Mortality prognosis of NGAL, NTproBNP, hsTnT, and GRACE score in patients with acute coronary syndrome

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ABSTRACT

Background: NGAL serum concentration have predictive value for cardiovascular events and mortality in patients with acute coronary syndrome (ACS).

Objectives: Assessed the all-cause mortarlity prognosis value of serum neutrophil gelatinase-associated lipocalin (NGAL), combination with N-terminal pro B-type natriuretic peptide (NT-proBNP), and hsTnT, and GRACE score in patients with ACS.

Materials and methods: We conducted a cross-sectional analysis study used in this study in 58 patients with ACS. Serum NGAL, NT-proBNP, hs-TnT concentration and GRACE score associated with death events (after 3 months of follow-up) were assessed by receiver operating characteristic (ROC) curve.

Results: High performance in predicting mortality of NGAL with a cut-off value of 154.55 ng/mL (AUC, 95% CI = 0.96, 0.90 – 1.0; p = 0.001), GRACE score with 140.50 scores (AUC, 95% CI = 0.76, 0.57 – 0.96; p = 0.051). Combination of NTproBNP plus NGAL indicated with the highest value (AUC, 95% CI = 0.96, 0.91 – 1.0; Se = 80.0; Sp = 92.5; p = 0.001). The relative risk assessment indicated a high value in mortality prediction of NGAL with a cut-off value of 154.55 (OR, 95% CI = 49.0, 4.3 – 549.2; p < 0.001), and GRACE score with 140.50 scores (OR, 95% CI = 11.1, 1.1 – 108.4; p = 0.013).

Conclusion: NGAL can be employed as a biomarker for the early prediction of mortality events in individuals with ACS. The combination of NGAL, NT-proBNP, hsTnT, and GRACE score showed the higher outcome but not worth mentioning.

1. Introduction

Acute coronary syndrome (ACS) was responsible for up to 4,800 patient deaths in the 2020 Europe report, and the prevalence increased with age [1]. There were 30% of patients with CAD died in the first month, and half of them died before reaching the hospital. Of those still alive, 1 in every 25 patients will die within the next year, and elderly patients have a four times higher risk of mortality [2]. Therefore, a variable for the prognosis of mortality in ACS is required for better treatment outcomes. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein found in mature neutrophil granules. Endothelial dysfunction, inflammation, and intercellular substance degradation all contribute to the development of atherosclerosis, resulting in the instability of atherosclerotic plaques. Serum NGAL concentrations rise dramatically in the presence of coronary artery disease, and blood NGAL levels are significantly greater in individuals with ACS compared to those with stable coronary artery disease. High blood NGAL levels were found in groups of patients with ACS who had cardiovascular events such as cardiogenic shock, pulmonary edema, new left bundle branch block, and statistically substantially more fatalities than the low blood NGAL group [3-5]. NGAL concentrations were greater in individuals with coronary artery disease than in people without coronary artery disease [6,7].

Although NGAL serum concentration have been researched across the world and in certain regions in Vietnam to have predictive value for cardiovascular events and mortality in patients with acute coronary syndrome, these studies are scarce and individual for each biomarker. In addition, clinical scale for prognosis of major adverse cardiovascular

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events (MACE) and mortarlity such as CHA_2DS_2-VASc-HS score and Framingham risk scores [8-10]. However, the GRACE score had a high value in mortality prognosis in ACS patients, but few studies in Vietnam assessed the combination with other variables. We conducted the study to assess the all-cause mortarlity prognosis value of serum NGAL, combination with N-terminal pro B-type natriuretic peptide (NT-proBNP), and high sensitivity troponin T (hsTnT), and The Global Registry of Acute Coronary Events (GRACE) score in patients with ACS.

2. Materials and methods

2.1. Study design and population

We conducted a cross-sectional analysis study used in this study in 58 patients with ACS at Can Tho University of Medicine and Pharmacy Hospital's Department of Interventional Cardiology – Neurology from March 2021 to May 2022.

Including criteria: All patients with ACS were selected for the study, including 3 clinical forms [11]: (1) Unstable angina; (2) Acute myocardial infarction without ST elevation; (3) Acute ST-segment elevation myocardial infarction.

Excluding criteria: (1) Medical history of previous surgery within 6 months and cerebral infarction or transient ischemic attack within 1 year; (2) Acute kidney injury (serum creatinine increase > 0.3mg/dl for 2 consecutive days or serum creatinine increase >50% within 7 days or oliguria); (3) chronic kidney disease stage 4 or higher; (4) Heart failure; (5) Cancer.

