PREDICTIVE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO FOR HOSPITAL MORTALITY RISK IN PATIENTS WITH ACUTE CORONARY SYNDROME

YUQIN ZHOU[1,*], CHAOJUN YANG[2,*], WANYIN CAI[2]
[1]Department of Cardiology, 904th Hospital of Joint Logistic Support Force of PLA, Wuxi, 214044, China - [2]Department of Cardiology, the First College of Clinical Medical Sciences, China Three Gorges University, Yichang 443000, Hubei Province, China, Hubei Province, China

ABSTRACT

Objective: *To investigate the value of neutrophils to lymphocyte ratio (NLR) in predicting the risk of hospitalization death in patients with acute coronary syndrome (ACS).*

Methods: *A total of 308 patients with ACS admitted to the first college of clinical medical sciences of China Three Gorges University and 904th Hospital of Joint Logistic Support Force of PLA from January 2016 to December 2020 were enrolled. The results of blood examination were collected and NLR was calculated. The receiver operating characteristic (ROC) curve was used to evaluate the value of NLR in predicting the hospitalization death, and multivariate logistic regression model was used to analyze the risk factors of hospitalization death.*

Results: *ACS patients with NLR>6.39 had a higher mortality during hospitalization than those with NLR≤6.39 (P<0.05). ROC curve showed that when the cut-off value of NLR was 6.39, the sensitivity and specificity of predicting hospitalization death were 90.5% and 52.4% respectively. Multivariate logistic regression analysis showed that NLR was a predictor of hospitalization death in patients with ACS (OR=9.85, 95%CI: 1.46~21.26, P=0.02).*

Conclusions: *NLR may be a valuable biomarker as a predictor of mortality risk during hospitalization in patients with ACS.*

Keywords: *Acute coronary syndrome, neutrophils, lymphocyte.*

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Introduction

Acute coronary syndrome (ACS), a leading cause of death in most countries, is pathologically characterized by unstable atherosclerotic lesions and included ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)[1]. Relevant studies showed that 5.5%~18.2% of ACS patients died during hospitalization, and the mortality rate during long-term follow-up is as high as nearly 15%[2, 3]. The risk of death in patients with ACS is influenced by the patient's age, ejection fraction, hypertension[4]. At the same time, some other laboratory indicators such as cardiac troponinI (cTnI), n-terminal brain natriuretic peptide precursor (NT-proBNP), and neutrophils can also independently predict mortality or major adverse cardiac events (MACEs) of ACS patients[5-7]. Chronic inflammatory responses have been shown to be a critical element in the pathogenesis of atherosclerosis[8, 9].

Neutrophils and lymphocytes are inflammatory factors that have been shown to be associated with the prognosis of neoplastic diseases such as metastatic renal cell carcinoma and metastatic pancreatic cancer[10, 11]. The neutrophil to lymphocyte ratio

(NLR) is an indicator of systemic in-flammation and a prognostic marker in many diseases[12-14]. In cardiovascular disease, NLR is also an independent predictor of left ventricular dysfunction and can predict the long term mortality in patients hospitalized with ST elevation myocardial infarction (STEMI) and in patients under-going percutaneous coronary intervention (PCI)[15-16]. In a word, measurement of a simple inflammatory marker like NLR may improve the risk stratification of ACS patients.

Blood analysis is a routine test during the patient's hospitalization. In this study, the blood analysis, myocardial enzymes and basic diseases of hospitalized ACS patients were analyzed. The goal of this study was to investigate and evaluate the predictive ability of NLR in determining the risk of death in patients with ACS, independent of other standard risk factors for ACS.

Patients and methods

Patients

392 ACS patients hospitalized in the first college of clinical medical sciences of China Three Gorges University and 904th Hospital of Joint Logistic Support Force of PLA from January 2016 to December 2020 were selected, and 308 ACS patients were finally included according to the inclusion and exclusion criteria. Clinical data were collected with the consent of the patient or his/her family. The diagnostic criteria for ACS are based on the diagnostic and treatment guidelines for ACS issued by the Chinese Medical Association in 2016.

Exclusion criteria:

- With stable angina pectoris;
- With acute cerebrovascular accident;
- Combined with hepatic and renal insufficiency;
- With acute infection, trauma and surgery;
- Oral steroid hormone;
- Combined with blood diseases and other malignant neoplastic diseases;
- The medical history is incomplete.

Methods

Basic clinical data such as gender, age, history of hypertension, diabetes, dyslipidemia and other related history were collected. Basic laboratory tests including blood analysis and myocardial enzymes were completed for each patient within 2h after admission. Indicators associated with the inflammatory response in blood were collected, such as white blood cell count, neutrophil count, lymphocyte count, etc. Besides, the NLR and neutrophils to monocytes ratio (NMR) were also calculated. The endpoint was the patient's death or recovered and discharged.

