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Original Article

Neutrophil-to-lymphocyte ratio (NLR) predicts mortality and adverse-outcomes after ST-segment elevation myocardial infarction in Chinese people

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Abstract: Neutrophil-to-lymphocyte ratio (NLR) has been reported to predict cardiovascular risks and mortality in coronary artery diseases. We aimed to evaluate the capacity of NLR to predict long-term mortality in Chinese patients presenting with ST-segment elevation myocardial infarction (STEMI). We recorded NLR at admission, 24 or 72 hours after admission, and at discharge (14±2 days) of 692 patients presenting with STEMI at Xuanwu hospital, Beijing between 2002 and 2005, and assessed the capacity of NLR to predict mortality during follow up (median 9.43, interquartile range (IQR) 8.65-10.28 years). Backward stepwise multivariate Cox regression revealed that average inpatient NLR ($NLR_{average}$) predicted all-cause mortality (Hazard ratio 1.481) more accurately than absolute leukocyte and neutrophil counts (P<0.001). When patients were stratified into tertiles by $NLR_{average}$ (T_1 NLR<3.16, T_3 NLR>4.75), patients in T_3 exhibited a 4.621-fold higher risk of mortality than patients in T_1 (P=0.002). Patients in T_3 had a significantly higher incidence of all-cause mortality (10.00%) than T_1 (2.17%) and T_2 (4.31%), cardiac-mortality (8.70%) than T_1 (2.17%) and T_2 (4.31%), hypotension (20.00%) than T_1 (5.65%) and T_2 (12.93%), arrhythmia (43.91%) than T_1 (24.14%) and T_2 (24.35%), and defibrillation (7.83%) than T_1 (1.74%) and T_2 (5.17%) in hospital; and suffered from higher mortality (46.09%) than T_1 (9.13%) and T_2 (29.74%), cardiac mortality (27.83%) than T_1 (5.22%) and T_2 (15.52%) and MACE events (36.52%) than T_1 (13.04%) and T_2 (31.9%) during long-term follow-up. Average NLR was a useful and powerful predictor of mortality and adverse-outcomes in Chinese patients presenting with STEMI.

Keywords: Myocardial infarction, inflammation, biological markers, leukocyte count, prognosis

Introduction

Leukocytes play a major role in both initiation and progression of atherosclerosis, and have been implicated in acute rupture of atherosclerotic plaques with superimposed thrombus formation [1-6]. During acute myocardial infarction (AMI), activated-neutrophils infiltrate into the infarcted zone [2, 3] contributing to fibrotic scar formation, a cause of arrhythmia [7, 8]. Furthermore, neutrophils aggregate with platelets to exacerbate vascular plugging in the microcirculation [4, 5, 9], and induce no-reflow phenomenon [10-14]. Neutrophils also prompt the secretion of inflammatory mediators [15], aggravating myocardial ischemia [16, 17] and extending the infarct area [3, 18, 19]. Depressed levels of circulating lymphocytes are often observed to follow AMI in response to elevated cortisol secretion and apoptotic stress reactions [3, 20, 21]. Lower lymphocyte levels were associated with advanced heart failure [2, 19] and mortality [5] in STEMI patients.

Recently, neutrophil-to-lymphocyte ratio (NLR) has emerged as a potent composite inflammatory marker [10, 15, 20]. NLR, obtained on admission [4-7, 9-13, 15-20, 22-26], 24-hour after percutaneous coronary intervention (PCI) [14], or calculated as an average [21] or maximum value [27], has been found to be an independent predictor of mortality [1, 4-9, 11-27] and adverse-outcomes including major adverse cardiovascular events (MACE) [5, 13, 16, 18,

