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The Role of Neutrophil Gelatinase-Associated Lipocalin and N-Terminal Pro B-Type Natriuretic Peptide in the Prediction of Heart Failure in Patients with Acute Coronary Syndrome

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Abstract

BACKGROUND: Heart failure, where the heart cannot pump blood effectively, significantly affects patient quality of life and impacts national health-care services. Acute coronary syndrome is a common underlying cause of acute heart failure. Neutrophil gelatinase-binding lipocalin (NGAL) and N-terminal pro B-type natriuretic peptide (NT-proBNP) are biomarkers released during myocardial injury. Thus, the measured levels of these chemicals may be associated with heart failure events in patients with acute coronary syndrome.

AIM: The present study determined the serum levels and measured increases in NGAL and NT-proBNP, as well as recorded heart failure events in patients with acute coronary syndrome in Vietnam.

METHODS: A descriptive cross-sectional method was used to recruit 58 patients with acute coronary syndrome and assess the degree to which the two markers could predict ejection fraction (EF).

RESULTS: The median values of NGAL and NT-proBNP concentrations in the group with EF ≥40% (7.14 ng/mL and 952.00 pg/mL) were significantly lower than those with EF <40% (166.10 ng/mL and 27,498.00 pg/mL). NGAL was used to predict heart failure events at a threshold of 94.86 ng/mL with a sensitivity of 83.3%, a specificity of 90.4%, and an area under the curve (AUC) of 0.83. Similarly, NT-proBNP predicted heart failure events at a threshold of 8660.5 pg/mL with a sensitivity of 83.3%, a specificity of 84.6%, and an AUC of 0.79.

CONCLUSIONS: Serum NGAL and NT-proBNP levels can be used as reliable biomarkers for predicting heart failure events in patients with acute coronary syndrome.

Introduction

Heart failure (HF), a condition in which the heart is incapable of pumping blood effectively, significantly affects the quality of life and burdens national health-care services. HF is commonly the consequence and/or final stage of a number of cardiac disorders, including coronary syndrome. Worldwide, the incidence of HF is approximately 1−2% of the general population (i.e., >64 million people globally), and this significantly increases to 8−10% in the elderly (those aged over 75 years) [1]. In Asia-Pacific and Europe, the prevalence ranges from 1.26% to 6.70% and from 0.4% to 2.0% of the region's population, respectively [2]. HF has been acknowledged as a leading cause of premature death in patients with cardiovascular diseases (Ponikowski *et al*., 2016), with a mortality rate ranging from 10% to 60%, dependent on the disease stage [3].

Although there have been recent advancements in the clinical guidelines for HF prevention, diagnosis, and treatment, the HF prevalence, rate of hospitalization, mortality rate, and economic burden are still increasing steadily. Therefore, a novel approach for the early diagnosis and prognosis of HF events in patients, especially those in high-risk groups such as patients with acute coronary syndrome (ACS), is in great need [4].

Early diagnosis is vital for optimal treatment outcomes. Consequently, the accurate prediction of HF is likely to result in cost savings, increased treatment efficiency, and improved overall survival rates [2]. Identifying cardiovascular diseases, specifically HF, in their early stages depend on the sensitivity and specificity

of the diagnostic tools. As such, the development and application of novel biomarkers (i.e., chemicals that are present specifically in the early stages of a specific disease) for laboratory tests have gained much attention recently [5]. For HF, cardiac biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and N-terminal pro B-type natriuretic peptide (NT-proBNP) have been demonstrated to have associations with the diagnosis and prediction of HF [6]. NGAL, a glycoprotein (molecular weight of 25 kDa) belonging to the lipocalin superfamily, is produced in the bone marrow and deposited in specific neutrophils in a complex form with gelatinase [7]. NGAL serum level is commonly associated with inflammation, matrix degradation, and cell death [1]. The myocardial expression of NGAL has been shown to increase significantly after acute myocardial infarction. NT-proBNP, a peptide elevated in patients with cardiac issues such as tachycardia and myocardial ischemia [8], is stable ($t_{1/2}$ = 90–120 min) in the systemic circulation and is thus more clinically accessible [9].

