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Monocyte/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients with non-ST-elevation myocardial infarction

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Abstract

Monocyte/lymphocyte ratio (MLR), a widely used inflammation maker for prognosis of cancer, tuberculosis, and autoimmune diseases, has attracted more and more attention for its application to cardiovascular disease. The aim of the present study was to investigate the relationship of MLR with the severity of coronary lesion and clinical outcomes in non-ST-elevation myocardial infarction (NSTEMI) patients.

963 consecutive NSTEMI patients (mean age, 60.77 ± 11.34; 758 male) undergoing coronary angiography were analyzed and followed in 3 groups according to the average MLR tertile (low MLR <0.23, n = 321; intermediate MLR 0.23–0.35, n = 322; high MLR >0.35, n = 320) in this study. The severity of coronary lesion was determined by Gensini score. Multiple linear regression analysis was used to examine the correlation between MLR and the severity of coronary lesion. Kaplan–Meier curve was performed to compare the long-term major adverse cardiac event (MACE)-free survival. Logistic regression analysis and Cox proportional hazard regression model were used to assess the independent predictors for in-hospital and long-term MACE.

MLR (*B*: 0.281, 95% confidence interval [CI]: 0.130–0.432, $P < .001$) and high-sensitivity C-reactive protein (*B*: 0.017, 95% CI: 0.010–0.024, $P < .001$) were both independently correlated with the severity of coronary lesion, while neutrophil/lymphocyte ratio was not. The frequencies of in-hospital MACE (1.6%, 2.2%, 4.7%, $P = .016$) and long-term MACE (13.3%, 16.2%, 27.2%, $P < .001$) both increased among the 3 groups. Kaplan–Meier curve analysis indicated that patients in high MLR group had worse long-term MACE-free survival than the patients in low MLR group ($P_2 < .001$) and intermediate MLR group ($P_3 = .004$) during a median follow-up of 22 (12–35) months. MLR was an independent predictor for in-hospital MACE (adjusted odds ratio: 2.891, 95% CI: 1.265–8.354, $P = .026$) and long-term MACE (adjusted hazard ratio: 1.793, 95% CI: 1.169–2.515, $P = .012$) in NSTEMI patients.

MLR is independently correlated with the severity of coronary lesion and has better performance to reflect the severity of coronary lesion than NLR. MLR is an independent predictor for the MACE in NSTEMI patients.

Abbreviations: ACS = acute coronary syndrome, BMI = body mass index, CAD = coronary artery disease, CKMB = creatine kinase isoenzyme, DBP = diastolic pressure, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin, HDL-C = high density lipoprotein cholesterol, HR = heart rate, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low density lipoprotein cholesterol, MACE = major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, NSTEMI = non-ST-elevation myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, SBP = systolic blood pressure, SCr = serum creatinine, STEMI = ST-elevation myocardial infarction, TC = total cholesterol, TG = triglyceride.

Keywords: Gensini score, major adverse cardiac event (MACE), monocyte/lymphocyte ratio (MLR), non-ST-elevation myocardial infarction (NSTEMI)

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1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide,[1,2] and non-ST-elevation myocardial infarction (NSTEMI) is one of the leading causes of death in patients with CAD.[3] Patients with NSTEMI tend to have multivessel coronary artery lesions and more unfavorable long-term outcome than the patients with ST-elevation myocardial infarction (STEMI).[4,5] Therefore, the early risk stratification and management of patients in NSTEMI are crucial for improving the prognosis of these patients. The severity of coronary artery lesions is an important index for risk stratification of CAD and directly determines the optimal treatment strategy.

The role of inflammation in the initiation and progression of coronary atherosclerosis is well described, high levels of inflammatory markers have been found in association with the severity of CAD and the prognosis of CAD patients.[6,7] Therefore, an appropriate coronary inflammatory marker is of great significance for early risk stratification and prognostic evaluation of CAD patients. High-sensitivity C-reactive protein (hs-CRP), a nonspecific inflammatory marker, has been reported to be related to the risk of coronary heart disease and cardiovascular events in patients with acute coronary syndrome (ACS),[8,9] but it is susceptible to tissue injury, infection, abnormal liver and kidney function, and other noncardiac factors. White blood cell subtypes have been considered to play a crucial role in the pathogenesis of atherogenesis and atherothrombosis, which are closely related to the cardiovascular adverse events.[10,11] Currently, numerous studies have shown that neutrophil/lymphocyte ratio (NLR) is related to the severity of CAD, the degree of myocardial damage and the clinical outcome of CAD.[12–14]