Table 1. Baseline characteristics of patients according to average NLR tertiles

	Tertile1 (n=230)	Tertile2 (n=232)	Tettile3 (n=230)	*P* values			
	(NLR<3.16)	(3.16-4.75)	(NLR>4.75)	1 vs. 2	1 vs. 3	2 vs. 3	Overall
$NLR_{average}$	2.49±0.52	3.89±0.47	6.87±2.42	<0.001*	<0.001*	<0.001*	<0.001*
Age	57.09±11.57	60.03±11.04	63.69±11.31	0.004*	<0.001*	0.001*	<0.001*
Body mass index (kg/m^2)	25.45±6.13	25.15±5.20	25.14±3.15	0.648	0.660	0.980	0.874
Men/Women	184/46	170/62	192/38	0.076	0.359	0.007*	0.024*
History							
Hypertension	53.91% (124)	64.66% (150)	57.39% (132)	0.019*	0.448	0.113	0.057
Dyslipidemia	27.83% (64)	30.60% (71)	14.78% (34)	0.483	0.001*	<0.001*	<0.001*
Diabetes mellitus	25.65% (59)	27.59% (64)	23.91% (55)	0.635	0.670	0.368	0.666
Cerebral Stroke	15.22% (35)	15.52% (36)	14.78% (34)	0.929	0.897	0.826	0.976
Smoking	68.70% (158)	65.95% (153)	69.57% (160)	0.527	0.842	0.405	0.685
Previous myocardial infarction	6.09% (14)	6.03% (14)	6.96% (16)	0.982	0.703	0.685	0.902
Previous PTCA	1.74% (4)	0.86% (2)	1.74% (4)	0.431	1.000	0.431	0.660
History of heart pass	0.43% (1)	0.86% (2)	0.00% (0)	0.485	0.478	0.159	0.371
Admission condition							
Systolic blood pressure (mmHg)	126.20±21.46	128.69±21.25	126.59±23.63	0.692	0.991	0.764	0.678
Diastolic blood pressure (mmHg)	77.88±13.22	78.92±13.51	76.77±13.37	0.569	0.544	0.237	0.497
Heart rates (beats/min)	72.33±11.14	76.25±15.81	81.62±17.36	0.013*	<0.001*	<0.001*	<0.001*
Killip class (≥2)	30.00% (69)	31.90% (74)	50.43% (116)	0.669	<0.001*	<0.001*	<0.001*
Biochemical measurements							
Peak of CKMB (ng/ml)	384.97±468.69	327.98±577.39	352.82±317.04	0.221	0.238	0.944	0.389
Peak of creatine kinase (ng/ml)	2278.15±1862.42	2076.35±1710.98	2863.90±2186.00	0.505	0.049*	0.007*	0.019*
Creatinine (mg/dl)	1.09±0.96	1.11±0.97	1.12±0.31	0.709	0.669	0.956	0.898
Cholesterol (mg/dl)	193.76±58.28	188.45±43.26	180.73±36.40	0.235	0.011*	0.136	0.038*
Triglyceride (mg/dl)	205.85±137.12	150.62±101.77	136.44±80.81	0.001*	<0.001*	0.388	<0.001*
HDL (mg/dl)	43.35±14.72	42.36±11.20	40.79±9.67	0.547	0.130	0.335	0.308
LDL (mg/dl)	119.07±40.61	116.82±35.18	112.33±33.30	0.654	0.189	0.363	0.404
Glucose (mg/dl)	156.79±64.59	163.11±79.34	177.79±79.97	0.376	0.004*	0.039*	0.012*
Hematological measurements on admission							
Leukocyte counts ($10^9/L$)	9.04±2.55	10.41±3.34	11.17±2.87	0.001*	<0.001*	0.045*	<0.001*
Neutrophils ($10^9/L$)	6.11±2.28	8.25±2.66	9.77±2.75	<0.001*	<0.001*	<0.001*	<0.001*
lymphocytes ($10^9/L$))	2.56±1.03	1.80±0.66	1.14±0.37	<0.001*	<0.001*	<0.001*	<0.001*
Monocytes ($10^9/L$)	0.33±0.18	0.30±0.21	0.22±0.16	0. 389	<0.001*	<0.001*	<0.001*
Platelets ($10^9/L$)	212.19±56.14	210.20±61.33	199.61±56.38	0.827	0.173	0.245	0.341
Red blood cell counts ($10^{12}/L$)	4.57±0.52	4.54±0.59	4.53±0.57	0.660	0.553	0.866	0.829
Hemoglobin (g/L)	140.08±21.05	138.09±16.46	140.29±17.9	0.453	0.940	0.396	0.644

T_1 $NLR_{average}$<3.16, T_2 3.16≤$NLR_{average}$≤4.75, T_3 $NLR_{average}$>4.75. Data shown are % (n), median (IQR) or mean ± SD. *P<0.05. CK-MB: MB isoenzyme of creatine kinase; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; NLR: neutrophil-to-lymphocyte ratio; PCTA: percutaneous transluminal coronary angioplasty.

25], advanced heart failure [3, 19, 23], re-infarction [12], and arrhythmia [8, 21, 27] in patients with ST-segment elevation myocardial infarction (STEMI) [4, 5, 7, 10-15, 17-20, 24-27], non-STEMI [21, 23] or stable chronic coronary artery disease [6, 9, 16, 22]. NLR measured at admission was also an independent predictor of poor myocardial perfusion [9, 16] and worse angiographic outcomes pre- [7, 10, 15, 26] or post- [13, 17] PCI.

However, catecholamine release [4, 21], dehydration [4, 21] or reperfusion therapy [24] may artificially increase the levels of circulating neutrophils and lymphocytes, and blur their truthful prognostic value. Additionally, NLR is not static, and varies with progression of critical illness [27]. It is unclear when NLR values should be calculated to offer the best prognostic value for Chinese STEMI patients. Therefore, we conducted this study to identify the predictive value of NLR calculated at different time points in Chinese patients presenting with STEMI.

Materials and methods

Patients

We enrolled 826 STEMI patients hospitalized at Xuanwu hospital, Beijing, China between