The previous studies have demonstrated the potential for using NGAL and NT-proBNP to predict HF events in patients with ACS [10], [11]. However, the previous studies have only investigated NGAL levels for the prognosis and follow-up of HF patients undergoing coronary artery bypass graft surgery [12], [13]. Further, in Vietnam, there is limited information on the implementation of this technique. No previous study in Vietnam has investigated both NGAL and NT-proBNP as biomarkers for HF. Consequently, this study explored the possibility of utilizing NGAL and NT-proBNP in predicting HF events in patients with ACS. These findings will inform cardiovascular clinicians of the potential for using NGAL and NT-proBNP to predict the risk of HF in patients across multiple clinical settings.

Materials and Methods

Study design and participants

A cross-sectional descriptive method was used in this study, with a sample size calculated based on the Cochran formula (Equation 1).

$$n = Z^2_{1-\alpha/2} \frac{p \times (1-p)}{d^2} \quad (1)$$

In which, n is the sample size of patients with ACS, α is the reliability (α = 0.05), d is the desired error (d = 0.09), and p is 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*., this rate was 87% [10] (thus, p = 0.87). Therefore, the calculated sample size is 54 participants. In this study, we recruited 58 patients.

Hospitalized patients diagnosed with ACS between October 2020 and December 2021 were recruited to participate in the study. The inclusion criteria were patients with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina. The exclusion criteria were cerebral infarction/ischemia within 6 months of the study period; blood deficiency within 1 year; or acute injury or Stage 3 or higher kidney disease (serum creatinine increase of >0.3 mg/dL for 2 consecutive days or >50% within 7 days, or renal insufficiency), cancer, lung diseases, hepatic disease, prior malignancy, infectious disease, sepsis, or advanced chronic diseases.

Data collection

Participants' sociodemographic and associated clinical data were collected, including age, sex, body mass index (BMI), low-density lipoprotein (LDL) cholesterol, triglycerides, echocardiogram, electrocardiogram, and ejection fraction (EF). Clinical biomarker levels of NGAL, NT-proBNP, and high-sensitivity troponin T (hs-TnT) were measured. The specificity, sensitivity, threshold values, and AUC concentrations of NGAL, CRP-hs, NT-proBNP, and hs-TnT associated with HF events (after 3 months of follow-up) were assessed in ACS patients.

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 Medical Ethics Committee of Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam.

Statistical analysis

Data were analyzed using SPSS version 25.0 and presented as frequency (percentage), mean (±standard deviation, SD), and median (interquartile range, IQR) as appropriate. The normality of the data was first checked by calculating the skewness and kurtosis values and by forming a Q–Q plot. Differences between patients with EF <40% and EF ≥40% were tested using Mann–Whitney U or Student's t tests, where appropriate. The predictive value of each biomarker was evaluated using receiver operating characteristic (ROC) curves. Statistical significance was considered at a threshold of $p < 0.05$.

Results

The sociodemographic, associated clinical, and clinical characteristics of the study participants

are presented in Table 1. Of the 58 patients, the mean age was 67.48 (1.52) years and 48.3% of the sample were men. The mean BMI was 22.68 (0.43) kg/m^2. 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%.

Table 1: Sociodemographic, associated clinical, and clinical characteristics of the participants (n=58)

Characteristics	Values
Sociodemographic	
Male, n (%)	28 (48.3)
Age (year), mean ± SD	67.48 ± 11.63
Smoke, n (%)	24 (41.4)
Associated and clinical, n (%)	
EF<40%	6 (10.3)
Dyspnea	23 (43.5)
Chest pain	57 (98.3)
Hypertension	41 (70.7)
Dyslipidemia	46 (79.3)
Type-2 diabetes	14 (24.1)
ST-segment elevation MI	21 (36.2)
Non-ST-segment elevation MI	27 (46.6)
Unstable angina	10 (17.2)
Biochemical, mean ± SD or median (IQR)	
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)
Incident events, n (%)	
Overall	13 (22.4)
Death	5 (8.6)
Recurrent MI	5 (8.6)
HF	6 (10.3)

BMI: Body mass index, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, HF: Heart failure, EF: Ejection fraction, MI: Myocardial infarction, SD: Standard deviation, IQR: Interquartile range.