2.2. Sample size

The sample size was calculated based on the Cochran formula $n = z_{1-\frac{\alpha}{2}}^2 \frac{P(1-P)}{d^2}$. With $\alpha = 0.05$, d = 0.09, and p = 0.87 which was the rate of increased area under the curve (AUC) of NT-proBNP concentration in the patients with ACS when used as a predictive value for HF events according to the findings of Helanova et al. [5]. We calculated the sample size was 54 participants. In this study, we recruited 58 patients.

2.3. Data collection

Participants' sociodemographic and associated clinical data were collected, including age, sex, body mass index (BMI), smoke (harmful if quit at least 5 years [12]). Comorbidity including hypertension (based on ESC/ESH 2018, hypertension when systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg at least 2 measurements or using antihypertensive [13]), type 2 diabetes mellitus (T2DM) (according to American Diabetes Association (ADA) recommendations 2020 [14]). Biochemical tests collecting venous blood include: low-density lipoprotein cholesterol (LDL-c), triglycerides, NGAL, NT-proBNP, highsensitivity troponin T (hs-TnT). Patients with ACS within 24 hours of admission will have a blood sample of about 2mL placed in a standard sampling tube (test tube must contain anticoagulant) and sent for testing.

Quantification of serum NGAL concentrations was conducted within 24 hours of hospitalization by sandwich Enzyme-linked Immunosorbent assay (ELISA) method. Analysis on a 4-tray automatic Immunomat machine from Germany can quantify NGAL blood concentrations from 25 ng/mL to 3000 ng/mL. This was an ELISA test performed on microwells containing monoclonal antibodies to human NGAL. NGAL was detected with a horseradish peroxidase (HRP)-linked monoclonal antibody and the assay was continued by incubation with a chromogenic substrate. This was a rapid test consisting of 2 steps as follows: Step 1: The sample is diluted and then incubated with antibodies that detect HRP binding in microwells. Only NGAL is attached, other components are removed; Step 2: Peroxidase chromogenic substrate containing tetramethylbenzidine (TMB) is added to each test well, the reaction will produce a colored product and the color intensity will be read at 450nm with an ELISA reader. The color intensity will indicate the NGAL concentration in each well. The results will be compared with the control sample. Echocardiograms were conducted for complication assessment. Death and complication events were assessed after 3 months of follow-up in ACS patients (Figure 1).

2.4. Statistical analysis

Data were analyzed using SPSS version 25.0, qualitative variables are presented as frequency (percentage), mean (±standard deviation, SD) for quantitative variables with normal distribution, and median (interquartile range, IQR) for quantitative variables with non-normal distribution. The normal distribution of the variable was checked using the skewness and kurtosis values (p > 0.05). The difference between qualitative variables described by the Chi-squared test, sample t-test or ANOVA for normally distibution variables, Mann-Whitney test or Kruskal-Wallis test for non-normally distibution variables, p < 0.05 considered to be statistically significant. The specificity (Sp), sensitivity (Se), threshold values, and area under the curve (AUC) of NGAL, GRACE, NT-proBNP, and hs-TnT associated with death events (after 3 months of follow-up) were assessed by receiver operating characteristic (ROC) curve. The relative risk was assessed by OR with a cut-off threshold based on the ROC curve. Model 1 of the relative risk analysis was assessed with one variable predicting mortality. Model 2 was assessed with a combination of variables with coefficient 1.

2.5. Ethical approval

All patients were informed of the aims and methodology of the study and gave written consent before taking part. Patients were advised that they could withdraw from the study at any stage without impacting their treatment. The study was approved by the Ethics Committee in Biomedical Research of Can Tho University of Medicine and Pharmacy.

3. Results

The sociodemographic, associated clinical, and clinical characteristics of the study population are presented in Table 1. Of the 58 patients, the mean age was 67.48 ± 11.63 years and 48.3% of the sample were men. The mean BMI was 22.68 ± 3.29 kg/m². The proportion of patients with dyspnea accounted for 43.5%, chest pain 98.3%, ST-segment elevation myocardial infarction 36.2%, non-ST-segment elevation myocardial infarction 46.6%, and unstable angina 17.2%.

