A combination of the neutrophil-to-lymphocyte ratio and the GRACE risk score better predicts PCI outcomes in Chinese Han patients with acute coronary syndrome

Dong Zhou[1], Zhaofei Wan[1], Yan Fan[1], Juan Zhou[1], Zuyi Yuan[1,2]

[1]Department of Cardiovascular Medicine, First Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an-*Xi'an-People's Republic of China*
[2]Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University, Ministry of Education; Xi'an-*People's Republic of China*

Abstract

Objective: The aims of this study are to evaluate the relationship between the Global Registry of Acute Coronary Events (GRACE) risk score and neutrophil to lymphocyte ratio (NLR) and to determine whether a combination of these factors improves the predictive value for long-term cardiovascular events in Chinese Han patients with acute coronary syndrome (ACS).

Methods: In this prospective, observational, and single-center study, NLRs (neutrophil count/lymphocyte count) were calculated from the complete blood count of 1050 patients with ACS, whereas GRACE risk scores were calculated from patients' clinical parameters obtained on arrival at our hospital. Cox proportional hazards models were used to determine independent factors associated with cardiovascular events.

Results: NLR was positively correlated with the GRACE risk score (r=0.66, p<0.001), and both the GRACE risk score (HR: 1.01; 95% CI: 1.01–1.02; p<0.001) and NLR (HR: 1.09; 95% CI: 1.06–1.14; p<0.001) independently predicted cardiovascular events. The area under the receiver operating characteristic (ROC) curve was 0.69 (95% CI: 0.64–0.72; p<0.001) when the GRACE score was calculated alone; however, it significantly increased (p<0.001) to 0.77 (95% CI: 0.74–0.80; p<0.001) when the GRACE score was combined with NLR.

Conclusion: This study shows for the first time that NLR is positively associated with the GRACE risk score and demonstrates that a combination of these two factors may improve the predictive value for cardiovascular events in Chinese Han patients with ACS. *(Anatol J Cardiol 2015; 15: 995-1001)*

Keywords: neutrophil/lymphocyte ratio, GRACE risk score, acute coronary syndrome, MACE

Introduction

Acute coronary syndrome (ACS), a leading cause of death in most countries, is pathologically characterized by unstable atherosclerotic lesions. Chronic inflammatory responses have been shown to be a critical element in the pathogenesis of atherosclerosis (1).

White blood cell (WBC) count is an independent predictor of inflammatory state and long-term cardiovascular mortality in ACS (2). An increased total WBC count is related to a higher risk of coronary artery disease (CAD) (hazard ratio: 1.04; 95% CI: 1.02–1.07; p=0.001) (2). Neutrophils have also been demonstrated to play a critical role in the progression of atherogenesis (3). However, low lymphocyte count can also predict the risk of reduced hemodynamics and aerobic capacity (4). Therefore, the ratio of the absolute number of neutrophils to the number of lymphocytes [neutrophil to lymphocyte ratio (NLR) is a biomarker that can be used to predict the risk of future cardiovascular events (5). This ratio is well known to connect with two different immune pathways in formation inflammatory response. Neutrophils are closely related to ongoing inflammation, and lymphocytes reflect the immune regulatory pathway (6, 7). Therefore, NLR is an important marker of the chronic inflammatory status of the body.

The Global Registry of Acute Coronary Events (GRACE) risk score has been reported as a potential predictor of major adverse cardiac events (MACEs) (8, 9). To date, no study has specifically evaluated the relationship between NLR and the GRACE risk score. Hence, the purpose of the present study was to evaluate whether NLR is associated with the GRACE risk score and to determine whether a combination of these two factors could improve the predictive value for long-term MACEs in post-percutaneous coronary intervention (PCI) patients with ACS.