Compared with neutrophils, monocytes, and monocyte-derived macrophages play more important roles in the initiation and progression of atherosclerotic disease.[15,16] There have been several studies showing that high monocyte count or low lymphocyte are closely related to the adverse cardiovascular events of CAD patient.[11,17] Monocyte/lymphocyte ratio (MLR), a combined inflammatory marker with monocyte count divided by lymphocyte count, has been widely used to the studies of cancer, tuberculosis, and autoimmune diseases.[18–21] In recent years, more and more attention has been attracted to MLR's applications for cardiovascular diseases.[22–24] However, the relationship of MLR with the severity of coronary artery lesions and clinical outcomes in NSTEMI patients has not been fully elucidated.

The aim of this study was to investigate the relationship of MLR with the severity of coronary lesion (through Gensini scoring system) and the major adverse cardiac event (MACE) in NSTEMI patients Table S1, Fig. S1 and Fig. S2, http://links.lww.com/MD/D75.

2. Methods

2.1. Study population and protocol

One thousand three hundred sixty-five participants who were diagnosed with NSTEMI were consecutively screened at the First Affiliated Hospital of Xi'an Jiao Tong University from December 2013 to December 2017. The diagnosis of NSTEMI was based on 2014 AHA/ACC guideline.[25] Exclusion criteria included age <18 years, congenital heart disease, cardiomyopathy, valvular disease, hematologic disease, severe liver or renal dysfunction, stroke, tumor, thyroid disease, autoimmune disease, acute and chronic infectious disease, chronic obstructive pulmonary disease, the patients without coronary angiography, and the patients without informed consent. Of the 1365 patients, only 963 were eligible for study inclusion. According to the average MLR tertile (low MLR <0.23, n = 321; intermediate MLR 0.23–0.35, n = 322; high MLR >0.35, n = 320), all the included patients were divided into 3 groups for data analysis, and then followed up until October 2018 or until the occurrence of a MACE (Fig. 1). Global registry of acute coronary events (GRACE) risk score and thrombolysis in myocardial infarction (TIMI) risk score were calculated for each eligible index case on admission according to 2014 AHA/ACC guideline.[25] The study protocol was approved by the Ethical Committee of the First Affiliated Hospital of Xi'an Jiao Tong University, and the study conforms to the Declaration of Helsinki.

2.2. Definition of coronary risk factors

Hypertension was defined as >140/90 mm Hg or taking antihypertensive medication. Diabetes mellitus was defined by the patient having been informed of this diagnosis by a physician before admission or was receiving hypoglycemic treatments (dietary, oral anti-diabetic agents, or insulin) or the patients who presented to the serum glycosylated hemoglobin (HbA1c%) levels ≥6.5%. Dyslipidemia was defined by fasting serum total cholesterol (TC) >220 mg/dL, low density lipoprotein cholesterol (LDL-C) >140 mg/dL, high-density lipoprotein cholesterol (HDL-C) <35 mg/dL, triglyceride (TG) >150 mg/dL or the use of lipid-lowering medications. Smoking index was calculated from the average number of smoking root per day multiplied by the number of smoking years.

2.3. Measurement of blood parameters

Venous blood samples of all patients were drawn from upper limb. The blood parameters were measured by clinical laboratory of the First Affiliated Hospital of Xi'an Jiao Tong University. The leukocyte count, monocyte count, neutrophil count, lymphocyte count, and serum hs-CRP were measured on admission. The MLR and NLR were respectively computed using the absolute monocyte or neutrophil count divided by the absolute lymphocyte count. Patients were advised to fast at least for 12 hours before biochemical indicators investigations. The biochemical indicators included HbA1c%, TC, LDL-C, HDL-C, TG, serum creatinine (SCr), and uric acid. Plasma hs-troponin T, creatine kinase isoenzyme (CKMB) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured on admission and serially every 6 hours until the detection of 2 consecutive declining measurements and for at least 36 hours to determine the Peak hs-troponin T, Peak CKMB, and peak NT-proBNP in NSTEMI patients.