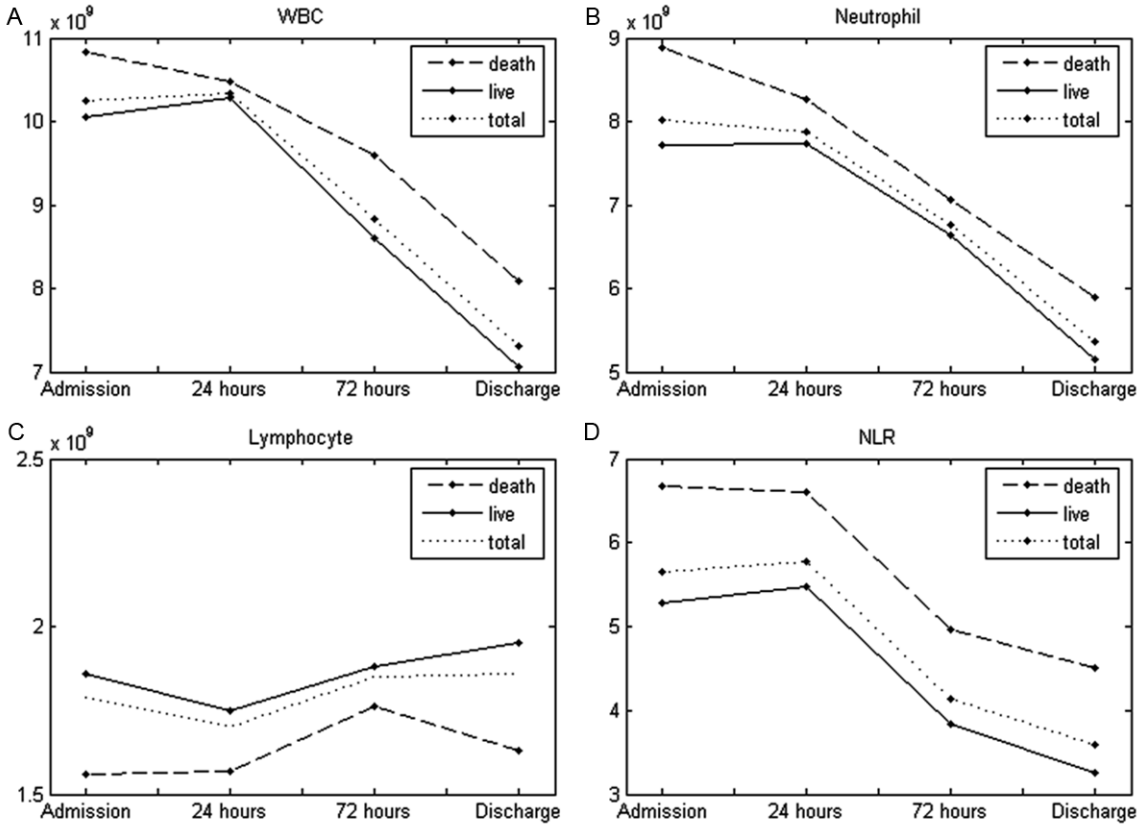

Figure 1. Leukocyte counts and NLR in patients presenting with ST-segment elevation acute myocardial infarction that died or survived during follow up. The leukocyte counts were assessed in patient blood samples at admission (6.12-7.60 hours after symptom onset, n=692); 24 hours after admission (n=692); 72 hours after admission (n=614); Before discharge (14±2 days after symptom onset, n=632). Patients that died during follow up had higher total leucocyte or neutrophil counts and higher NLRs, and lower lymphocyte counts in comparison with patients that did not die during the follow up period.

January 2, 2002 and January 16, 2005 within the first 12 hours of symptom onset. The study was approved by the ethics committee of Xuanwu hospital and was carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all included patients (or their relatives). STEMI was defined according to the criteria defined by the American College of Cardiology and the European Society of Cardiology [28].

Patients with clinical evidence of active cancer, severe renal failure (creatinine exceeding the upper limit of the normal value on admission by 150%), hematological proliferative disorders, active hepatobiliary diseases, active infection, chronic inflammatory disease, or receiving steroid therapy for autoimmune disease were excluded from this study. A total of 692 patients were included in the analysis. We recorded age, gender, personal and family history, systolic/diastolic blood pressure, heart rate, killip class, and complications from complete medical history records.

Hematology

Routine blood tests were carried out at admission, 24 and 72 hours later, and at discharge. Leukocyte, neutrophil, lymphocyte, monocyte counts were determined using an automated blood cell counter (MEK-7222K, NIHON KOHEN, JAPAN). NLR was calculated as the ratio of neutrophils to lymphocytes, and both obtained from the same blood sample. And average, maximum and minimum NLR values were recorded.

Biochemical parameters (**Table 1**) were determined using commercially available methods and kits (7170, HITACHI, JAPAN), as determined by the attending cardiologist.

Table 2. Angiographic and ECG characteristics, Echocardiography results according to average NLR tertiles

	Tertile1 (n=230)	Tertile2 (n=232)	Tettile3 (n=230)	1 vs. 2	1 vs. 3	2 vs. 3	Total P
Pain to reperfusion time (hours)	6.36±0.66	6.62±0.41	6.14±0.33	0.698	0.865	0.478	0.833
Admission Electrocardiography							
Number of leads with ST segment elevation	3.01±5.57	4.23±6.81	4.49±7.85	0.145	0.076	0.745	0.165
The elevation degree of ST segment (mm)	4.74±1.95	4.80±1.91	5.19±1.91	0.800	0.057	0.098	0.118
Intervention methods							
Primary PCI	55.22% (127)	51.72% (120)	58.26% (134)	0.451	0.512	0.159	0.369
PCI after thrombolysis	44.78% (103)	48.28% (112)	41.74% (96)				
TIMI flow classification							
Pre-procedure TIMI flow (<3)	72.17% (166)	81.90% (190)	81.74% (188)	0.011*	0.012*	0.967	0.014*
Post-procedure TIMI flow (<3)	3.04% (7)	5.60% (13)	7.83% (18)	0.227	0.024*	0.294	0.079
Number of coronary arteries narrowed							
Single-vessel disease	50.87% (117)	49.13% (114)	40.87% (94)	0.727	0.004*	0.001*	0.002*
Two-vessel disease	27.83% (64)	34.05% (79)	30.00% (69)				
Three-vessel disease	20.00% (46)	15.52% (36)	22.61% (52)				
With left main coronary artery disease	1.30% (3)	1.29% (3)	6.52% (15)				
Echocardiography							
Ejection fraction (%)	57.88±9.83	58.08±9.22	54.90±9.74	0.876	0.023*	0.017*	0.028*
End-systolic volume (ml)	60.01±25.51	58.62±21.45	69.43±29.40	0.690	0.007*	0.003*	0.004*
End-diastolic volume (ml)	137.49±32.90	137.37±27.98	149.80±37.11	0.978	0.006*	0.007*	0.008*

T_1 $NLR_{average}$<3.16, T_2 3.16≤$NLR_{average}$≤4.75, T_3 $NLR_{average}$>4.75. Data shown are % (n), median (IQR) or mean ± SD. *P<0.05. PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

Electrocardiograph (ECG) and echocardiograph examinations

Each patient received an 18-lead ECG immediately after admission and repeated per 2-4 hours. The number of leads with ST-segment elevation, sites of myocardial infarction, episodes of sustained arrhythmia (ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrio-ventricular block and/or new bundle branch block) were recorded. All patients underwent a complete two-dimensional echocardiography evaluation within 48 hours of admission, and left ventricular ejection fraction (LVEF) was calculated by Simpson's method [29].