Address for Correspondence: Zuyi Yuan, Key Laboratory of Environment and Genes Related to Diseases Xi'an Jiaotong University, Ministry of Education, Xi'an, Shaanxi 710061-*People's Republic of China*
E-mail: zuyiyuan@mail.xjtu.edu.cn
Accepted Date: 23.06.2015 **Available Online Date:** 29.07.2015

DOI:10.5152/AnatolJCardiol.2015.6174

Table 1. Clinical characteristics of patients grouped by tertiles of NLR at baseline

	Tertile 1 (350)	Tertile 2 (350)	Tertile 3 (350)	*P*
Age, years	49.06±7.73	52.82±8.92	56.39±9.89	<0.001
Male, n (%)	249 (71.14%)	291 (83.14%)	301 (86.00%)	<0.001
Smoking, n (%)	219 (62.57%)	250 (71.43%)	232 (66.29%)	0.044
HT, n (%)	171 (48.86%)	167 (47.71%)	160 (45.71%)	0.701
DM, n (%)	61 (17.43%)	57 (16.29%)	61 (17.43%)	0.898
History of MI, n (%)	18 (5.14%)	28 (8.00%)	23 (6.57%)	0.312
BMI, kg/m^2	23.62±2.88	24.86±2.93	25.55±2.91	<0.001
SBp, mm Hg	128.79±18.75	129.19±50.61	120.83±18.17	0.001
DBp, mm Hg	82.00±12.83	79.89±12.61	77.53±12.52	<0.001
HR, bpm	72.21±12.13	74.32±11.64	77.20±14.96	<0.001
WBC, k/μL	7.40±2.22	8.11±2.61	10.97±3.31	<0.001
Lymphocyte, k/μL	2.42±0.77	1.92±0.62	1.46±0.56	<0.001
Neutrophil, k/μL	4.51±1.48	5.69±2.04	9.10±2.96	<0.001
RBC, M/μL	4.26±0.59	4.23±0.70	4.33±0.81	0.113
Hemoglobin, g/dL	13.41±1.76	13.34±1.89	13.44±1.81	0.203
Platelet, k/μL	182.27±73.24	182.58±69.83	185.67±66.78	0.778
TC, mmol/L	3.90±1.08	4.10±1.33	4.36±0.97	<0.001
TG, mmol/L	1.61±0.74	1.72±0.74	1.82±0.78	0.001
HDL-C, mmol/L	1.09±0.24	1.02±0.21	0.97±0.22	<0.001
LDL-C, mmol/L	2.18±0.43	2.23±0.40	2.32±0.34	<0.001
hs-CRP, mg/L	2.00±0.93	3.00±1.34	3.53±1.29	<0.001
HCY, μmo/L	21.46±11.84	22.98±12.18	22.74±11.99	0.198
LVEF, %	61.55±11.38	58.32±11.41	53.68±11.62	<0.001
Statin, n (%)	328 (93.71%)	334 (95.43%)	329 (94.00%)	0.573
Aspirin, n (%)	342 (97.71%)	339 (96.86%)	331 (94.57%)	0.405
ß-Blocker, n (%)	330 (94.29%)	332 (94.86%)	333 (95.14%)	0.874
CCB, n (%)	66 (18.86%)	57 (16.29%)	42 (12.00%)	0.042

BMI - body mass index; CCB - calcium channel blockers; DBp - diastolic blood pressure; DM - diabetes mellitus; HCY - homocysteine; HDL-C - high-density lipoprotein cholesterol; HR - heart rate; hs-CRP - high-sensitivity C-reactive protein; HT - hypertension; LDL-C - low-density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; MI - myocardial infarction; NLR - neutrophil to lymphocyte ratio; RBC - red blood cell; SBp - systolic blood pressure; TC - total cholesterol; TG - triglyceride; WBC - white blood cell count. The differences among the groups were assessed using one-way ANOVA for the comparison of multiple groups or the Chi-square test for categorical variables.