2.4. Assessment of the severity of coronary lesion

Coronary angiogram was assessed by 2 interventional physicians blindly. The diseased coronary vessel was defined as a lesion with ≥50% stenosis. The results of coronary angiograms were scored based on the Gensini scoring system. Gensini score is a widely used evaluation system to reflect the severity of coronary lesion, which is determined according to the severity of stenosis as

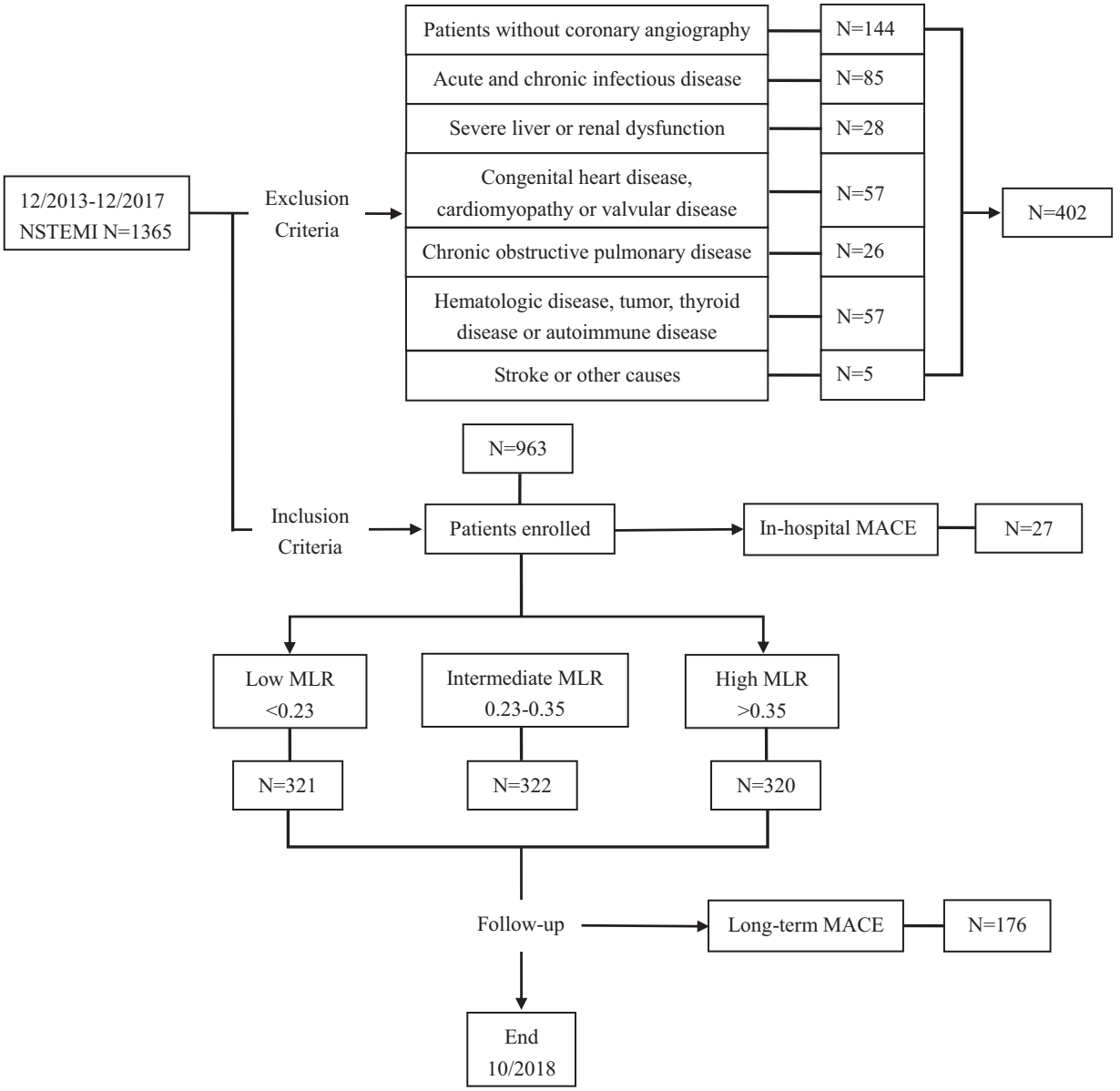

Figure 1. The research flow chart. In-hospital MACE = in-hospital major adverse cardiac event, long-term MACE = long-term major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NSTEMI = non-ST-elevation myocardial infarction.