The mean values of NGAL, hs-TnT, and NT-proBNP were 12.39 (0.71−42.07) ng/mL, 0.51 (0.16−1.83) ng/mL, and 1249.00 (324.50−7,973.50) pg/mL, respectively. At the 3-month follow-up, the overall incident event rate was 22.4%, of which mortality, recurrent myocardial infarction, and HF were 8.6%, 8.6%, and 10.3%, respectively. The number of cases with high NGAL (≥35.3 ng/mL) and NT-proBNP (≥125 pg/mL) concentrations accounted for 29.3% and 93.1% (Figure 1). NGAL levels were significant correlated with NT-proBNP levels (r = 0.56, p < 0.001) (Figure 2).

In the EF<40% group (n = 6), the median hs-TnT, NT-proBNP, and NGAL values were significantly higher than those in the EF≥40% group (Table 2).

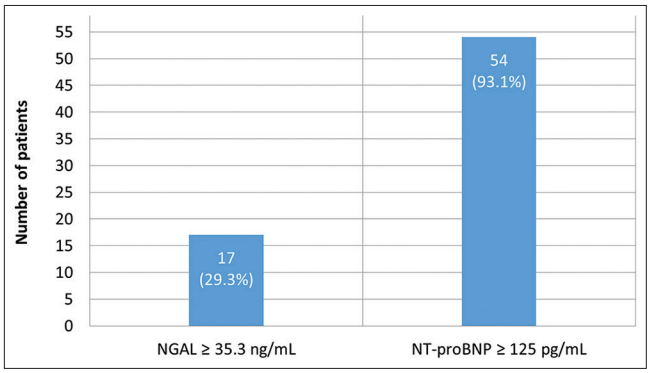

Figure 1: Absolute numbers (percentages in brackets) of patients with high NT-proBNP concentration (≥125 pg/mL) and high NGAL concentration (≥35.3 ng/mL). NT-proBNP: N-terminal pro-B-type natriuretic peptide; NGAL: Neutrophil gelatinase-associated lipocalin

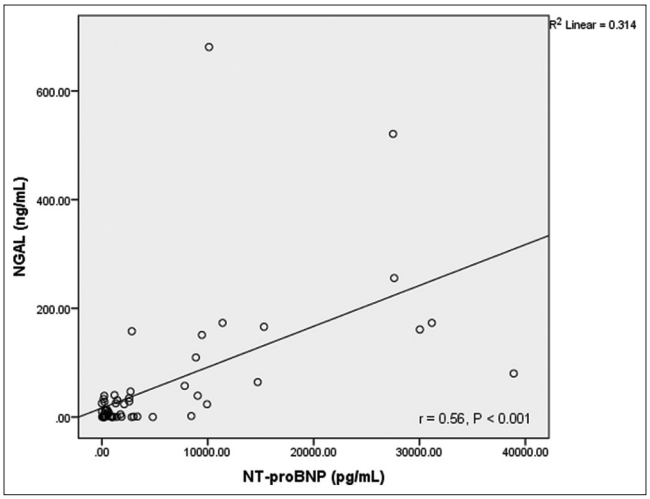

Figure 2: The association between serum NT-proBNP and urinary NGAL levels. NT-proBNP: N-terminal pro-B type natriuretic peptide; NGAL: Neutrophil gelatinase-associated lipocalin

As shown in Table 3, the predictive value of NGAL level for predicting HF events had a threshold of 94.86 ng/mL, a sensitivity of 83.3%, a specificity of 90.4%, and an AUC of 0.83. Similarly, the predictive value of NT-proBNP for predicting HF events had a threshold of 8660.5 pg/mL, a sensitivity of 83.3%, a specificity of 84.6%, and an AUC of 0.80.