Methods

Study protocol and population

In a prospective, observational, single-center study, 1050 Chinese Han subjects were recruited from January 2009 to July 2013. All patients, who were aged 24–84, were admitted into the Department of Cardiology at the First Affiliated Hospital of Xi'an Jiaotong University and underwent coronary angiography and their first PCI because of severe CAD. ACS was defined as acute ST-segment elevation myocardial infarction (MI), acute non-ST-segment elevation MI, and unstable angina (10). An acute MI was diagnosed by an abnormal cardiac biomarker value with at least one value above the 99th percentile upper reference limit and with at least one of following parameters: ischemic symptoms, ECG changes indicative of ischemia, pathological Q waves on ECG, or coronary artery intervention. The definition of unstable angina is recurrence or worsening angina with normal myocardial enzymes. In total, 142 patients had MI and 908 patients had unstable angina. We excluded patients from the study if they had one of the following clinical conditions: acute infection, post-revascularization, acute stroke, advanced liver disease, renal failure, cancer, blood diseases, or known malignancies with life expectancy of <1 year. The study protocol was approved by the Ethics Committee of the hospital and was performed in accordance with the Declaration of Helsinki guidelines. All participants were provided with appropriate research information, and all gave their informed consent.

Demographic and clinical data

Well-trained nurses gathered all samples and clinical data. Investigators collected subject information, including basic

Table 2. Comparison of the severity of acute coronary syndrome in different tertiles of NLR

	Tertile 1 (350)	Tertile 2 (350)	Tertile 3 (350)	*P*
3-VD, n (%)	97 (27.71%)	120 (34.29%)	146 (41.71%)	0.001
1-VD, n (%)	128 (36.57%)	102 (29.14%)	93 (26.57%)	0.012
Gensini score	37.05±14.34	49.01±23.33	74.64±32.67	<0.001
GRACE risk score	105.79±28.86	138.90±30.71	163.80±36.91	<0.001

GRACE risk score - Global Registry of Acute Coronary Events risk score; NLR - neutrophil to lymphocyte ratio; 1-VD - acute coronary syndrome patients with 1-vessel disease; 3-VD - acute coronary syndrome patients with 3-vessel disease. The differences among the groups were assessed using one-way ANOVA for the comparison of multiple groups or the chi-square test for categorical variables.

demographic data, past medical history, smoking habits, and consumption of statin. A history of smoking was defined as either a past or current history of smoking cigarettes. Hypertension was defined as a state where systolic blood pressure (SBP) was >140 mm Hg and diastolic blood pressure was >90 mm Hg. Patients with diabetes mellitus (DM) were defined as those with an elevated fasting plasma glucose concentration of >126 mg/dL or those taking hypoglycemic medications. The body weight (kg) and height (m) of each subject were acquired during the initial visit. Their body mass index (BMI) was calculated as body weight (kg)/height^2 (m^2).

Coronary angiographies and PCIs were performed according to the Judkins technique. All patients were provided target vessel revascularization, and a coronary stent was implanted in severe coronary arteries with >70% luminal narrowing. Based on the results of coronary angiography, the severity of CAD was reflected by the number of stenosed arteries and the Gensini scores (11).

The design and rationale of the GRACE risk score has been previously described (12). Here the GRACE risk score was calculated for each patient on arrival at hospital using the following eight clinical parameters: age, SBP, heart rate, serum creatinine, cardiac arrest, Killip classification, ST-segment deviation on ECG, and elevated cardiac enzymes.

Laboratory measurements

Blood samples (5 mL) were collected into tubes containing an anticoagulant and were stored at 4°C. Within 24 h of a patient's admission to the hospital, a complete blood count and subgroup number were obtained at the laboratory in the hospital using an XT-4000 automated hematology analyzer (Sysmex, Japan). The number of WBCs, neutrophils, and lymphocytes were recorded; NLR was then calculated as neutrophil count/lymphocyte count. The concentrations of serum homocysteine, high-sensitivity C-reactive protein (hs-CRP), high-density lipoprotein cholesterol, and triglyceride were also determined in the laboratory of our hospital. Low-density-lipoprotein cholesterol was calculated using the Friedewald formula.