follows: 1 point for <25% stenosis, 2 points for 26% to 50% stenosis, 4 points for 51% to 75% stenosis, 8 points for 76% to 90% stenosis, 16 points for 91% to 99% stenosis, and 32 points for total occlusion. The score is then multiplied by a factor representing the importance of the lesion's position in the coronary artery system. For example, 0.5 for small branch of coronary artery, 1 for the distal left anterior descending, overall region of right coronary artery or mid-distal region of the left circumflex artery, 1.5 for the mid-region, 2.5 for the proximal left anterior descending or proximal left anterior descending or proximal left circumflex artery, and 5 for the left main coronary artery.[26]

2.5. Definition of in-hospital MACE and long-term MACE

The in-hospital MACE was defined as cardiac death, cardiac arrest, cardiac rupture, cardiogenic shock, cardiogenic syncope, acute congestive heart failure, malignant arrhythmic events during hospitalization. The long-term MACE, including cardiac death, myocardial infarction, unstable angina pectoris, malignant arrhythmia, cardiac arrest, cardiogenic shock, cardiogenic syncope, and rehospitalization for heart failure decompensation or coronary revascularization, were ascertained from a review of medical records and confirmed by direct dialogue with the patients, their families, and physicians following discharge.

2.6. Statistical analysis

Continuous variables were defined as mean ± standard deviation or median (interquartile range); categorical variables were expressed as percentages. For continuous variables, the Kolmogorov–Smirnov test was applied to test the normality of distribution, 1-way analysis of variance or Kruskal–Wallis test was used to compare depending on the probability distribution of

the variables. For categorical variables, the chi-square test was used. Because of a positively skewed distribution, Gensini score was lg-transformed for linear regression analysis. Linear regression analysis was used to test univariate correlations in the whole study population, and the significant correlation variables were further taken into multiple linear regression analysis (stepwise). Kaplan–Meier curve analysis was performed and comparisons of the long-term MACE-free survival was

Table 1

Baseline characteristics of the NSTEMI patients based on the tertile of MLR.