Table 2: Associations between biomarker levels and ejection fraction in groups of patients with ejection fraction<40% and ejection fraction≥40%

Parameter	Median (IQR)		p
	EF<40% (n=6)	EF≥40% (n=51)	
hs-TnT (ng/mL)	0.569 (0.09–2.88)	0.47 (0.177–1.74)	0.41
NT-proBNP (pg/mL)	27,498.00 (11,392.00–30,032.00)	952.00 (234.00–2816.00)	< 0.01
NGAL (ng/mL)	166.10 (151.10–255.70)	7.14 (0.57–31.03)	< 0.01

NT-proBNP: N-terminal pro-B type natriuretic peptide, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T , EF: Ejection fraction, IQR: Interquartile range.

The ROC curves for the prediction of HF events for NGAL, NT-proBNP, hs-TnT, as well as NGAL and NT-proBNP in combination are shown in Figure 3. Table 4 shows the association between participant characteristics and HF. The NGAL and NT-proBNP values in the group of patients with HF were significantly higher than those without HF.

Table 3: The value of using each biomarker for predicting heart failure events in patients with acute coronary syndrome

Parameter	AUC	p	Cut-off	Sensitivity	Specificity
hs-TnT (ng/mL)	0.417	0.507	0.028	100	9.6
NGAL (ng/mL)	0.829	0.009	94.86	83.3	90.4
NT-proBNP (pg/mL)	0.792	0.020	8660.5	83.3	84.6
Combined NGAL and NT-proBNP	0.776	0.028		83.3	88.5

AUC: Area under the curve, NT-proBNP: N-terminal pro-B type natriuretic peptide, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T.

Discussion

Most of the participants had hypertension (70.7%), dyslipidemia (79.3%), and high BMI (22.68 ± 0.43 kg/m^2). These cardiovascular risk factors have increased the risk of HF events [14], [15], [16]. Gharishvandi *et al*. found higher NGAL levels in

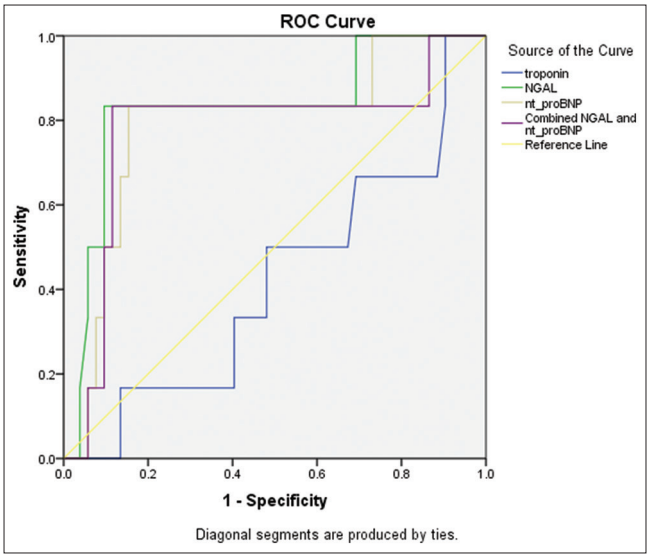

Figure 3: Receiver operating characteristic (ROC) curve analysis of the heart failure event prediction values of NGAL, NT-proBNP, hs-TnT, and combined NGAL and NT-proBNP. NT-proBNP: N-terminal pro-B-type natriuretic peptide; NGAL: Neutrophil gelatinase-associated lipocalin; hs-TnT: High-sensitivity troponin T

hypertensive patients with early stages of renal failure [17]. Elrin *et al*. found higher NGAL levels in patients with renovascular hypertension [18].