Interventions and pharmacotherapy

All patients received primary PCI (n=381) or PCI within 90 minutes of thrombolysis (n=311), and the reperfusion strategy was chosen by the attending cardiologists. Concomitant medical treatments during hospitalization and after discharge were prescribed according to American College of Cardiology/American Heart Association guidelines [28] and the judgment of attending cardiologists.

Clinical follow-up and study end points

Patients were followed for a median of 9.43 years (Interquartile range (IQR) 8.65-10.28 years, maximum 11.42 years) by regular clinical examinations, telephone contact with patients or their family, and/or by consulting the Chinese population register.

All-cause mortality, cardiac mortality and MACE events were recorded. MACE events were defined as non-fatal re-infarction, target vessel revascularization, ischemia stroke and cardiac mortality.

Statistical analysis

All data was analyzed using SPSS software (Version 17.0, SPSS Chicago, USA). One-sample Kolmogorov-Smirnov and Levene's tests were employed to determine the distribution characteristics of variables and variance homogeneity. Continuous normally distributed variables were given as mean±standard deviation (SD). Skewed distributed variables were given as median IQR.

The study population was subdivided into tertiles by average NLR (T_1<3.16, T_3>4.75). One-way analysis of variance (ANOVA) was employed to compare clinical characteristics of the tertiles. Categorical variables were given as percentages and compared with the Chi-square test.

The predictive capacity of leukocyte parameters was investigated in 2 ways. Firstly, the

Table 3. Medical therapies and clinical outcomes of population according to average NLR tertiles

	Tertile1 (n=230)	Tertile2 (n=232)	Tettile3 (n=230)	1 vs. 2	1 vs. 3	2 vs. 3	Total P
Medical therapies							
ACEI/ARB	84.35% (194)	87.93% (204)	78.26% (180)	0.298	0.078	0.005*	0.018*
β-receptor blocker	82.61% (190)	78.45% (182)	65.25% (150)	0.293	<0.001*	<0.001*	<0.001*
Nitrate	86.09% (198)	85.34% (198)	71.30% (164)	0.837	<0.001*	<0.001*	<0.001*
Calcium channel blocker	14.78% (34)	12.07% (28)	6.96% (16)	0.355	0.008*	0.082	0.026*
Statin	67.83% (156)	69.83% (162)	53.91% (124)	0.652	0.002*	<0.001*	0.001*
Low molecular heparin	79.13% (182)	79.31% (184)	67.82% (156)	0.964	0.005*	0.004*	0.005*
Anti-platelet therapies							
Aspirin	25.65% (59)	26.29% (61)	30.00% (69)	0.660	0.253	0.474	0.514
Clopidogel	0.87% (2)	2.16% (5)	1.30% (3)				
Aspirin+Clopidogel	52.17% (120)	47.41% (110)	49.57% (114)				
Aspirin+Ticlid	19.13% (44)	21.12% (49)	17.83% (41)				
Aspirin+clopidogel+Ticlid	2.17% (5)	3.02% (7)	1.30% (3)				
In hospital events							
Hospital stay (days)	14.65±9.44	14.32±7.08	14.24±10.21	0.550	0.577	0.967	0.798
Hypotension‡	5.65% (13)	12.93% (30)	20.00% (46)	0.018*	<0.001*	0.022*	<0.001*
Usage of IABP	1.30% (3)	9.05% (21)	11.30% (26)	0.001*	<0.001*	0.344	<0.001*
Arrhythmia†	24.35% (56)	24.14% (56)	43.91% (101)	0.960	<0.001*	<0.001*	<0.001*
Defibrillation	1.74% (4)	5.17% (12)	7.83% (18)	0.087	0.003*	0.185	0.010*
Cardiac mortality	2.17% (5)	4.31% (10)	8.70% (20)	0.292	0.001*	0.031*	0.005*
All cause Mortality	2.17% (5)	4.31% (10)	10.00% (23)	0.310	<0.001*	0.007*	0.001*
Long-term events							
Survival time (years)	9.40±1.69	8.80±2.46	7.16±3.92	0.023*	<0.001*	<0.001*	<0.001*
Cardiac mortality	5.22% (12)	15.52% (36)	27.83% (64)	0.002*	<0.001*	<0.001*	<0.001*
All-cause mortality	9.13% (21)	29.74% (69)	46.09% (106)	<0.001*	<0.001*	<0.001*	<0.001*
MACE events§	13.04% (30)	31.90% (74)	36.52% (84)	<0.001*	<0.001*	0.054	<0.001*

T_1 $NLR_{average}$<3.16, T_2 3.16≤$NLR_{average}$≤4.75, T_3 $NLR_{average}$>4.75. Data shown are % (n), median (IQR) or mean±SD. *P<0.05. ACEI/ARB, Angiotensin-converting enzyme inhibitors/Angiotensin II receptor antagonists; IABP: intra-aortic balloon pump. †Arrhythmia was defined as ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrio-ventricular block and new bundle-branch block during hospitalization. ‡Hypotension was defined as lower blood pressure which was continuously less than 90/60 mmHg, and need to volume expansion therapy or step-up therapy. §MACE events was defined as non-fatal re-infarction, target vessel revascularization, ischemia stroke, and cardiac mortality at 9.43-year clinical follow-up.

mean of leukocyte differential and NLR at given time points was compared between survivor and mortality groups using receiver-operating characteristics (ROC) curve analysis, and Z test was used to disclose the significant difference of area under the curve (AUC) values. Secondly, the influence of NLR and leukocyte differential on long-term mortality were assessed by Cox regression analysis, and crude and adjusted hazard ratios (HR) were presented with their respective 95% confidence intervals (95% CI). Candidate covariates for multivariable analysis were chosen based on previous medical knowledge and independent of their *p* value. From this initial model, a parsimonious, highly predictive model was derived using backward step down selection. The discriminative ability of all multivariable models was assessed by Harrell's C statistics.