Variable	Overall (n = 963)	Low MLR (n = 321)	Intermediate MLR (n = 322)	High MLR (n = 320)	*P*-value for trend
Age, yr	60.77 ± 11.34	58.55 ± 11.08	61.14 ± 11.16	62.63 ± 11.45	.000
Male, n (%)	758 (78.7%)	240 (74.8%)	255 (79.2%)	263 (82.2%)	.022
BMI, kg/m^2	25.0 ± 4.5	25.6 ± 5.0	24.9 ± 4.0	24.4 ± 4.3	.015
Hypertension, n (%)	592 (61.5%)	185 (57.6%)	197 (61.2%)	210 (65.6%)	.038
DM, n (%)	292 (30.3%)	103 (32.1%)	90 (28.0%)	99 (30.9%)	.751
Dyslipidemia, n (%)	613 (63.7%)	203 (63.2%)	212 (65.8%)	198 (61.9%)	.720
History of CAD, n (%)	447 (46.4%)	134 (41.7%)	144 (44.7%)	169 (52.8%)	.005
History of MI, n (%)	76 (7.9%)	21 (6.5%)	18 (5.6%)	37 (11.6%)	.019
History of revascularization, n (%)	111 (11.5%)	36 (11.2%)	36 (11.2%)	39 (12.2%)	.700
Family history, n (%)	135 (14.0%)	49 (15.2%)	46 (14.3%)	40 (12.5%)	.306
Smoking index	200 (0–600)	200 (0–600)	240 (0–600)	205 (0–600)	.632
HR	72.6 ± 14.3	70.3 ± 13.3	72.7 ± 13.6	74.7 ± 15.6	.000
SBP	133.2 ± 20.6	134.8 ± 20.0	133.0 ± 21.5	131.7 ± 20.4	.151
DBP	79.6 ± 12.8	80.6 ± 12.5	79.5 ± 13.0	78.7 ± 13.0	.166
Killip class III or IV	30 (3.1%)	3 (0.9%)	7 (2.2%)	20 (6.3%)	.000
TIMI risk score	3.4 ± 1.3	3.2 ± 1.3	3.4 ± 1.3	3.7 ± 1.3	.000
GRACE risk score	115.0 ± 32.9	104.9 ± 28.9	115.6 ± 30.4	124.7 ± 36.1	.000
Laboratory parameters					
HbA1c%	6.22 ± 1.33	6.39 ± 1.51	6.14 ± 1.27	6.13 ± 1.17	.023
TC, mg/dL	156.50 ± 47.53	161.98 ± 63.34	156.22 ± 39.07	151.45 ± 35.32	.024
LDL, mg/dL	93.41 ± 31.47	95.31 ± 30.57	95.10 ± 33.28	89.85 ± 30.25	.054
HDL, mg/dL	36.66 ± 9.63	36.70 ± 10.93	36.08 ± 8.87	37.19 ± 8.98	.368
TG, mg/dL	154.50 ± 110.32	174.88 ± 135.67	154.54 ± 95.94	134.62 ± 91.41	.000
SCr, μmol/L	66.77 ± 17.21	64.24 ± 14.46	66.83 ± 18.51	69.27 ± 18.04	.001
UA, μmol/L	324.59 ± 86.78	331.99 ± 86.88	321.99 ± 82.54	319.84 ± 90.57	.171
Leukocyte, 10^9/L	8.53 ± 2.87	7.91 ± 2.26	8.38 ± 2.69	9.29 ± 3.40	.000
Monocyte, 10^9/L	0.46 ± 0.23	0.34 ± 0.12	0.44 ± 0.15	0.61 ± 0.28	.000
Neutrophil, 10^9/L	6.37 ± 2.70	5.49 ± 2.10	6.26 ± 2.50	7.37 ± 3.08	.000
Lymphocyte, 10^9/L	1.58 ± 0.67	1.96 ± 0.72	1.56 ± 0.53	1.22 ± 0.52	.000
MLR	0.28 (0.21–0.40)	0.18 (0.15–0.21)	0.28 (0.26–0.31)	0.46 (0.40–0.58)	.000
NLR	3.89 (2.64–5.93)	2.65 (1.99–3.69)	3.71 (2.78–5.37)	5.66 (4.26–8.37)	.000
hs-CRP, mg/L	3.81 (1.36–9.65)	2.22 (0.98–5.30)	3.58 (1.32–9.44)	7.52 (2.67–10.10)	.000
Peak hs-troponin T, ng/ml	0.46 (0.15–1.10)	0.25 (0.08–0.66)	0.53 (0.22–1.13)	0.74 (0.25–1.67)	.000
Peak CKMB, IU/L	39.0 (16.0–91.0)	30.0 (13.6–71.0)	40.7 (16.0–96.3)	51.0 (20.9–114.0)	.000
Peak NT-proBNP, IU/L	623.6 (264.8–1596.8)	337.5 (152.2–881.7)	675.9 (328.8–1444.0)	1039.5 (372.9–2538.5)	.000
Prior medications					
Aspirin, n (%)	205 (21.3%)	66 (20.6%)	66 (20.5%)	73 (22.8%)	.487
Beta-blocker, n (%)	89 (9.2%)	34 (10.6%)	29 (9.0%)	26 (8.1%)	.281
Stain, n (%)	144 (15.0%)	49 (15.3%)	43 (13.4%)	52 (16.3%)	.715
ACEI/ARB, n (%)	123 (12.8%)	41 (12.8%)	47 (14.6%)	35 (10.9%)	.487
Angiographic characteristics					
Arteriography TIMI flow = 0/1, n (%)	409 (42.5%)	94 (29.3%)	142 (44.1%)	173 (54.1%)	.000
Diseased coronary vessels, n (%)					
Right coronary artery	621 (64.5%)	178 (55.5%)	216 (67.1%)	227 (70.9%)	.000
Left anterior descending artery	819 (85.0%)	260 (81.0%)	274 (85.1%)	285 (89.1%)	.011
Left circumflex artery	728 (75.6%)	220 (68.5%)	240 (74.5%)	268 (83.8%)	.000
Left main coronary artery	79 (8.2%)	17 (5.3%)	27 (8.4%)	35 (10.9%)	.010
Number of diseased vessels, n (%)					
Single	165 (17.1%)	69 (21.5%)	53 (16.5%)	43 (13.4%)	.007
Double	281 (29.2%)	102 (31.8%)	93 (28.9%)	86 (26.9%)	.173
Triple	489 (50.8%)	132 (41.1%)	166 (51.6%)	191 (59.7%)	.000
Number of stents	1.9 ± 1.2	1.7 ± 1.2	1.9 ± 1.2	2.0 ± 1.2	.007
Gensini score	69 (41–97)	60 (36–85)	68 (40–101)	85 (52–116)	.000

Low MLR <0.23, n = 321; intermediate MLR 0.23–0.35, n = 322; high MLR >0.35, n = 320.