Follow-up examination of the cohort patients with ACS

The subjects were provided with a follow-up examination, which took place 14–60 months after their initial visit (median time until follow-up: 42 months), and the incidence of MACE and rate of death were evaluated. In the cohort study, the 1050 patients that underwent PCI were followed-up at average intervals of 1, 3, 6, 12, 24, 36, 48, and 60 months after discharge. Follow-up information for all 1050 patients was obtained by telephone communication or face-to-face interviews with the patients or their family members. A trained research cardiologist conducted the follow-up examinations according to a structured questionnaire. MACE was defined as nonfatal MI, cardiovascular death, unstable angina, nonfatal ischemic stroke, and revascularization procedures. MACE and no cardiovascular event were obtained.

Statistical analysis

Continuous variables are shown as means±standard deviations. The Kolmogorov–Smirnov test was used to assess the normal distribution of quantitative variables. One-way ANOVA was performed to compare multiple groups. Differences between the two groups were assessed using the chi-square test or Fisher's exact test for categorical variables, as appropriate. The association between NLR and the GRACE risk score was assessed by Spearman's rank correlation. Univariate and multiple Cox proportional hazards models were used to determine independent factors associated with cardiovascular events. Kaplan–Meier survival curves were constructed to evaluate the prognostic value of NLR. Hazard ratios (HRs) were presented with 95% confidence intervals (CIs) to show the risk of an event when a factor was apparent. The predictive accuracy of the GRACE risk score alone and the combined NLR and the GRACE risk score were evaluated by assessing the area under the receiver operating characteristic (ROC) curves. The combination of biomarkers to improve diagnostic accuracy was described in other work (13). We used MedCalc to compare two partial areas of two ROC curves. All computations were performed with SPSS software 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium). Statistical significance was set at $p<0.05$ using a two-tailed test.

Results

Clinical characteristics of the study population

The 1050 patients were divided into three groups according to the tertiles of baseline NLR level (tertile 1: <2.20; tertile 2: 2.20–3.80; tertile 3: >3.80). The median NLR was 2.85 (range: 0.61–30.67). The main baseline characteristics and medications are shown in Table 1. There were no significant differences among the three groups with respect to smoking, hypertension, DM, and history of MI. However, an intergroup comparison revealed that BMI, hs-CRP, and other risk factors such as TCH, age, and the percentage of males all increased as NLR increased ($p<0.01$).

Table 3. Univariate Cox analysis of the factors predicting MACEs in patients with ACS

Variables	HR*	95% CI	*P*
Age, per year	1.07	1.06–1.08	<0.001
Male, vs. female	1.51	1.08–2.11	0.015
Smoker, vs. non-smoker	1.31	1.02–1.70	0.038
HT, vs. non-HT	1.29	1.02–1.63	0.035
DM, vs. non-diabetes	1.38	1.14–1.67	<0.001
BMI, per kg/m^2	1.15	1.11–1.20	<0.001
SBP, per mm Hg	0.99	0.98–0.99	0.011
DBP, per mm Hg	0.99	0.97–0.99	0.008
HR, per bpm	1.01	0.99–1.02	0.161
WBC, per k/uL	1.13	1.10–1.16	<0.001
RBC, per M/µL	1.06	0.91–1.23	0.441
Hemoglobin, per g/dL	1.01	0.99–1.01	0.103
Platelet, per k/µL	1.00	0.99–1.00	0.548
Lymphocyte, per k/uL	0.45	0.37–0.55	<0.001
Neutrophil, per k/uL	1.18	1.15–1.22	<0.001
NLR, per ratio	1.17	1.15–1.20	<0.001
TC, per mmol/L	1.13	1.06–1.21	<0.001
TG, per mmol/L	1.13	0.98–1.31	0.091
HDL-C, per mmol/L	0.37	0.22–0.63	<0.001
LDL-C, per mmol/L	1.32	0.98–1.77	0.063
log CRP, per log unit	1.44	1.34–1.56	<0.001
HCY, per µmol/L	1.01	0.99–1.02	0.118
LVEF, per %	0.99	0.98–1.00	0.184
GRACE score	1.02	1.01–1.02	<0.001