High performance in predicting mortality of NGAL with a cut-off value of 154.55 ng/mL (AUC, 95% CI = 0.96, 0.90 – 1.0; Se = 80.0; sp = 92.5; p = 0.001), NT-proBNP with 10.02 ng/mL (AUC, 95% CI = 0.92, 0.82 – 1.0; Se = 80.0; Sp = 90.6; p = 0.002), hsTnT with 2.14 ng/mL (AUC, 95% CI = 0.91, 0.84 – 0.99; Se = 80.0; Sp = 86.8; p = 0.002), GRACE score with 140.50 scores (AUC, 95% CI = 0.76, 0.57 – 0.96; Se = 80.0; Sp = 73.6; p = 0.051) as shown in Table 2.

Combination analysis of multivariate with coefficient 1 showed better mortality prediction value. Combination of NTproBNP plus NGAL indicated with the highest value (AUC, 95% CI = 0.96, 0.91 – 1.0; Se = 80.0; Sp = 92.5; p = 0.001) (Figure 2).

The relative risk assessment shown in Table 3, with the cut-off value based on the ROC curve, indicated a high value in mortality prediction of NGAL with a cut-off value of 154.55 (OR, 95% CI = 49.0, 4.3 – 549.2; p < 0.001), NT-proBNP with 10.02 ng/mL (OR, 95% CI = 26.3, 2.5 – 270.5; p < 0.001), hsTnT with 2.14 ng/mL (OR, 95% CI = 38.4, 3.6 – 413.7; p < 0.001), and GRACE score with 140.50 scores (OR, 95% CI = 11.1, 1.1 – 108.4; p = 0.013).

According to the findings in Table 4, the following covariates were shown to be statistically significantly linked with all-cause mortality in the multivariable logistic regression model: EF, NGAL, and NT-proBNP.
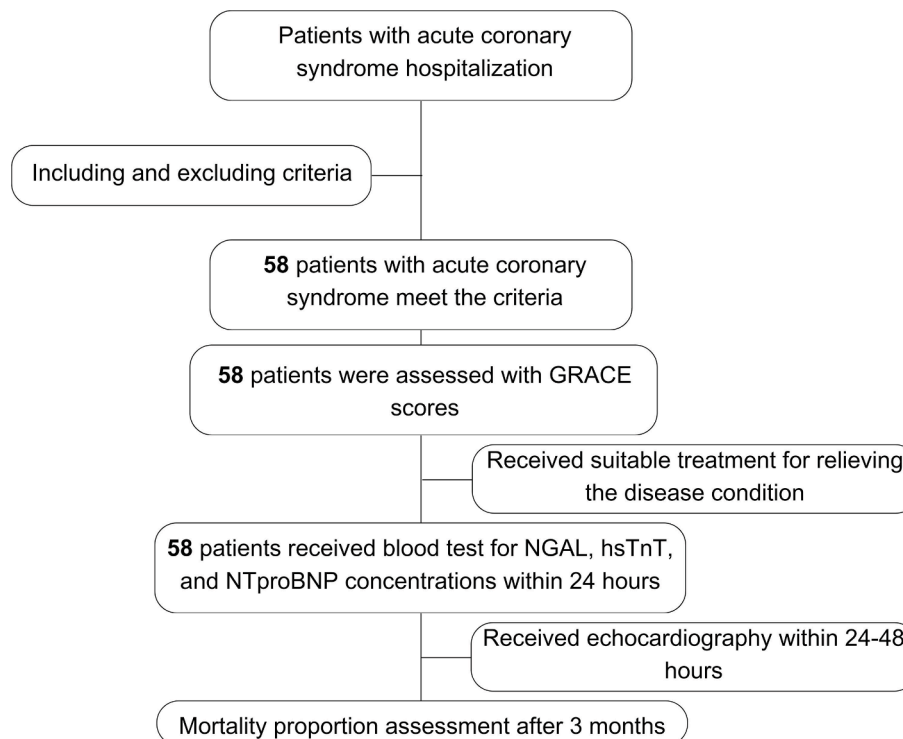
Fig. 1. Participants flow of the study.