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CAD = coronary artery disease, DBP = diastolic pressure, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin, HDL = high density lipoprotein cholesterol, HR = heart rate, Hs-CRP = serum high-sensitivity C-reactive protein, LDL = lipoprotein cholesterol, MI = myocardial infarction, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, NSTEMI = non-ST-elevation myocardial infarction, SBP = systolic blood pressure, SCr = serum creatinine, TC = total cholesterol, TG = triglyceride, TIMI flow = thrombolysis in myocardial infarction flow, UA = uric acid.

Table 2

Univariate correlation of lgGensini-score.

	Age	Male	BMI	Hypertension	DM	Dyslipidemia	History of CAD	History of MI	History of Revascularization	Smoking index	HR	SBP	DBP
r	0.198	0.055	0.030	0.046	0.111	−0.001	0.142	0.032	0.006	−0.021	0.075	0.012	−0.063
P	.000	.046	.424	.156	.000	.984	.000	.319	.843	.519	.020	.703	.052

	HbA1c%	TG	TC	Scr	UA	Leucocyte	Neutrophil	Lymphocyte	Monocyte	MLR	NLR	hs-CRP
r	0.078	−0.021	0.046	0.115	0.027	0.064	0.100	−0.162	0.115	0.260	0.186	0.235
P	.020	.535	.169	.000	.408	.048	.002	.000	.000	.000	.000	.000

BMI = body mass index, CAD = coronary artery disease, DBP = diastolic pressure, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin, HR = heart rate, Hs-CRP = serum high-sensitivity C-reactive protein, MI = miocardial infarction, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, SBP = systolic blood pressure, SCr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.

performed using the log-rank test among the 3 groups. Logistic regression analysis was used to assess the independent predictors for in-hospital MACE of all NSTEMI patients. The effects of different variables on in-hospital MACE were calculated using univariate analyses for related variables. The variables for which the unadjusted *P* value was less than .10 in logistic regression analysis were identified as potential risk markers and included in the full model. Cox proportional hazard regression model was used to estimate the long-term MACE hazard ratio (HR) and its 95% confidence interval (CI) in all NSTEMI patients by univariate and multivariate analysis, including various clinical and inflammatory indicators. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of MLR, NLR, and hs-CRP for in-hospital and long-term MACE of NSTEMI patients, and c-statistics was used to compare the difference of predictive value among MLR, NLR, and hs-CRP for in-hospital or long-term MACE. Statistical analyses were performed using IBM SPSS 20.0. All probabilities were 2-sided and *P* values $<.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics of NSTEMI patients based on the tertile of MLR

A total of 963 NSTEMI patients referred for coronary angiography at the First Affiliated Hospital of Xi'an Jiao Tong University are included in the final analysis. The mean age of study population is 60.77 ± 11.34, and 78.7% are males. The baseline characteristics of the study population based on the tertile of MLR (low MLR <0.23, n = 321; intermediate MLR 0.23–0.35, n = 322; high MLR >0.35, n = 320) are outlined in Table 1. The results show that there are significant differences in age, gender, heart rate (HR) and the frequencies of hypertension, history of CAD and history of MI among the different groups. Interestingly, low MLR group tends to have higher value of body mass index (BMI), HbA1c%, TC, and TG than that of the other 2 groups ($P<.05$). Leukocytes, neutrophils, monocytes, MLR, NLR, hs-CRP, and SCr levels in high MLR group are statistically higher than that of other 2 groups ($P<.01$), while there is a decrease of the absolute number of lymphocytes in the 3 groups (1.96 ± 0.72, 1.56 ± 0.53, 1.22 ± 0.52, $P<.001$). High MLR group has significantly higher levels of Killip grades, peak hs-troponin T, peak CKMB, and peak NT-pro BNP than the other 2 groups ($P<.001$), indicating that high MLR NSTEMI patients have worse clinical condition. Besides, there are significant increases of TIMI risk score and GRACE risk score among the 3 groups (3.2 ± 1.3, 3.4 ± 1.3, 3.7 ± 1.3, $P<.001$; 104.9 ± 28.9, 115.6 ± 30.4, 124.7 ± 36.1, $P<.001$). There is no significant difference in prior medications (aspirin, beta-blocker, stain and angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker) among the 3 groups ($P > .05$).