Table 4: The association between population characteristics and heart failure

Characteristics	HF, median (IQR)		p
	Yes	No	
Systolic blood pressure (mmHg)	140 (130–170)	130 (120–140)	0.125
BMI (kg/m^2)	21.25 (20.00–22.60)	22.40 (20.50–25.15)	0.325
NGAL (ng/mL)	158.60 (109.60–173.30)	10.12 (0.63–34.04)	0.009
hs-TnT (ng/mL)	0.40 (0.04–1.06)	0.51 (0.18–1.87)	0.607
NT-proBNP (pg/mL)	10,418.00 (8881.00–15,310.00)	1054.60 (268.00–2914.00)	0.020

BMI: Body mass index, NGAL: Neutrophil gelatinase-associated lipocalin, hs-TnT: High-sensitivity troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, HF: Heart failure, IQR: Interquartile range.

NGAL is a 25-kDa glycoprotein that plays a role in acute kidney injury. In normal conditions, only small amounts of NGAL could be found in plasma and urine. However, during and after cellular injury, NGAL levels increase rapidly and significantly [19]. High NGAL levels were associated with the development of early complications and mortality in patients with myocardial infarctions, along with acute and chronic heart failure [20], [21]. The previous studies have reported mean NGAL concentrations in patient groups with and without HF events of 134 ng/mL and 84 ng/mL, respectively, indicating that NGAL is also increased in the presence of cardiac injury [20]. Yndestad *et al*. investigated the role of NGAL in 236 patients with acute post-MI HF and 150 patients with chronic HF. Patients in NYHA Class III had significantly higher plasma NGAL levels than patients in NYHA Class I or II and controls. In addition, high baseline plasma NGAL levels were associated with an increased incidence of the composite endpoint (non-fatal MI, stroke, cardiovascular death, and all-cause death) at 27 months (median) follow-up. Finally, a significant association between plasma NGAL and N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) was reported [22]. In addition, in a study on 121 patients with acute HF, NGAL levels > 167.5 ng/mL (75th percentile) were associated with a 2.7-fold higher risk of death and a 2.9-fold higher risk of death or hospitalization [20], [23]. The level of urine NGAL early after myocardial infarction is associated with NT-proBNP concentration and even NGAL levels below 137 ng/ml, the usually reported normal cutoff value, had high specificity for HF [24].

Similarly, NT-proBNP is a pro-hormone with a cleavable 76-amino-acid-N-terminal-inactive protein. Plasma concentrations of NT-proBNP are significantly increased in patients with the left ventricular dysfunction, ACS, myocardial ischemia, and coronary artery disease. The present findings confirmed that significant increases in both biomarkers were observed in patients with HF events (i.e., EF <40%) compared to those without (i.e., EF ≥40%). Results were reported for NT-proBNP in the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study, evaluating 600 patients admitted to the emergency department for dyspnea. NT-proBNP < 300 ng/L ruled out effectively acute HF (99% negative predictive value [NPV]), and rule-in cutoffs of 450 ng/L in subjects with < 50 years (93% sensitivity, 95% specificity, and 95% accuracy) and 900 ng/L in subjects with ≥ 50 years (91% sensitivity, 80% specificity, and 85% accuracy) were proposed [25].

These findings are in agreement with those of Victoria *et al*. who reported a correlation between NGAL levels and an EF <40% in patients after 12 days of hospitalization (p = 0.04) [26]. These data suggest that early quantification of NGAL and NT-proBNP levels is crucial for predicting HF events in patients with ACS.