Table 1
Sociodemographic, associated clinical, and clinical characteristics of the participants

Characteristics		Total n = 58
Baseline characteristics		
Male, n (%)		28 (48.3)
Age (year), mean ± SD		67.48 ± 11.63
BMI (Kg/m^2)		22.68 ± 3.29
Smoke, n (%)		24 (41.4)
HfrEF (%)		6 (10.3)
Dyspnea (%)		23 (43.5)
Chest pain (%)		57 (98.3)
Hypertesion (%)		41 (70.7)
Dyslipidemia (%)		46 (79.3)
Type-2 diabetes (%)		14 (24.1)
ACS type (%)	ST-segment elevation MI	21 (36.2)
	Non-ST-segment elevation MI	27 (46.6)
	Unstable angina	10 (17.2)
Incident events (%)	Overal	13 (22.4)
	Death	5 (8.6)
	Recurrent MI	5 (8.6)
	HF	6 (10.3)
Biochemical test		
Systolic blood pressure (mmHg), median (IQR)		130.00 (120 – 140)
BMI (kg/m^2), mean ± SD		22.68 ± 0.43
NGAL (ng/mL), median (IQR)		12.39 (0.71 – 42.07)
hs-TnT (ng/mL), median (IQR)		0.51 (0.16 – 1.83)
NT-proBNP (pg/mL), median (IQR)		1249.00 (324.50 – 7973.50)
hsCRP (mg/L)		7.8 (2.27 – 14.05)

ACS: Acute coronary syndrome; BMI: Body mass index, hsCRP: high-sensitivity C-reactive protein, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, HF: Heart failure, HFrEF: Heart failure with reduce ejection fraction, EF: Ejection fraction, MI: Myocardial infarction, SD: Standard deviation, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment eleva-tion myocardial infarction, IQR: Interquartile range.

Table 2
Sensitivity and specificity of NGAL and NT-proBNP values with GRACE score in predicting mortality.

	Cut off	AUC (CI 95%)	Sensitivity (%)	Specificity (%)	p
Model 1					
NGAL (ng/mL)	154.55	0.96 (0.90 – 1.0)	80.0	92.5	0.001
NT-proBNP (ng/mL)	10.02	0.92 (0.82 – 1.0)	80.0	90.6	0.002
hsTnT (ng/mL)	2.14	0.91 (0.84 – 0.99)	80.0	86.8	0.002
hsCRP (ng/mL)	12650	84.5 (73.5 – 95.6)	80.0	79.6	0.011
GRACE score	140.50	0.76 (0.57 – 0.96)	80.0	73.6	0.051
Model 2					
NTproBNP + NGAL	160.68	0.96 (0.91 – 1.0)	80.0	92.5	0.001
GRACE + NGAL	260.05	0.95 (0.88 – 1.0)	80.0	90.6	0.001
hsTnT + NGAL	156.97	0.96 (0.90 – 1.0)	80.0	92.5	0.001
hsCRP + NGAL	12693	85.3 (74.7 – 95.9)	80.0	75.5	0.010
NTproBNP + NGAL + hsTnT + GRACE	277.63	0.95 (0.89 – 1.0)	80.0	90.6	0.001

AUC: Area under the curve, CI: Confidence interval, hsCRP: high-sensitivity C-reactive protein, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, GRACE: Global Registry of Acute Coronary Event
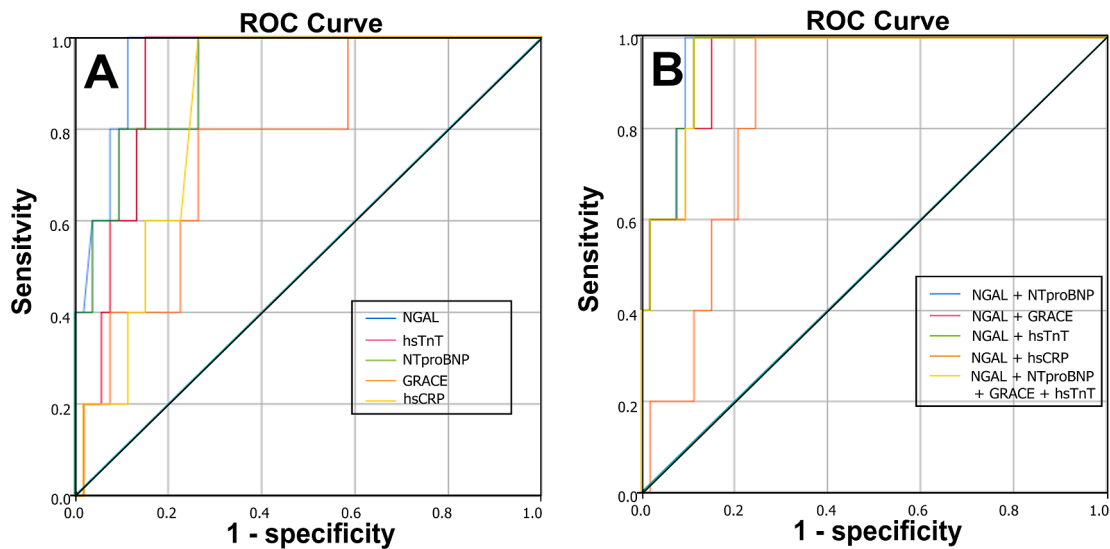
Fig. 2. Receiver operating characteristic (ROC) curve showed the mortality predictive performance of (A) Model 1 and (B) Model 2. hsCRP: high-sensitivity C-reactive protein, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, GRACE: Global Registry of Acute Coronary Event.