The Kaplan-Meier method was used in order to demonstrate the timing of events during long-term follow-up in relation to average NLR, and statistical evaluation was carried out using the Log-rank test. A *P* value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Of the 826 STEMI patients hospitalized at Xuanwu hospital, Beijing, China between January 2, 2002 and January 16, 2005 within the first 12 hours of symptom onset, 692 patients were available for the final analysis, of which 196 died during the clinical follow-up period (median 9.43 years). Blood samples were taken following admission, a median of

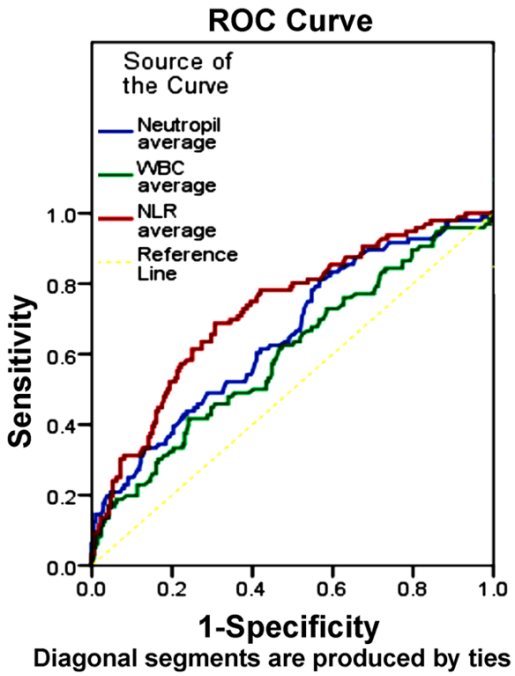

Figure 2. Receiver-operating characteristic curves for NLR and leukocyte counts prediction of mortality. ROC curves were plotted for the average NLR values and leukocyte and neutrophil counts. The $NLR_{average}$ curve AUC (0.726) was significantly higher than ther $leukocyte_{average}$ (0.600) and $Neutrophil_{average}$ (0.655). The optimal threshold maximizing the composite of specificity and sensitivity in the $NLR_{average}$ prediction of mortality was calculated to be 4.22. The optimal cut-off, 4.22, predicted mortality with a specificity of 68.8%, sensitivity of 69.3%, positive predictive value of 50.37%, and negative predictive value of 83.26%.

6.86 hours (IQR 6.12-7.60 hours) after symptom onset (n=692), 24 and 72 hours later (n=692, n=619, respectively), and before discharge (about 14±2 days after symptom onset, n=632).

Patients that survived during the follow up period (n=496) had lower leukocyte and neutrophil counts, lower NLR values, and higher lymphocyte counts throughout hospitalization than patients that did not survive (**Figure 1**).

Neutrophil-to-lymphocyte ratio

The average NLR value detected during hospitalization was calculated for each patient, and patients were divided into tertiles according to average NLR: T_1 $NLR_{average}$<3.16, T_2 3.16≤$NLR_{average}$≤4.75, T_3 $NLR_{average}$>4.75. Patients with $NLR_{average}$>4.75 tended to be older and were less likely to have a history of dyslipedimia. In addition, faster heart rates, advanced Killip class were more prevalent in T_3, and patients in T_3 had higher creatine-kinase and glucose levels, and lower triglyceride and cholesterol levels on admission. Furthermore, higher NLR was positively associated with higher leukocyte and neutrophil counts, and negatively related with lower lymphocyte and monocyte counts (**Table 1**).

Neither the reperfusion time, electrocardiography at admission, nor intervention methods employed differed significantly between T_1, T_2 or T_3. However, the fraction of patients with thrombolysis in myocardial infarction (TIMI) flow classification under three either pre- or post- surgery was significantly higher in T_3 than T_1 (P<0.05). The number of coronary arteries narrowed was significantly higher in T_3 than T_1 and T_2 (P<0.05) (**Table 2**). In addition, the average end systolic- and diastolic- volumes of T_3, were significantly higher than the other groups, and T_3 patients had the lowest LVEF (P<0.05) (**Table 2**).

While there was no significant difference in the length of hospital stay between T_1, T_2 and T_3, β-receptor blockers, calcium channel blockers, nitrates, statins and low molecular heparins were less often employed to treat T_3 than T_1 (P<0.05). Hypotension was observed significantly less frequently in T_1 (5.65% patients) than T_2 or T_3 (12.93% or 20.00% patients, P<0.001). Intra-aortic balloon pumps (IABP) were also used less often in T_1 (1.30%) than T_2 or T_3 (9.05% or 11.3%, P<0.001), and arrhythmia was less frequently observed in T_1 (24.35%) than T_2 or T_3 (24.14% or 43.91%, P<0.001), as was defibrillation (1.74% *vs.* 5.17% *vs.* 7.83%, P=0.010). Within the period of hospitalization cardiac mortality was less frequently observed in T_1 (2.17%) than T_2 (4.31% or 8.7%, P=0.005), as was all-cause mortality (2.17% *vs.* 4.31% *vs.*10%, P=0.001) (**Table 3**).

Patients in T_3 survived, on average, less long than patients in T_2 or T_1 (9.40±1.69 *vs.* 8.80±2.46 *vs.* 7.16±3.92 years, P<0.001), and had the highest incidence of cardiac mortality (5.22% *vs.*15.52% *vs.* 27.83%, P<0.001), all-cause mortality (9.13% *vs.* 29.74% *vs.* 46.09%, P<0.001) and MACE events (13.04% *vs.* 31.90% *vs.* 36.52%, P<0.001) within the follow up period (median 9.43 (8.65-10.28) years) (**Table 3**).