Kirbis *et al*. found NGAL levels to be individually correlated with NT-proBNP [24], there was a positive association between admission urine NGAL and in-hospital NT-proBNP (rhos 0.34, p = 0.003). Similarly, the present study also found a correlation between NGAL and NT-proBNP, which can be interpreted as evidence of the important roles of these biomarkers in HF. The degree of correlation between NGAL and NT-proBNP in the present study (r = 0.56) was higher than that reported by Okuyama *et al*. (r = 0.37) [18] and Yndestad *et al*. (r = 0.15) [22]. Conversely, Taskapan *et al*. [27] and Soren Lindberg *et al*. [28] found no association between either serum or urinary NGAL levels and NT-proBNP. The AUC values of NGAL (0.829) and NT-proBNP (0.792) in the present study were higher than reported previously (AUC = 0.700–0.755 for NGAL and 0.645–0.787 for NT-proBNP) [10], [20], [26]. Consequently, the AUC value of NGAL used in combination with NT-proBNP was better than in the previous reports. Further, we demonstrate that both markers' sensitivity and specificity are better than Katerina Helanova *et al*. [10]. In the present study, the sensitivity and specificity of NGAL were 83.3% and 90.4%, respectively, compared to the previously reported 79.1% and 65.5%, while

we found the sensitivity and specificity of NT-proBNP to be 83.3% and 84.6%, compared to 72.7% and 78.5%. Interestingly, the AUC of both indicators used in combination was 0.776, which was lower than the AUC of either biomarker alone. Maisel *et al*. investigated the prognostic value of plasma NGAL in patients with acute HF. Patients were followed for 30 days, and the primary combined endpoint was HF readmission or all-cause mortality. The AUC using ROC analysis was higher for NGAL [0.73] than for BNP [0.65], indicating that plasma NGAL is a good predictor of the combined endpoint after 30 days in acute HF patients. In addition, the combination of high NGAL and high BNP or high NGAL and low BNP was associated with higher risk of HF readmission or all-cause death than low NGAL and low BNP or low NGAL and high BNP [20]. This contradicts the findings of Schellings *et al*. who reported that the use of the thrombolysis in myocardial infarction (TIMI) score together with NT-proBNP provided an increase in the AUC ($p < 0.0001$) compared to either metric alone [29]. Conversely, the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA), involving 1415 HF patients, found plasma NGAL to be a univariate predictor of cardiovascular death and all causes of mortality, but that it became insignificant when adjusted for NT pro-BNP level [30]. Similarly, Alvelos *et al*. found NGAL to be an independent predictor of short-term death in patients with HF [20], [23]. These contradictory findings may be explained by differences in patient characteristics between the Vietnamese population and those from other nations/races. In addition, small sample sizes may not be adequate to generalize the findings. As such, further research on larger sample sizes of patients is needed.

Plasma NT-proBNP levels were higher in patients with HF than those without HF, indicating that NT-proBNP levels are valuable for diagnosing HF. This finding is in agreement with the previous work [31], [32]. In the present study, serum NGAL levels were significantly higher in patients with HF than those without HF, consistent with the previous studies [6], [33]. It can be concluded that NGAL is involved in the pathology of renal and cardiac diseases through multiple mechanisms and is a sensitive biomarker of renal injury and myocardial damage. NGAL levels in HF patients may reflect renal dysfunction, as renal dysfunction is often observed in HF patients and is associated with increased NGAL levels [11].

This study has some limitations. First, with a small number of subjects, our study was not powered to make firm conclusions about true predictors of HF using NGAL and NT-proBNP. In addition, these biomarkers can also be detected in other organ problems besides the heart such as with lung and liver organs [34]. This may also affect the results of this study. However, patients with these organ problems were included in the study's exclusion criteria. Finally, the combination of NGAL and NT-proBNP has not been found to increase the predictive value of HF after acute coronary syndrome. Therefore, future studies should be conducted with a larger sample size.

Conclusions

HF is one of the most critical and dangerous events in patients with ACS. This study confirms that NGAL and NT-proBNP can be used as biomarkers for the early prediction of HF events in patients with ACS. NGAL and NT-proBNP are correlated with each other and possess appropriate thresholds, high sensitivity and specificity, and significant AUC values. Cardiovascular physicians may benefit from using NGAL and NT-proBNP as predictors of a patient's risk of HF in clinical practice.

Acknowledgments

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