Table 3
The relative risk assessment of serum NGAL, NT-proBNP, hsTnT, GRACE score with mortality events

		Mortarlity		OR (95% CI)	p
		Yes (n=5) (%)	No (n=53) (%)		
NGAL (ng/mL)	High	80.0	7.5	49.0 (4.3 – 549.2)	< 0.001
	Low	20.0	92.5		
hsTnT	High	80.0	13.2	26.3 (2.5 – 270.5)	< 0.001
	Low	20.0	86.8		
NTproBNP	High	80.0	9.4	38.4 (3.6 – 413.7)	< 0.001
	Low	20.0	90.6		
GRACE score	High	80.0	26.4	11.1 (1.1 – 108.4)	0.013
	Low	20.0	73.6		

NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, GRACE: Global Registry of Acute Coronary Event, OR: Odd Ratio.

Table 4
Multivariable logistic regression model of clinical, paraclinical, and mortality events within 3 months

	Beta	**p**
EF (%)	2.4	0.02
eGFR	0.034	0.8
NGAL (ng/dL)	0.6	<0.0001
NT-proBNP (pg/mL)	0.4	0.001

eGFR: estimated glomerular filtration rate, NGAL: Neutrophil gelatinase-associated lipocalin, NT-proBNP: N-terminal pro B-type natriuretic peptide.

4. Discussion

Our study showed the proportion of female patients was 51.7%, and the mean age was 67.48 ± 11.63. The patient's baseline characteristics were mostly similar in mean age, and difference in sex proportion [5,6,15-18]. Sex proportion was major sex was male from the study of Adnan Burak Akcay (2016) [6], Katerina Helanova (2015) [5], Peng-Ju Lu (2020) [15], David Zahler (2022) [16], Ahmet Avci (2020) [17], and Alan S. Maisel (2011) [18]. Medical history of hypertension (70.7%); smoking (41.4%); lipid abnormalities (79.3%); and type 2 diabetes

(24.1%). Medical history was similar compared with other studies with a high prevalence of T2DM, hypertension, and dyslipidemia [5,6,15-18].

Model 1 analysis showed a high ability to predict the mortality of variables with AUC > 90% for NGAL, NT-proBNP, and hsTnT (p ≤ 0.002) and higher than GRACE score with AUC = 0.76 (p > 0.05) (Table 2, Figure 2). Model 2 showed the combination of NGAL and NT-proBNP had the highest value in ACS mortality prognosis (AUC = 0.96; 95% CI: 0.91 - 1.0; p = 0.001), followed by the combination of hsTnT and NGAL. GRACE score in the combination model showed a higher value in ACS mortality prognosis (Table 2). Study of David Zahler (2022) [16] found a higher rate of deaths in the group with a high concentration of NGAL (p = 0.04). Katerina Helanova (2015) [5] study on 673 STEMI patients showed a high prognosis value of 1-year mortarlity of NGAL (≥ 84.0 pg/mL) and BNP (≥ 150.2 pg/mL) with AUC, 95% CI = 75.5, 67.3 - 83.8 (p < 0.001); and 78.7, 68.7 - 88.8 (p < 0.001); respectively. The combination of variables also showed similar results with our study, NGAL combined with BNP, and with the thrombolysis in myocardial infarction (TIMI) + BNP showed higher prognosis value. Ahmet Avci (2020) [17] 6-month follow-up prospective study also found a high prognosis value of NGAL (cut-off ≥ 190 ng/mL) with AUC, 95%CI = 0.845, 0.722 – 0.968. In addition, NGAL also had a high value in prognosis of cardiovascular events [5,16,19]. Therefore, the combination of NGAL, hsTnT, NT-proBNP, and GRACE scores could be applied in clinical practice for focusing treatment in risk ACS patients.

