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Neutrophil-Albumin Ratio as a Predictor of in-Hospital Mortality in Patients with Cardiogenic Shock

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Abstract

AIM: This study aimed to evaluate the utilization of neutrophil-albumin ratio (NAR) in predicting in-hospital mortality in patients with cardiogenic shock (CS).

PATIENTS AND METHODS: This study was an observational study with cross-sectional design conducted at the Department of Cardiovascular, Harapan Kita Cardiovascular Hospital. The data were collected from the patient registry (January 2018 to April 2020). The study participants were all patients with CS admitted to our hospital. The endpoint was in-hospital mortality in CS patients. Predictors of hospital mortality were identified using multivariable logistic regression, followed by receiver operator characteristic (ROC) curve analysis and cutoff value for optimal NAR level.

RESULTS: A total of 130 patients hospitalized with CS were enrolled in this study, in-hospital mortality was found in 75 (57.7%) patients, among which 102 (78.5%) were male and 101 (77.7%) patients had the acute coronary syndrome. There was a significant positive correlation between NAR levels and in-hospital mortality. The multivariate logistic regression showed that NAR was independently associated with an increased risk of in-hospital mortality with an odds ratio of 5.81, 95% confidence interval 2.303–14.692, p < 0.001. NAR had a prognostic value in predicting in-hospital mortality of CS based on ROC curve analysis (area under the curve [AUC] 0,802), with an optimal NAR cutoff value of 25.

CONCLUSION: NAR is independently associated with in-hospital mortality in patients with CS.

Introduction

Cardiogenic shock (CS) is the most severe acute heart failure syndrome phase. CS is defined as decreased cardiac output caused by cardiac dysfunction, resulting in severe end-organ hypoperfusion, tissue hypoxia, and increased lactate levels [1], [2], [3]. The prevalence of CS is about 2%–5% of acute heart failure. In-treatment mortality rates vary from 30% to 60%; nearly half occur within the first 24 h. Meanwhile, the 1-year mortality rate is around 50%–60%, and the mortality rate for 30 to 60 days is 70%80% [4].

Inflammation plays an important role in the pathogenesis of CS [5]. One of the most widely studied inflammatory mediators in CS is neutrophils [6]. Albumin has several functions, including pressure regulation, plays a role as an antioxidant and anti-inflammatory agent. Several studies have shown the association of albumin levels with mortality in patients with CS [7], [8], [9]. These studies have combined these two markers and suggest the neutrophil-albumin ratio (NAR) as a prognostic predictor of inflammation in patients with acute myocardial infarction (AMI), acute renal failure, septic shock, rectal cancer, and pancreatic cancer [10].

This study aimed to evaluate the utilization of the NAR in predicting in-hospital mortality in patients with CS.

Materials and Methods

This study was an observational study with a cross-sectional design conducted at the Department of Cardiovascular, Harapan Kita Cardiovascular Hospital. The data were collected from the patient registry (January 2018 to April 2020).

The study participants were all patients with CS admitted to our hospital. The inclusion was patients aged ≥18 years admitted for CS. Cases with CS caused by bradyarrhythmias or tachyarrhythmias causing hemodynamic compromise, CS after cardiac surgery or noncardiac surgery, and incomplete records were excluded. Type I and Type II errors were set at 5%

and 10%, respectively. Taking into account the study power of 90% and dropout cases of 10%, a minimum of 129 sample sizes was obtained.

CS is defined as a clinical syndrome characterized by persistent hypotension, namely: Systolic blood pressure <90 mmHg for more than 30 min, or requiring inotropic or vasopressor drugs to maintain systolic blood pressure above 90 mmHg, or a decrease in mean arterial pressure (MAP) more than 30 mmHg from baseline accompanied by signs of impaired organ perfusion that meet one of the criteria in the form of mental status alteration, decreased urine production (oliguria) of <30 ml/hour, >2mmol/L increase in lactic acid level, and cold sensation in the extremities under the condition of adequate volume status (normal or excess volume). Eleven Confounding factors include age, gender, etiology (AMI and heart failure), vital signs (blood pressure and MAP), laboratory (hemoglobin, neutrophils, albumin, neutrophil-albumin creatinine ratio, pH, and lactate levels), comorbidities (Type II diabetes mellitus, hypertension, heart failure, and stroke), left ventricular ejection fraction, procedures (revascularization and intra-aortic balloon pump), and treatment (inotropic and vasoconstrictor).

Statistical analysis was conducted with Statistical Package for the Social Science (SPSS) software (version 26, IBM, New York, USA). Numerical data were presented in means ± standard deviation or median by quarterly values, while categorical data were shown in percentage. The Kolmogorov–Smirnov or Shapiro–Wilk normality test was performed to determine the data distribution. Differences in continuous data were analyzed using the unpaired *t*-test if the data were normally distributed and the Mann–Whitney test if the data distribution was not normal. Categorical data were compared using Chi-square (χ^2) or Fischer-exact tests. A multivariate analysis test using logistic regression was conducted to determine the utilization of neutrophil albumin ratio in predicting in-hospital mortality in patients with CS. Furthermore, a prognostic test (AUC) was conducted, followed by determining the optimal cutoff point.