ACS - acute coronary syndrome; BMI - body mass index; DBp - diastolic blood pressure; DM - diabetes mellitus; GRACE risk score - Global Registry of Acute Coronary Events risk score; HCY - homocysteine; HDL-C - high-density lipoprotein cholesterol; HR - heart rate; HR*- hazard ratio; hs-CRP - high-sensitivity C-reactive protein; HT - hypertension; LDL-C - low-density lipoprotein cholesterol; log CRP - logarithm of C-reactive protein; LVEF - left ventricular ejection fraction; MACE - major adverse cardiac event; NLR - neutrophil to lymphocyte ratio; RBC - red blood cell; SBp - systolic blood pressure; S-Cr - serum creatinine; TC - total cholesterol; TG - triglyceride; UA - uric acid; WBC - white blood cell count.

Comparison of severity of ACS in different NLR groups

Counting the number of stenosed arteries and applying the Gensini scoring system are well-used methods for evaluating the severity of coronary atherosclerosis based on angiographic findings. As shown in Table 2, patients with 3-vessel disease were more prevalent in the tertile 3 group than in the tertile 1 and 2 groups (p<0.01). However, the prevalence of 1-vessel disease was higher in the tertile 1 group than in the tertile 2 and 3 groups. The GRACE risk score and Gensini score were significantly higher in patients with higher NLR tertile compared with patients with lower NLR tertile. NLR was significantly and positively correlated with the GRACE risk score (r=0.62, p<0.01) and Gensini score (r=0.53, p<0.01). These results indicated that patients with higher NLRs had more severe coronary artery stenosis.

Table 4. Multiple Cox analysis of the factors predicting MACEs in ACS patients

Variables	HR	95% CI	*P*
Age, per year	1.04	1.02–1.05	<0.001
HT, vs. non-HT	1.42	1.10–1.82	0.006
DM, vs. non-diabetes	1.29	1.05–1.60	0.017
Smoker, vs. non-smoker	1.64	1.27–2.13	<0.001
BMI, per kg/m^2	1.13	1.08–1.18	<0.001
NLR, per ratio	1.10	1.06–1.14	<0.001
GRACE risk score	1.01	1.01–1.02	<0.001
log CRP, per log unit	1.21	1.10–1.32	<0.001

ACS - acute coronary syndrome; BMI - body mass index; DM - diabetes mellitus; GRACE risk score - Global Registry of Acute Coronary Events risk score; HT - hypertension; log CRP - logarithm of C-reactive protein; MACE - major adverse cardiac event; NLR - neutrophil to lymphocyte ratio.