Relative risk assessment of mortality proportion after 3 months of observation showed a high NGAL (≥ 154.55 ng/mL), NT-proBNP (≥ 10.02 ng/mL), hsTnT concentration (≥ 2.14 ng/mL), and GRACE score (≥ 140.50 scores) related to death events in ACS patients with OR from 11.1 to 49.0 (p ≤ 0.013) (Table 3). A multicenter, prospective, cohort study of Peng-Ju Lu (2020) [15] showed a similar result with a high concentration of NT-prBNP and hsTnT increased risk of mortality with a hazard ratio (HR) = 18.8 and 4.04, respectively (p < 0.0001). Ahmet Avci (2020) [17] study on 120 STEMI patients assessed for mortality at 1-year follow-Up, showed HR, 95% CI of NGAL was 1.13, 1.08 - 1.25 (p = 0.01). Lower than our study due to the difference in the cut-off threshold value. However, the result still showed increased mortality risk in high concentrations of the NGAL group. In addition, the Asian population could be affected by the CYP2C19 polymorphism, which could make the outcome difference [20]. Alan S. Maisel (2011) [18] study assessed all-cause mortality with single and combination models, high group of NGAL increased the risk of mortality approximately up to

30 (HR = 29.83, p < 0.000), and a combination assessment of NGAL (> 100 ng/mL), and BNP (> 330 ng/mL) had showed HR = 16.85, 95% CI: 2.26 - 125.94, p = 0.006. Changshin K.'s research, serum NGAL was independently related with a high SYNTAX score: OR = 1.109, 95% CI: 1.104 -1.14, p 0.001 [21]. A study by Ståle H. Nymo et al. (2018) [22], measured NGAL in the cutoff value of quartile 4 in blood from 1121 consecutive ACS patients showed NGAL concentration predicted long-term mortality with a hazard ratio (HR) = 1.33 (95% CI: 1.10 – 1.61, P = 0.003). Another assessment of NGAL in ACS was indicated in Hyungdon Kook et al. (2020) [23] assessment of plaque ruptures in ACS patients, the AUC of NGAL in ROC was not significant with AUC = 0.609, p= 0.0874.

Our findings reveal that the EF, troponin T-hs, NGAL, and NT-proBNP were statistically linked with mortality events. Multivariable logistic regression analysis of NGAL fix with eGFR and EF showed the increase of NGAL by 10 ng/mL increased the proportion of death by 6%, and 10 ng/mL of NT-proBNP was 4% (Table 4). Ahmet Avci (2020) [17] the study also found a similar result, with beta = 0.017 (p = 0.01) and dependent variables including age, hypertension, T2DM, dyslipidemia, smoking, sex, heart failure, and troponin. NGAL concentration could be biased due to the progression of chronic kidney disease (CKD) or Acute Kidney Injury as shown in the study by Højagergaard MA et al (2023) [24]. However, our study had strictly excluded the patients with kidney conditions, thus the outcome of our study had value meaning for clinical practice.

Our study had a small sample size and was conducted with a single-center. A multicenter study with a larger sample size or meta-analysis was needed to give a better view of the all-cause mortarlity prognosis value of NGAL, NT-proBNP, hsTnT, GRACE score. In addition, our study only evaluated 5 mortality events which could be more in clinical practice. However, our study had a well-designed method, the study sample was assessed for significant representation of the population.

5. Conclusions

Our study indicates that NGAL can be employed as a biomarker for the early prediction of mortality events in individuals with ACS. NGALs are associated with one another and have acceptable thresholds, high sensitivity and specificity, and considerable AUC values. Cardiovascular specialists may benefit from employing NGAL as predictors of a patient's risk of mortality in practical practice. In addition, the combination of NGAL, NT-proBNP, hsTnT, and GRACE score showed the higher outcome for all-cause mortality prognostic value. However, the difference between the NGAL in combination and alone assessed was not worth mentioning, thus NGAL assessed alone in clinical practice is more recommended.

The Registration number of clinical studies and Ethical approval: No.167 Date:16/3/2021 by the Ethics Committee in Biomedical Research of Can Tho University of Medicine and Pharmacy.

Declarations of interest: None

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CRediT authorship contribution statement

An Viet Tran: . **Nguyet To Tran:** Writing – original draft, Formal analysis, Conceptualization. **Khue Duy Nguyen:** . **Diem Thi Nguyen:** Writing – review & editing, Data curation. **Toan Hoang Ngo:** .

Declaration of competing interest

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