Table 4. Hazard ratios for long-term all-cause mortality according to leukocyte and neutrophil counts by univariate Cox regression analysis and stepwise multivariate Cox regression

	Univariate Cox regression analyses					Multivariate COX regression analyses#		
Variables	Non-adjusted HR (95% CI)	*P* value	Variables	Non-adjusted HR (95% CI)	*P* value	Variables	Adjusted HR (95% CI)	*P* value
$NLR_{Average}$	1.407 (1.301-1.521)	<0.001*	Gender	2.288 (1.569-3.336)	<0.001*	$NLR_{Average}$	1.481 (1.279-1.715)	<0.001*
Maximum	1.064 (1.040-1.088)	<0.001*	Age	1.078 (1.056-1.100)	<0.001*	Maximum	1.043 (1.003-1.083)	0.033*
Admission	1.244 (1.172-1.320)	<0.001*	IABP use	2.000 (1.029-3.884)	0.041*	Admission	1.298 (1.183-1.425)	<0.001*
24hours	1.135 (1.077-1.195)	<0.001*	Smoking	0.613 (0.419-0.895)	0.011*	24hours	1.166 (1.058-1.285)	0.025*
72hours	1.145 (1.095-1.198)	<0.001*	HR	1.040 (1.030-1.051)	<0.001*	72hours	1.160 (1.058-1.271)	0.002*
Last	1.057 (1.032-1.082)	<0.001*	SBP	0.993 (0.984-1.001)	0.099	Last	1.046 (1.009-1.085)	0.015*
$WBC_{Average}$	1.261 (1.167-1.362)	<0.001*	Defibrillation	3.330 (1.964-5.464)	<0.001*	$WBC_{Average}$	1.222 (1.077-1.386)	0.002*
Maximum	1.128 (1.070-1.189)	<0.001*	Diabetes mellitus	1.258 (0.838-1.888)	0.268	Maximum	1.130 (1.040-1.228)	0.004*
Admission	1.169 (1.100-1.243)	<0.001*	OMI	0.538 (0.198-1.463)	0.225	Admission	1.238 (1.143-1.341)	<0.001*
24hours	1.087 (1.024-1.154)	<0.001*	Pacemaker use	1.802 (0.094-3.448)	0.075	24hours	1.054 (0.965-1.152)	0.241
72hours	1.167 (1.093-1.247)	<0.001*	EF values	0.035 (0.003-0.398)	0.007*	72hours	1.228 (1.108-1.360)	<0.001*
Last	1.179 (1.114-1.247)	<0.001*	ACEI use	0.397 (0.262-0.601)	<0.001*	Last	1.070 (0.969-1.181)	0.179
$N_{Average}$	1.279 (1.218-1.344)	<0.001*	Statin use	0.573 (0.399-0.823)	0.003*	$N_{Average}$	1.475 (1.278-1.702)	<0.001*
Maximum	1.165 (1.106-1.228)	<0.001*	Glucose	1.004 (1.002-1.006)	<0.001*	Maximum	1.212 (1.113-1.319)	<0.001*
Admission	1.257 (1.175-1.344)	<0.001*	Creatinine	1.063 (0.880-1.284)	0.525	Admission	1.369 (1.244-1.507)	<0.001*
24hours	1.150 (1.081-1.222)	<0.001*	Impaired vessels	1.734 (1.399-2.148)	<0.001*	24hours	1.103 (0.994-1.225)	0.065
72hours	1.209 (1.135-1.288)	<0.001*	P-to-R time	0.997 (0.968-1.027)	0.852	72hours	1.267 (1.140-1.408)	<0.001*
Last	1.216 (1.157-1.279)	<0.001*	Invention methods	0.926 (0.824-1.041)	0.197	Last	1.245 (1.112-1.395)	<0.001*
$L_{Average}$	0.556 (0.404-0.766)	<0.001*				$L_{Average}$	0.559 (0.337-0.926)	0.024*
Minimum	0.495 (0.343-0.713)	<0.001*				Minimum	0.499 (0.258-0.996)	0.039*
Admission	0.625 (0.462-0.847)	0.002*				Admission	0.584 (0.388-0.878)	0.010*
24hours	0.809 (0.626-1.045)	0.105				24hours	1.050 (0.691-1.597)	0.818
72hours	0.796 (0.602-1.054)	0.111				72hours	1.265 (0.814-1.966)	0.295
Last	0.561 (0.393-0.801)	0.001*				Last	0.506 (0.316-0.808)	0.004*
$M_{Average}$	0.195 (0.069-0.550)	0.002*				$M_{Average}$	0.183 (0.032-1.057)	0.058
Maximum	0.310 (0.147-0.653)	0.002*				Maximum	0.530 (0.191-1.466)	0.221
Admission	0.266 (0.069-1.022)	0.054				Admission	0.732 (0.211-2.543)	0.624
24hours	0.333 (0.124-0.891)	0.028*				24hours	0.734 (0.229-2.347)	0.602
72hours	0.331 (0.142-0.768)	0.010*				72hours	0.166 (0.026-1.057)	0.057
Last	0.170 (0.052-0.559)	0.004*				Last	0.034 (0.003-0.3600	0.005

HR: hazard ratio; CI: confidence interval; *P<0.05. ACEI/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor antagonists; EF: ejection fraction; SBP: systolic blood pressure; IABP: intra-aortic balloon pump; HR: heart rates; P-to-R time: pain to reperfusion time; NLR: neutrophil-to-lymphocyte ratio; N: neutrophil count; M: monocyte count; L: lymphocyte count; OMI: previous myocardial infarction. Imparied vessels, numbers of coronary arteries narrowed (>70%). #Final Cox model adjusted by: average NLR, gender, age, systolic blood pressure, heart rates, ejection fraction, statin use, ACEI/ARB use, defibrillation, glucose, usage of pacemaker, usage of IABP, previous myocardial infarction, smoking, diabetes mellitus, impaired vessels (numbers of coronary arteries narrowed >70%), invention methods (including: primary PCI or PCI after thrombolysis).