NLR as an independent predictor of MACE in patients with ACS

The mean Gensini scores post-PCI for tertiles 1, 2, and 3 were 13.53±5.76, 12.97±6.01, and 13.77±6.38, respectively. There was no statistical difference among the three groups (p=0.198). Table 3 shows the results of univariate Cox analysis of the factors predicting MACEs in patients with ACS. Significant predictors were being male, age, BMI, smoking, hypertension, DM, WBC count, lymphocyte cell count, neutrophil cell count, apolipoprotein-B, lipoprotein(a), NLR, the GRACE risk score, and hs-CRP. As shown in Table 4, the results of multiple Cox analysis showed that NLR was a significant and independent predictor for MACEs (HR: 1.09; 95% CI: 1.06–1.14, p<0.01). Similarly, the GRACE score was also an independent predictor of cardiovascular events in patients with ACS (HR: 1.01; 95% CI: 1.01–1.02, p<0.01). Kaplan–Meier curves showed that patients with higher NLRs had a higher incidence of MACE than those with lower NLRs. As shown in Figure 1a, a log-rank test on the curves for the three groups of patients showed a significant intergroup difference (chi-square, 108.46, p<0.001). During the follow-up period, the MACE rate of 44.57% in the tertile 3 group was higher than that in the tertile 2 (21.14%) and tertile 1 (13.14%) groups (p<0.01). Patients with higher NLRs were more likely to experience MACEs than those who had lower NLRs. As shown in Figure 1b, the Kaplan–Meier curve for the rate of death indicated that patients with higher NLRs had a higher rate of death than those with lower NLRs. The rate of death was 8.29% in the tertile 3 group, and this was 3-times higher than that in the tertile 1 group (2.57%, p=0.001). These data indicated that elevated NLR was an independent predictor of MACEs in patients with ACS.

Combining NLR with the GRACE risk score

ROC analysis was used to evaluate the predictive power of combining NLR with the GRACE score in relation to long-term outcomes in patients with ACS. As shown in Figure 2, the area under the ROC curve was 0.69 (95% CI: 0.64–0.72) for the GRACE