Results

A total of 130 patients were included in this study. Among them, 102 (78.5%) patients were male with a mean age of 59 (51–66) years. The most common cause of CS was an acute coronary syndrome, namely 101 (77.7%) patients, including 64 (49.2%) patients with ST-Elevation Myocardial Infarction and 37 (28.5%) patients with NonST Elevation Myocardial Infarction, while 29 (22.3%) patients were caused by other than ACS. Table 1 illustrates the characteristics of the study participants.

Seventy five (57.7%) patients died during the hospitalization of all study subjects. The variables significantly associated with mortality in patients with CS were creatinine levels, eGFR, pH levels, lactate, NAR,

Table 1: Characteristics of study participants

Variables	Mean (n = 130)	Mortality		p
		Survival (n = 55)	Mortality (n = 75)	
Demographic characteristics				
Age (years)	59 (51–66)	58 (49.5–65.5)	60 (52–66)	0.110
Sex (male)	102 (78.5)	49 (75.4)	53 (81.5)	0.393
BMI (kg/m^2)	23.87 (22.04–26.45)	23.87 (21.92–25.9)	23.86 (22.27–26.32)	0.617
Vital signs (mmHg)				
Blood pressure	87 (75.75–99)	85 (72.5–97)	87 (76.5–102)	0.263
MAP	63.34 (57.25–76.08)	64 (56.83–77.5)	64.67 (57.83–75.83)	0.789
Diagnosis				
AMI-STE	64 (49.2)	32 (49.2)	32 (49.2)	1.000
AMI-NSTE	37 (28.5)	15 (23.1)	22 (33.8)	0.174
Other than ACS	29 (22.3)	18 (27.7)	11 (16.9)	0.140
LVEF	30 (22–40)	32 (22.5–40)	28 (22–35.5)	0.439
Laboratory and BGA				
Hb (%)	12.9 (11.4–14.6)	12.7 (11.35–14.05)	12.9 (11.5–14.95)	0.296
Creatinine (mg/dl)	1.61 (1.16–2.51)	1.4 (1.035–2.030)	1.87 (1.27–2.995)	0.018
eGFR (mL/min/1.73 m^2)	44 (24.75–67.25)	50 (32–79.5)	38 (22–58)	0.018
pH	7.39 (7.3–7.43)	7.4 (7.35–7.43)	7.37 (7.29–7.44)	0.005
Lactate (mmol/L)	3.55 (2.2–6.5)	3 (1.9–5.55)	4.7 (2.45–7.1)	0.017
Hs-Trop T (ng/L)	1422 (503–3715.5)	1245 (379–2757)	1653 (507.5–4902)	0.419
Albumin-neutrophil ratio	25.63 (22.25–29.54)	22.97 (20.03–25.63)	28.87 (25.03–31.18)	<0.001
Comorbidities				
Heart failure	42 (32.3)	21 (32.3)	21 (32.3)	1.000
Hypertension	61 (46.9)	29 (44.6)	32 (49.2)	0.598
Diabetes mellitus	57 (43.8)	27 (41.5)	30 (46.2)	0.596
Dyslipidemia	30 (23.1)	12 (18.5)	18 (27.7)	0.212
Stroke	17 (13.1)	7 (10.8)	10 (15.4)	0.435
Atrial fibrillation	19 (14.6)	7 (10.8)	12 (18.5)	0.214
Inotropic	111 (85.4)	58 (89.2)	53 (81.5)	0.214
Vasopressor	65 (50.0)	31 (47.7)	34 (52.3)	
In-hospital management				
IABP	55 (42.3)	25 (38.5)	30 (46.2)	0.375
RRT	26 (20.0)	8 (12.3)	18 (27.7)	0.028
MV	97 (74.6)	41 (63.1)	56 (86.2)	0.035
Revascularization	72 (55.4)	39 (60.0)	33 (50.8)	0.290

BMI: Body mass index, MAP: Mean arterial pressure, AMI-STE: Acute myocardial infarction-ST segment elevation, AMI-NSTE: Acute myocardial infarction-non-ST segment elevation, ACS: Acute coronary syndrome, LVEF: Left ventricle ejection fraction, BGA: Blood gas analysis, eGFR: Estimated glomerular filtration rate, IABP: Intra-aortic balloon pump, Hs-Trop T: High-sensitivity troponin test, Hb: Hemoglobin, RRT: Renal replacement therapy, MV: Mechanical ventilation.

patients on renal replacement therapy, and mechanical ventilation (MV). However, no significant differences were found in terms of age, sex, comorbidities, and the use of inotropes and vasopressors in these two groups (Table 2).

