAL correlation with CRS1.

Building forecasting model for CRS1 with NGAL and creatininD1

Building forecasting model by dividing data into two small data sets: training set accounting for 60% of data and testing set accounting for 40% of data. Developing a forecasting model in a "training set":

Odds ratio = e^y , where $y = -2.39 + 0.0037 \times NGAL + 0.17 \times CreatininD1$

Then validate the forecasting model on a "testing set" using 10-fold cross-validation to evaluate the model in the "testing set" by methods with accuracy 79.82%, kappa=0.54; AUC = 0.79; accuracy: 75.93%; sensitivity: 76.74%; specificity: 72.73%; positive predictive value: 91.67%; negative predictive value: 44.44% indicated by confusion matrix in Table 5.

Table 5
Confusion matrix in model predicting CRS1

Predicted outcome	Not present	Present
Predicted CRS1 ⁻	33 (true negative)	3
Predicted CRS1 ⁺	10	8 (true positive)

Nomogram in predicting CRS1 with 2 variables NGAL và creatininD1 (Figure 3)

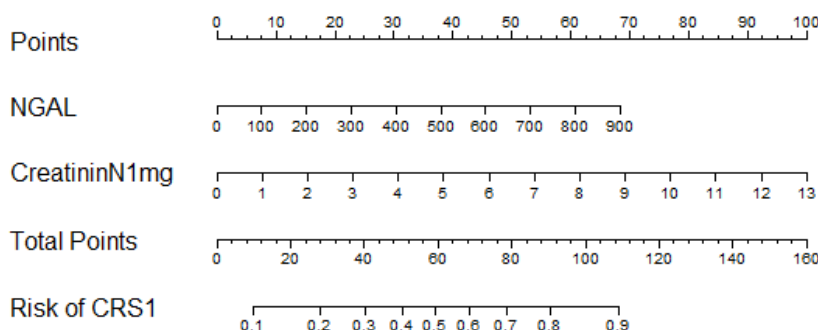


Figure 3. Nomogram in predicting CRS1 of plasma NGAL on first day and creatininD1

Clinical application of the nomogram with plasma NGAL and creatininD1

Take 2 cases to illustrate the application of nomogram in predicting CRS1:

First case had a creatinine concentration of 4.59 mg/dl on the first day corresponding to 35 points and the plasma NGAL concentration on day 1 was 631.71 ng/ml corresponding to 47 points. The total score was $35 + 47 = 82$ points, the probability of having CRS1 is more than 70%. In fact, this patient was diagnosed CRS1.

The second case had a creatinine concentration of 0.87 mg/dl on the first day corresponding to 5 points and the plasma NGAL concentration on day 1 was 222.25 ng/ml corresponding to 7 points. The total score was $5 + 7 = 12$ points, the probability of developing CRS1 was less than 10%. The risk of CRS1 is very low. In fact, this patient did not suffer from CRS1.

Discussion

The mean age of patients 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 Breidhardt T et al (Breidhardt 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 A et al (César A Belziti, et al., 2010) which percentage of women 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%) were 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, 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 ± 4.3 mEq/l; $eGFR$ 45.9 ± 24.3 ml/min/1.73m² (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 diagnosing CRS1 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%. The plasma NGAL concentration and cut-off point for the diagnosis of CRS1 in our study was higher than that of the author Margarida et al (Margarida Alvelos, 2011) in the CRS1 group which was 212 [189- 307] ng/ml and in the Non-CRS1 group was 83 [60-136] ng/ml with a cut-off point > 170 ng/ml. This can be explained by the different NGAL test kit, so the results would be different.

When entering the variables into a univariate logistic regression analysis 6 variables predicted the occurrence of early CRS1. During multivariable regression analysis $eGFR_{CKDEPID1}$ remained the strongest independent predictor of CRS1. Plasma NGAL failed to predict the occurrence of early CRS1. In case of without $eGFR_{CKD-EPID1}$, there were two variable (creatininD1 and NGAL) independently predicted of CRS1.

We built a predictive model for CRS1 with two variables plasma NGAL and creatinineD1 by the equation: Odds Ratio e^y , where: $y = - 2.39 + 0.0037 \times NGAL + 0.17 \times CreatininD1$ and nomogram as shown in **Figure 3**. With the plasma NGAL concentration on the 1st day, we will have the corresponding score and creatinineD1 concentration will have the corresponding score and the total score will correspond to the risk of CRS1. This result was different from the research

results of the author Zeyuan Fan et al nomogram including 6 variables: age, diabetes mellitus, hsCRP, eGFR, NYHA and urine albumin/creatinine ratio(Zeyuan Fan, et al., 2018). The reason for this difference is that in our research, when building the optimal regression model, only two variables NGAL and creatinine were the best models.

Limitations

There are some 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) 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 kidney condition. 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 concentration.

Conclusion

Plasma NGAL was valuable for the diagnosis of CRS1 with a cut-off point > 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 predictive value 84%. Predictive model of CRS1 including 2 variables plasma NGAL and creatinineD1 had accuracy: 75.93%, sensitivity: 76.74%, specificity: 72.73%, positive predictive value: 91.67%, negative predictive value: 44.44%.

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

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