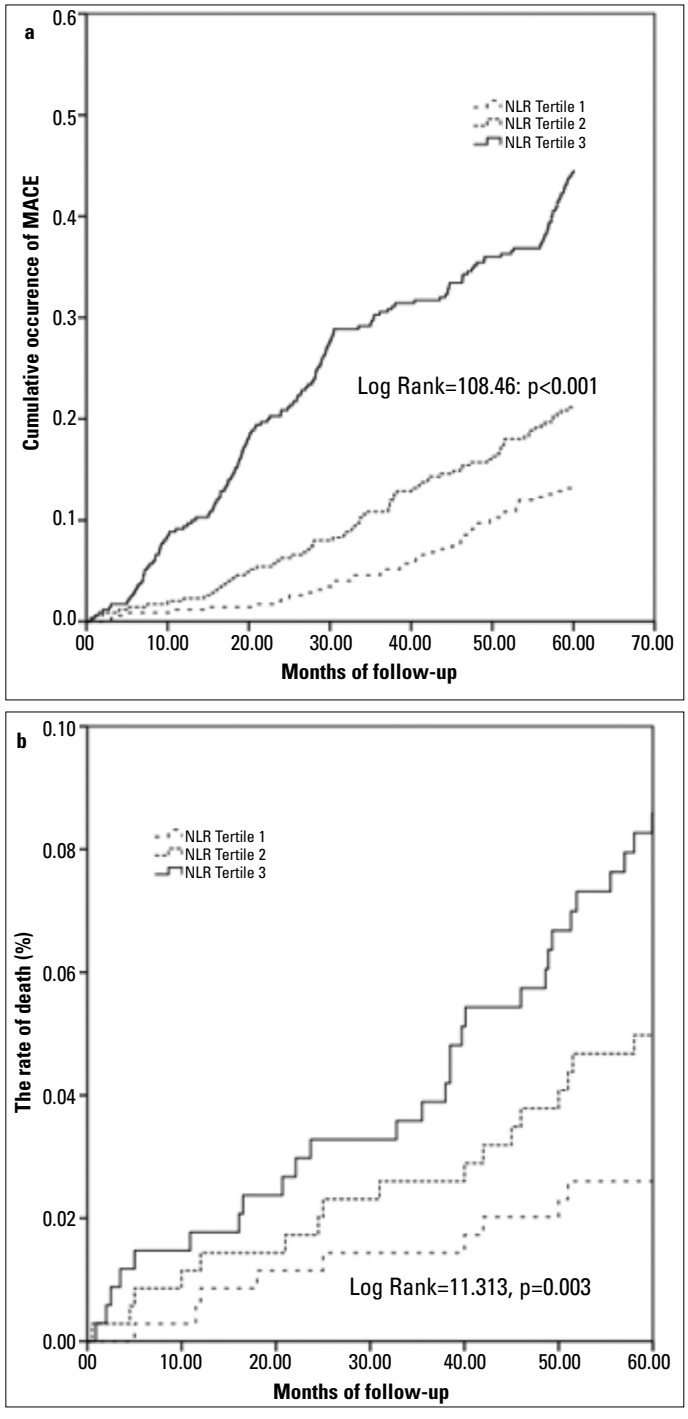

Figure 1. a, b. Kaplan–Meier survival curves based on NLR levels. Based on the tertiles of NLR levels, the 1050 subjects were divided into the following three groups: tertile 1 (<2.2), tertile 2 (2.2–3.8), and tertile 3 (>3.8).
a: The rate of MACE increased with increasing NLR (log-rank test=108.46, p<0.001).
b: The rate of death increased with increasing NLR (log-rank test=11.313, p<0.01)

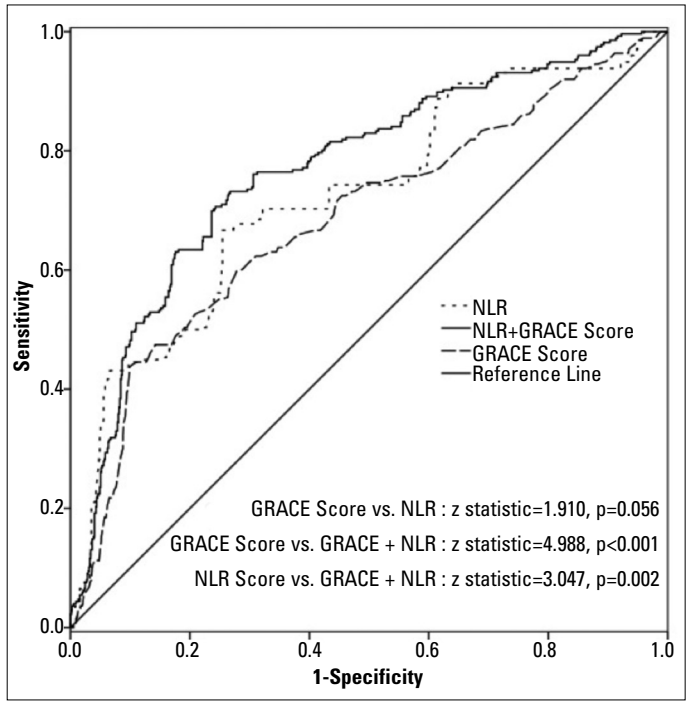

Figure 2. Receiver operating characteristic (ROC) curve analysis. The combination of NLR and the GRACE risk score significantly improved (p<0.001) the MACE prediction power of the scoring system for patients with long-term ACS

risk score alone and 0.72 (95% CI: 0.69–0.76) for NLR alone. There was no significant difference between these ROC areas (z statistic=1.910, p=0.056). However, the area under the ROC curve increased to 0.77 (95% CI: 0.74–0.80, p<0.001) when NLR and the GRACE risk score were combined. The increase of the area under the ROC curve in the score was significant (z statistic=5.993, p<0.001). These findings indicated that the combination of NLR and the GRACE risk score could better predict long-term MACEs in patients with ACS.

Discussion

Our results demonstrated that both NLR and the GRACE risk score could independently predict the post-PCI prognosis of patients with ACS. The GRACE risk score increased with an increase of NLR at baseline; thus, these factors were positively correlated. Moreover, the combination of NLR with the GRACE risk score improved the predictive value for long-term MACEs in Chinese Han patients with ACS. The Gensini score and the percentage of 3-vessel disease also increased with an increase of NLR at baseline, which indicated a positive correlation between the severity of coronary disease and NLR. Therefore, NLR may be a marker of the progression of CAD.