Statistical analysis

SPSS22.0 was used for statistical analysis. Continuous variables were summarized as mean±SD (standard deviation). One-way ANOVA was performed to compare multiple groups and independent sample t-test was used for comparisons between groups. Count data are expressed as percentages, and the χ^2 test or Fisher's exact test was used for comparisons between groups. ROC curve was applied to assess the sensitivity and specificity of NLR to predict the prognosis of ACS patients. Multivariate analysis was performed using binary logistic regression. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of the included patients

Of the 308 patients included, 188 were male (61.04%) and 120 were female (38.96%), with an average age of 71.4±10.8 years. There were 102 cases (33.11%) with hypertension, 33 cases (10.71%) with diabetes, and 21 cases (6.81%) with dyslipidemia. 11 cases (3.57%) died in hospital. White blood cell count (WBC) (10.50±3.84)×10^9/L, neutrophil count (N) (7.62±3.48)×10^9/L, Lymphocyte count (L) (1.38±0.94)×10^9/L, monocyte count (M) (0.38±0.21)×10^9/L, NLR 7.26±3.21, NMR 20.04±9.62. Creatine kinase isoenzyme lactate (CK-MB) (55.32±22.65) U/L, dehydrogenase (LDH) (408.44±156.36) U/L, alpha hydroxybutyrate dehydrogenase (α-HB) (314.24±101.55) U/L.

Correlation analysis between NLR and mortality rate of ACS patients in hospital

According to NLR level, patients were divided into NLR>6.39 group and NLR≤6.39 group. Correlation analysis between NLR and mortality rate of ACS were observed. The in-hospital mortality of NLR>6.39 group was higher than that of NLR≤ 6.39 group ($P<0.05$). As shown in Table 1.

Analysis of risk factors influencing the mortality rate of ACS patients during hospitalization

Multivariate logistic regression model analysis showed that NLR was a predictor of in-hospital mortality in ACS patients (OR=9.85,

95%CI:1.46~21.26, P=0.02). As shown in Table 2.

Project	NLR≥6.39 group (n=125)	NLR<6.39 group (n=183)	P value
Male/n (%)	74 (59.20)	114 (62.29)	0.584
Age/year	72.14±10.22	69.98±12.23	0.094
Hypertension/n (%)	43 (34.40)	59 (32.24)	0.693
Diabetes/n (%)	12 (9.60)	21 (11.47)	0.601
Dyslipidemia/n (%)	7 (5.60)	14 (7.65)	0.483
WBC/($\times10^9\cdot L^{-1}$)	12.23±3.98	9.32±3.66	<0.001
N/($\times10^9\cdot L^{-1}$)	10.32±3.68	5.97±2.99	<0.001
L/($\times10^9\cdot L^{-1}$)	0.92±0.44	1.68±0.98	<0.001
M/($\times10^9\cdot L^{-1}$)	0.39±0.27	0.37±0.18	0.436
NMR	26.46±10.63	16.14±9.61	<0.001
CK-MB/($U\cdot L^{-1}$)	93.24±30.58	34.42±14.68	<0.001
LDH /($U\cdot L^{-1}$)	458.62±142.10	354.51±103.18	<0.001
α-HB /($U\cdot L^{-1}$)	398.14±162.15	282.07±112.36	<0.001
In-hospital death/n (%)	9 (7.20)	2(1.09)	*0.009*

Table 1: Correlation analysis between NLR and mortality rate of ACS patients in hospital.
WBC: white blood cell; N:neutrophil; L:lymphocyte; M:monocyte; NLR: neutrophils to lymphocyte ratio; NMR: neutrophils to monocytes ratio; CK-MB: creatine kinase isoenzyme; LDH: lactate dehydrogenase; α-HB: alpha hydroxybutyrate dehydrogenase.

Influence factor	OR	95%CI	P value
Gender	0.45	(0.16, 1.48)	0.28
Age	1.21	(0.92, 1.58)	0.84
WBC	0.94	(0.78, 1.36)	0.28
NLR>6.39	9.85	(1.46, 21.26)	*0.02*
NMR	1.12	(0.96, 1.53)	0.75
CK-MB	0.96	(0.92, 1.18)	0.62

Table 2: Multivariate logistic regression analysis.
WBC: white blood cell; NLR: neutrophils to lymphocyte ratio; NMR: neutrophils to monocytes ratio; CK-MB: creatine kinase isoenzyme lactate.