The multivariate analysis resulted in three variables that were significantly associated with mortality in CS patients, namely, the NAR, lactate levels, and the use of MV. The NAR was significantly associated with mortality (odd ratio 5.817, 95% confidence interval 2.303 – 14.692, p < 0.001) with the highest likelihood compared to other confounding variables, as shown in Table 2.

Table 2: Univariate and multivariate analysis of mortality predictors in patients with cardiogenic shock (n = 130)

Variables	Univariate analysis		p	Multivariate analysis		p
	OR	95% CI		OR	95% CI	
NAR	7.304	3.307–16.133	<0.001	5.817	2.303–14.692	<0.001
Lactate	3.578	1.715–7.467	0.001	3.973	1.534–10.289	0.004
Creatinine	3.005	1.456–6.202	0.003	2.385	0.233–24.398	0.464
eGFR	0.381	0.186–0.781	0.008	0.836	0.081–8.606	0.880
pH of BGA	0.570	0.281–1.157	0.118	1.528	0.579–4.031	0.391
RRT	2.327	0.901–6.007	0.076	1.488	0.461–4.797	0.506
MV	6.979	2.823–17.254	<0.001	4.480	1.577–12.724	0.005

OR: Odds ratio, CI: Confidence interval, NAR: Neutrophil-albumin ratio, eGFR: Estimated glomerular filtration rate, BGA: Blood gas analysis, RRT: Renal replacement therapy, MV: Mechanical ventilation.

The receiver operator characteristic (ROC) curve (Figure 1) was made to assess further the potential prognostic value of the NAR in predicting mortality in patients with CS, yielding an AUC value of 0.802 (95% CI). A NAR of 25 (sensitivity 74.7% and specificity 74.5%) was obtained as the optimal cutoff value (Figure 2) in predicting mortality.

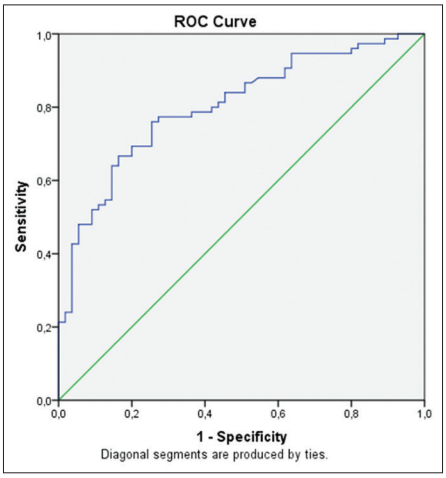

Figure 1: NAR as a predictor of mortality in CS. NAR: Neutrophil-albumin ratio, CS: Cardiogenic shock

Discussion

In today's era of vasodilation, post-MI hypotension and shock reduce cardiac output (myocardial contractility) when mechanical complications such as the interventricular septum, free wall, and papillary muscle lacerations are rare. Vasodilatation is induced by inflammatory cytokines (such as *tumor necrosis factor-*α and nitrogen monoxide). The prevalence of these various causes of CS was estimated as follows:

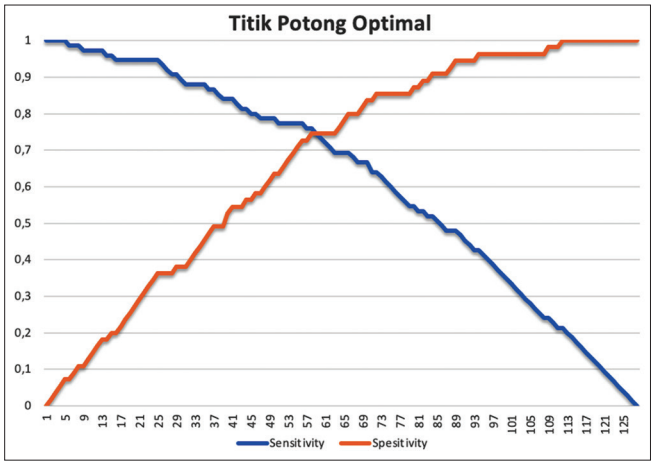

Figure 2: Optimal NAR cut-off value. NAR: Neutrophil-albumin ratio

Progression of chronic heart failure (11%–30%), valvular and other mechanical causes (6%), stress-induced/Takotsubo cardiomyopathy (2%), and acute myocarditis (2%). Patients with chronic heart failure who progress to ADHF and eventually become CS may differ from those with acute coronary syndrome-related CS. Chronic upregulation of the renin-angiotensin-aldosterone axis and elevated circulating catecholamines observed in these situations induce vasoconstriction and ventricular remodeling, creating different phenotypic substrates during CS presentation. In fact, the prognosis of CS patients surrounding AMI is different from that of patients with progressive chronic heart failure [1].