Predictive value of NLR

We sought to determine the relative capacities for leukocyte counts to predict mortality via ROC curve analysis. The area under the curve (AUC) for $NLR_{average}$ (0.726, 95% CI 0.683-0.769, P<0.001) was greater than that for $neutrophil_{average}$ (AUC=0.655, 95% CI 0.608-0.701, P<0.001) and $leukocyte_{average}$ (AUC =0.600, 95% CI 0.551-0.649, P<0.001) (Z test: $NLR_{average}$ *vs.* $neutrophil_{average}$, Z value=2.96>1.96, P<0.05; $NLR_{average}$ *vs.* $leukocyte_{average}$, Z value=3.78>1.96, P<0.05) (**Figure 2**). The optimal $NLR_{average}$ cut-off, 4.22, predicted mortality with a specificity of 68.8%, sensitivity of 69.3%, positive predictive value of 50.37%, and negative predictive value of 83.26%.

Independent predictors of long-term mortality were determined by a backward stepwise multivariate COX regression analysis (**Table 4**). In univariable COX regression analysis, the HR for mortality according to $NLR_{average}$ was 1.407 (p<0.001); After adjustment for confounding factors (gender, age, smoking, previous myocardial infarction, diabetes mellitus, systolic blood pressure, heart rates, glucose level, invention methods, impaired vessels, ejection fraction, defibrillation, usage of pacemaker, usage of IABP, statin use or ACEI/ARB use)

Table 5. Hazard ratios for all-cause mortality according to $NLR_{average}$ in different multivariate Cox regression models

	Multivariate Cox regression models								
	Model 1 (NLR as continuous variables)			Model 2 (NLR as binary variables)[†]			Model 3 (NLR as tertile variables)[&]		
Variable	Adjusted HR (95% CI)	*P* value	C Statistics	Adjusted HR (95% CI)	*P* value	C Statistics	Adjusted HR (95% CI)	*P* value	C Statistics
Smoking	0.559 (0.285-1.099)	0.092	0.837	-	-	0.852	-	-	0.861
Diabetes mellitus	3.115 (1.481-6.554)	0.003*		-	-		-	-	
Gender (women)	1.997 (0.971-4.111)	0.060		2.036 (1.061-3.905)	0.032*		1.957 (1.323-2.894)	0.001*	
Heart rates	-	-		1.026 (1.007-1.046)	0.008*		1.022 (1.003-1.041)	0.023*	
Defibrillation	14.040 (4.439-44.407)	<0.001*		9.998 (3.993-25.035)	<0.001*		13.226 (4.957-35.289)	<0.001*	
Impaired-vessels	1.787 (1.239-2.577)	0.002*		1.918 (1.286-2.960)	0.001*		1.957 (1.323-2.894)	0.001*	
ACEI use	-	-		0.476 (0.220-1.026)	0.058		0.452 (0.206-0.992)	0.048*	
NLR	1.481 (1.279-1.715)	<0.001*		-	-		-	-	
NLR>4.22	-	-		2.989 (1.238-7.215)	0.015*		-	-	
NLR tertiles	-	-		-	-			0.004*	
Tertile2	-	-		-	-		2.138 (0.823-5.557)	0.119	
Tertile3	-	-		-	-		4.621 (1.776-12.025)	0.002*	

HR: hazard ratio; CI: confidence interval; *P<0.05. ACEI/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor antagonists; Impaired vessels: numbers of coronary arteries narrowed (>70%). [#]Final Cox model adjusted by average NLR, gender, age, systolic blood pressure, heart rates, ejection fraction, statin use, ACEI/ARB use, defibrillation, glucose, usage of pacemaker, usage of IABP, previous myocardial infarction, smoking, diabetes mellitus, impaired vessels (numbers of coronary arteries narrowed >70%), invention methods (including primary PCI or PCI after thrombolysis). [†]NLR as a binary variable: average NLR as binary variables categorized by best cut-offs of ROC analysis (4.22). [&]NLR tertiles: average NLR as categorical variables stratified into tertiles with cut offs of NLR at the 33rd percentile (NLR=3.16) and 67th percentile (NLR=4.75) when arranged in ascending order.

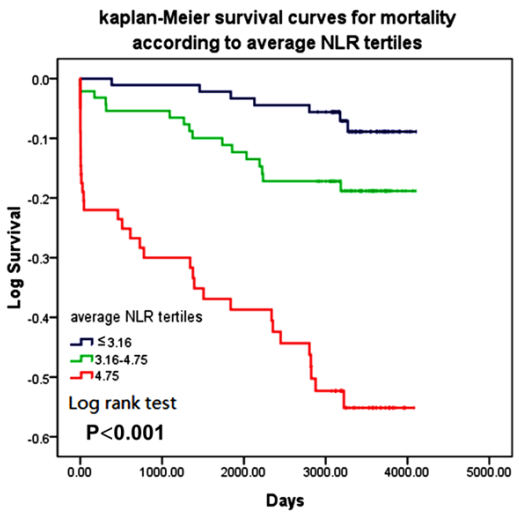

Figure 3. Kaplan-Meier survival curves for 9.43 (8.65-10.28) years mortality according to $NLR_{average}$ at tertiles, T_1 $NLR_{average}$<3.16, T_2 3.16≤$NLR_{average}$≤4.75, T_3 $NLR_{average}$>4.75) (Log rank test, P<0.001).

$NLR_{average}$ remained a strong predictor of long-term mortality, with an HR of 1.481 (P<0.001); Furthermore, stratified into tertiles, the HR increased by 2.138, 95% CI (0.823-5.557) per tertile (P=0.119) and 4.621, 95% CI (1.776-12.025), (P=0.002) for mortality. Otherwise, when $NLR_{average}$ was assessed as binary variables, the HR was 2.989, 95% CI (1.238-7.215), (P=0.015). Higher Harrell's c statistic values were obtained from the model including $NLR_{average}$ Tertiles (0.861) or $NLR_{average}$ binary (0.852), in contrast with the lower values derived from the model employing NLR as a continuous variable (0.837) (**Table 5**).