ROC curve analysis for predicting in-hospital death of ACS patients

As shown in Figure 1, according to the ROC curve, the area under the curve was 0.755, sensitivity was 90.5%, and specificity was 52.4% when the cutoff value of in-hospital death of ACS patients predicted by NLR was 6.39.

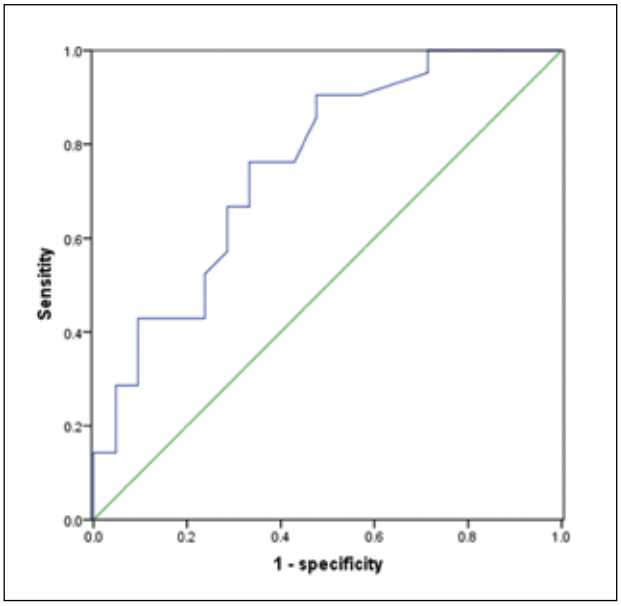

Figure 1: Prediction of hospitalized death in patients with ACS by ROC curve.

Discussion

Blood analysis is a basic investigation done in all admitted patients and NLR can be easily calculated from it. Review of literature suggested that NLR can be used as marker of systemic inflammation and it may be an independent prognostic marker[17, 18]. More interestingly, several studies have indicated that NLR may not be affected by other cardiac risk factors like hypertension, diabetes, obesity, hyperlipidemia, and smoking[19]. At the present study, we also found NLR could be a valuable biomarker as a predictor of mortality risk during hospitalization in ACS patients.

ACS has high hospitalization and long-term mortality, which seriously increases the social medical burden[20]. Early prognosis assessment can guide further diagnosis and treatment of ACS patients. The role of inflammatory markers in cardiovascular disease has been extensively studied in the past, and it has been proved that inflammatory markers play an important role in the occurrence and development of cardiovascular diseases[21, 22]. Neutrophils can induce and stimulate inflammatory response, and participate in adverse reactions such as plaque rupture and thrombosis in ACS[23, 24].

Guasti et al. confirmed that neutrophils were an independent risk factor for prognosis of patients with ACS in a systematic evaluation study of the number of >34000 cases[25]. While lymphocytes have endothelial protection and anti-inflammatory

functions[26]. NLR is a cheap and widely available inflammatory marker that better reflects the body's inflammation. In a study about relation of NLR with presence of complexity of CAD, it was observed that patients with complex CAD had a significantly higher NLR value 2.3 median compare to1.6 median[27]. Another study also found that increasing NLR was associated with more severe CAD[28].

The present study showed that NLR was associated with in-hospital death in ACS patients, and that patients with high NLR had a higher risk of in-hospital death compared with those with low NLR. Previous studies also indicated that NLR was associated with the severity of heart failure and NLR has certain predictive value for postoperative recurrence in patients with atrial fibrillation[29, 30]. In addition, a study also has suggested that the NLR cut-off value of 3.00 in cerebrovascular diseases was of good prognostic value for patients with intracranial hemorrhage[31].

Chang et al. suggested that NLR in 2.72 has a predictive value for drug-eluting stent restenosis in patients with coronary heart disease[32]. In this study, the optimal cutoff value for predicting the in-hospital mortality risk of ACS patients with NLR was 6.39, and the sensitivity and specificity were 90.5% and 52.4% respectively. Compared with the total number of white blood cells that are more affected by external factors, NLR has higher sensitivity and better specificity in the prognosis judgment of ACS patients. In summary, NLR could be used as a predictor of mortality risk assessment during hospitalization for ACS patients.

The disadvantage of this study is that the number of cases is small firstly. Secondly, this study is an observational study, which lacks follow-up outcome of malignant cardiovascular events outside the hospital. In addition, when combined with infectious diseases, hematologic diseases, tumor diseases and immune system diseases, NLR alone cannot fully assess the prognosis of ACS patients.

However, this study still suggests that NLR, as the simplest and most common detection indicator in clinical work, can play a predictive role in the risk of death during hospitalization of ACS patients.

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Corresponding Author:
Chaojun Yang
Email: 942686648@qq.com
(China)
YUQIN ZHOU
Email: 1413862864@qq.com
(China)