The main discussion is based on one study (Yue *et al*) only! (when I started this study, there were only two similar studies by Peng *et al*. and Yue *et al*.)

A significant relationship between the NAR and in-hospital mortality in patients with CS was shown in this study. A high NAR (≥25) predicts mortality in patients with CS. This result is in accordance with the results of previous studies. Peng *et al*. demonstrated the association of a high-level NAR (>27.86) with an increase in mortality in patients with CS.[12] Yue *et al.* also showed that the high NAR (≥25.3) was associated with mortality both in-hospital admission and at 30 and 365 days. In addition, the NAR was also an independent predictor of clinical outcome of CS and was better than albumin and neutrophil levels alone in predicting the clinical outcomes [10], [11]. The ROC curve analysis showed that the NAR in our study was better in predicting in-hospital mortality in patients with CS than in the previous studies (0.82 vs. 0.651 and 0.69). This may be due to differences in several variables of earlier studies, such as age, body mass index (BMI), creatinine, eGFR, and lactate levels.

The mean BMI in this study population was lower than the value shown in the study by Yue *et al*. (23.87 vs. 27.6 kg/m^2). Patients who died in this study had a higher mean creatinine level of 1.87 mg/dL compared to the study of Yue *et al*. (1.4 mg/dL). Furthermore, the study also demonstrated a lower mean eGFR level of

38 mL./min/1.73m^2 compared to this study, indicating that this study included more patients with moderate-severe kidney damage (Stage 3b: 30–44 mL/min/1.73m^2). Kikuchi *et al*. (2016) demonstrated that low BMI (<23.5 kg/m^2) and low albumin levels (<4g/dL) were associated with a higher risk of progression in chronic kidney disease (CKD). However, BMI alone is unable to show the components of the body clearly; therefore, it cannot be used to assess nutrition and fat, especially in patients with heart failure and kidney failure [13]. Inflammation contributes to CKD progression, and neutrophils play an important role in tissue damage of kidney failure.[14] Patients with chronic kidney failure are under nutritional deficiencies and inflammation that contribute to protein-energy wasting. Thus, the mortality of study subjects was plausibly caused by inflammation due to CS and exaggerated inflammatory processes due to kidney damage.

The mean lactate level in this study was higher than in a previous study conducted by Yue *et al*. (4.7 vs. 3.8 mmol/L), indicating the more severe CS in patients included in this study. The increased lactate levels in our patients indicated tissue hypoperfusion or hypoxia [10].

The prevalence of MV in CS patients ranges from 78% to 88% and is often required for acute hypoxemia, increased respiratory work, airway protection, and management of hemodynamic or electrical instability [4]. In this study, when comparing univariate and multivariate mortality predictors in CS patients with MV, in univariate analysis, adjusting demonstrated (OR 6.979; 95% CI 2.823–17.25) and a similar trend after multivariate analysis (OR 4.480; 95% CI 1.577–12.724), respectively (Table 2). Use of MV has been associated with an increased risk of mortality in CS patients in several studies, a study by Hongisto *et al*. showed overall mortality of 41%, and the 90-day mortality was higher in the MV group, respectively [15].

Van Diepen *et al*. found that MV can improve oxygenation and tissue perfusion especially in CS patients, although it needs a larger sample on this research highlight the need for more extensive randomized studies into the optimal use of MV in this high-risk population. Moreover, Van Diepen *et al*. hypothesized the mechanism in MV can also decrease mortality in CS patients. However, there are some factors Van Diepen *et al*. acknowledge the capability for confounding, the modest size, loss of hemodynamics, cardiac arrest, lactate, neurologic variables, or air flow statistics within side the observe and that mechanical circulatory guide with remoted LV disorder can also additionally obviate those advantages [3].

The strength of this study is that this is the first study investigating the utilization of neutrophil albumin ratio in predicting mortality in patients with CS in Indonesia. The results of this study are valuable given the limited laboratory tests available in Indonesia, especially acute inflammation markers in patients with CS. This study has several limitations. First, it can only assess the incidence of short-term mortality during hospitalization. In addition, it was unable to rule out infection as a comorbid. Finally, this study failed to identify the presence of other causes of hypoalbuminemia.

The limitation of this study is fewer options for troponin assay. We only used Troponin T because of availability at the hospital.

Conclusion

A high NAR (≥25) is associated with increased in-hospital mortality in patients with CS. The NAR can be used as an independent predictor of in-hospital mortality in patients with CS. This study highlights the routine utilization of neutrophils and albumin ratio in patients with CS. Further studies are warranted to confirm the finding of this study.

Ethical Consideration

This study was approved by the Institutional Ethics Committee, National Cardiovascular Center Harapan Kita Hospital, Jakarta, Indonesia, prior to the study being conducted

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