The clinical data in this study showed that NLR is closely associated with coronary stenosis. The positive correlations between NLR and the GRACE risk score and NLR and the Gensini score can be attributed to its role as a marker of systemic inflammation. The development of coronary stenosis is primarily due to the progress of inflammation. Severe stenosis will result in ischemic cardiovascular disease and clinical cardiovascular events. As the main inflammatory cells, leukocytes and their subpopulations play a crucial pathophysiologic role during atherosclerotic plaque development and rupture (14). Neutrophils have been implicated as a major contributing factor

in inflammatory responses. Many prospective studies have proved that the number of neutrophils is related, usually in a positive manner, to atherosclerotic load and myocardial ischemia (15, 16). Neutrophil invasion of atherosclerotic plaques can be directly visualized in an animal model (17) or patients with CAD (18). Activated WBCs can release fibrogenic mediators, such as specific peptide growth factors, which can accelerate the replication of smooth muscle cells and promote atherosclerotic plaques toward more advanced lesions (19). Neutrophils participate in many biochemical mechanisms, including release of arachidonic acid metabolites, cytotoxic oxygen-derived free radicals, and hydrolytic enzymes. Additionally, various types of leukocyte adhesion molecules are expressed by activated endothelial cells, which lead to blood cells adhering at the site of activation. All inflammatory reactions can cause a waterfall effect, including the activation and rupture of plaques, thrombosis, and ischemia (20). As the pivotal element, neutrophils accelerate inflammatory processes by these biological effects. On the other hand, some prospective studies have shown that lymphocytes, including relative and absolute concentrations, are drastically lower in patients who have suffered from cardiac events. Lymphocytes are not essential for the development and progression of CAD (21). Furthermore, infiltrating lymphocytes in the ischemic and reperfused myocardium can modulate the mononuclear cell phenotype and induce the tissue inhibitor of metalloproteinase-1 expression. Therefore, lymphocytes may play an explicit role in healing (22). Similarly, lymphocytopenia has been observed in critical inflammatory states and is independently related to poor prognosis in patients with acute myocardial infarction (23). Above all, the combination of elevated neutrophils and low levels of lymphocytes may convey important information about complex inflammatory activity in the vascular bed of CAD as well as pathological progression. As a readily available biomarker, NLR may dynamically reflect the inflammatory state of a patient. NLR has already been demonstrated as an independent predictor of outcome in patients with heart failure (24), cancer (25), and bacteremia (26). Our results showed that post-PCI patients with elevated NLR have a higher possibility of suffering from severe ACS and a poor prognosis.

The GRACE risk score is a validated predictor of cardiovascular events in patients with ACS. Previous studies have revealed that the predictive value of cardiovascular events was enhanced when the GRACE risk score was combined with other potential risk factors of ACS, such as B-type natriuretic peptide (27) and mean platelet volume (28). Our study has revealed for the first time that NLR at baseline is significantly and positively correlated with the GRACE risk score and that the combination of these two factors better predicts the long-term outcome of post-PCI patients with ACS.

Study limitations

Our present study has some limitations. First, our results were obtained from a single center, and the sample size was relatively small. Second, the subjects were limited to the Chinese Han population; therefore, our results should be extrapolated to other ethnic groups with caution.

Conclusion

In conclusion, both NLR and the GRACE risk score are effective predictive factors for cardiovascular events. However, combining NLR with the GRACE risk score improves the accuracy of prediction of the MACEs in Chinese Han patients with long-term ACS. NLR may also be a marker of the progression of CAD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - D.Z., ZY.; Design - D.Z., ZY.; Supervision - Z.W.; Materials - Y.F.; Data collection &/or processing - J.Z.; Analysis &/or interpretation - D.Z.; Literature search - D.Z.; Writing - D.Z.; Critical review - Z.Y.

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