Kaplan-Meier analysis revealed significantly reduced long-term event-free survival in patients in the highest T_3 in comparison with those in T_1, and all-cause mortality differed significantly between tertiles. (Log rank test, p <0.001) (**Figure 3**).

Discussion

Many studies have demonstrated a correlation between NLR and clinical adverse outcomes [3, 6-9, 12, 13, 15-17, 19, 20], but few have compared the prognostic value of NLR and leukocyte subgroups at different time points following myocardial infarction. We conducted this study to determine the predictive value of NLR in Chinese patients presenting with STEMI.

Average NLR was a significant predictor of subsequent all-cause mortality and outperformed the predictive ability of absolute leukocyte, lymphocyte or neutrophil counts. After adjustment for potential confounding factors, average NLR remained a significant predictor of mortality. When patients were divided into tertiles according to NLR, the highest incidence of adverse events, both during hospitalization and follow-up, was recorded in patients in the third tertile.

Only three studies have been previously published concerning the predictive capacity of NLR in STEMI or NSTEMI [14, 21, 27] in different time. Park *et al.* reported that when patients were stratified by NLR measured 24 hours after admission for STEMI, NLR predicted mortality more accurately than when NLR at admission was used [14]. However, Azab *et al.* employed average NLR, calculated as an average of the NLR during hospitalization, was a better predictor of outcome than other max NLR, or NLR at admission or discharge in patients presenting with NSTEMI [21]. And Núñez *et al.* reported that the maximum NLR recorded during the first 96 hours after STEMI predicted mortality better than the maximum value of leucocyte [27].

We found that NLR measured at admission, 24- and 72-hour after admission, before discharge, and both max and average NLR during hospitalization all predicted mortality in patients presenting with STEMI [4, 13, 18]. $NLR_{average}$ predicted more accurately than other absolute leucocyte, lymphocyte or neutrophil counts. Confirming the work of Azab *et al.* [21] we found that $NLR_{average}$ was significantly associated with clinical adverse-outcomes (including: lower TIMI grade pre- [15] or post- [13, 17] PCI, multivessel disease [6, 7, 16], advanced heart failure [19, 23] and arrhythmia [27]), a high incidence of MACE events [13, 16, 18, 25] and mortality [12, 20], both during hospitalization or long-term follow-up, consistent with previous studies of $NLR_{admission}$ [6, 7, 13, 15-17, 19, 23, 27]. Furthermore, we found high $NLR_{average}$ predicted distinctive cardiac dilatation, and elevated incidence of hypotension and defibrillation during hospitalization, representing activated-neutrophils, activation of sympathetic nervous, the first report of this finding to our knowledge. After adjustment for recognized risk factors (gender, heart rates, defibrillation and multivessel disease and etc.) $NLR_{average}$ remained a

significant predictor of mortality. Therefore we conclude that $NLR_{average}$ represents a useful indictor for risk stratification and prognostics.

One major obstacle to implementing NLR-based predictive prognostic matrices is determining an appropriate cut-off value. The appropriate NLR cut-off is likely to change with the stage of illness, laboratory techniques employed, concomitant infection and patient demographic characteristics [4]. Previous studies have recommended NLR cut-off points between 4.0-5.4 in AMI via ROC analysis [13, 14, 21, 25]. However, In this study, a multivariable models in which patients were stratified into tertliles by $NLR_{average}$ achieved a higher c value than a model employing a binary $NLR_{average}$ categorized by ROC cutoffs, and the tertile cut-offs were very close to those employed by Azab *et al.* [21]. Therefore, a large multicenter study employing a clinically significant NLR cutoff rather than NLR interval grouping will be required to develop an appropriate cut-off for NLR [21].

We found that patients' $NLR_{average}$ corelatred negatively with employment of medical therapies, suggesting that either medication promoted reduction of NLR via anti-inflammatory actions [15, 21], or that high $NLR_{average}$ indicated that currently employed medical strategies were inapropriate. Patients in highest $NLR_{average}$ tertile presented with the highest frequency of severe illness (hypotension or arrhythmia) inhibiting the use of medicine, and suggesting treatment intolerance of patients themselves. Therefore, high $NLR_{average}$ might represent an index for therapeutic modulation [13].

Consistent with previous reports, we observed that older patients had highest tertile $NLR_{average}$. Older patients more frequently present with a higher inflammatory burden and age-associated diseases [20, 23]. Furthermore, we found that the lowest tertile $NLR_{average}$ was associated with hyperlipidemia. Low NLR may result from both increased migration of neutrophils from blood vessels to peripheral tissues, and increased lymphocyte counts in the acute phase of STEMI [12-14, 21]. We also found the highest $NLR_{average}$ tertile to be associated with increased heart rates, glucose and CK, suggesting activation of the sympathetic nervous system and renin-angiotensin system [19]. These observations highlight the hypothesis that NLR may be a pathogenesis factor of atherosclerosis, not only represent a mere systemic inflammatory response to an infarcted myocardium, and these issues require further study [21].

Limitations

The limitations of our study were (1) This was a non-randomized single center study that included a relatively small number of patients was subject to selective bias; (2) NLR might be a useful marker in risk scoring, while the cut-off points and normal ranges should be furthermore determined by randomized multicenter trials. (3) We did not compare the prognostic value of NLR with other inflammatory markers such as: Hs-CRP, pro-BNP and etc.

Conclusions

This study demonstrated that average NLR was a useful and powerful indicator of mortality and adverse-outcomes both during hospitalization and long-term follow-up in Chinese patients presenting with STEMI.

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Disclosure of conflict of interest

None.

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