3.2. Angiographic characteristics of NSTEMI patients based on the tertile of MLR

The angiographic characteristics of the NSTEMI patients based on the tertile of MLR are shown in Table 1. The results demonstrate that the frequency of coronary arteriography TIMI flow = 0/1 in high MLR group is statistically higher than that of other 2 groups. With the increase of MLR level, the frequencies of diseased vessels in each coronary artery branch increase ($P<.05$). The high MLR group has higher frequency of triple diseased vessels ($P<.001$) and lower frequency of single diseased vessels ($P=.007$) than that of other 2 groups. The number of stents in

Table 3

Independent correlation of variables with lgGensini-score in multiple linear regression analysis.

	Unstandardized coefficient				
Variable	***B***	**SEM**	**Standardized coefficient β**	**95% CI for B**	***P***
Age	0.005	0.001	0.153	0.002–0.007	.000
Male	0.115	0.031	0.137	0.054–0.177	.000
History of CAD	0.090	0.026	0.127	0.039–0.140	.001
MLR	0.281	0.077	0.141	0.130–0.432	.000
hs-CRP	0.017	0.004	0.188	0.010–0.024	.000

Adjusted R^2 for this model = 0.135; *P* for this model $<.001$.

CAD = coronary artery disease, Hs-CRP = serum high-sensitivity C-reactive protein, MLR = monocyte/lymphocyte ratio, SEM = standard error of the mean.

high MLR group is also higher than that of other 2 groups ($P=.007$). There is an increase in the Gensini score in the 3 groups (60 [36–85], 68 [40–101], 85 [52–116]; $P<.001$).

3.3. Correlation between MLR and lgGensini-score

In the univariate correlation analysis, age, male, DM, history of CAD, HR, HbA1c%, Scr, leucocyte, neutrophil, lymphocyte, monocyte, MLR, NLR, hs-CRP all have significant correlation with the lgGensini-score, and MLR has a positive correlation with the lgGensini-score ($r=0.260$, $P<.001$) (Table 2). All above significant correlation variables are taken into multiple linear regression analysis (stepwise) for further analysis. The results show that age, gender, history of CAD, MLR (B: 0.281, 95% CI: 0.130–0.432, $P<.001$) and hs-CRP (B: 0.017, 95% CI: 0.010–0.024, $P<.001$) still have strong significant correlations with lgGensini-score (Table 3), while NLR does not.

3.4. MLR and Gensini score are independent predictors for in-hospital MACE and long-term MACE

A total of 27 NSTEMI patients have in-hospital MACE, including 10 patients with acute left heart failure, 2 patients with cardiac arrest, 3 patients with malignant arrhythmia, 10 patients with cardiogenic shock, and 2 patients with cardiac rupture. The frequency of in-hospital MACE increases among 3 groups (1.6%, 2.2%, 4.7%, $P=.016$) (Fig. 2). During a median follow-up of 22 (12–35) months, 176 long-term MACE are recorded in the total cohort of NSTEMI patients, and there is a significant increase of long-term MACE in 3 groups (13.3%, 16.2%, 27.2%, $P<.001$) (Fig. 2). The long-term MACE-free survival result of Kaplan–Meier curve analysis based on the tertile of MLR is shown in Figure 3. Patients in high MLR group have significantly worse long-term MACE-free survival than patients in low MLR group ($P_2<.001$) and intermediate MLR group ($P_3=.004$). While the long-term MACE-free survival of the low MLR group and Intermediate MLR group does not significantly differ ($P_1=.203$). Logistic regression analysis reveals history of CAD (adjusted odds ratio [OR]: 1.461, 95% CI: 1.118–4.301, $P=.006$), MLR (adjusted OR: 2.891, 95% CI: 1.265–8.354, $P=.026$), NLR (adjusted OR: 1.102, 95% CI: 1.012–1.201, $P=.022$), hs-CRP (adjusted OR: 1.207, 95% CI: 1.033–1.410, $P=.018$), and Gensini score (adjusted OR: 1.018, 95% CI: 1.008–1.028, $P=.001$) are all independent predictors for in-hospital MACE in patients with NSTEMI (Table 4). Cox proportional hazard regression analysis indicates that age (adjusted HR: 1.016, 95% CI: 1.007–1.028, $P=.011$), MLR (adjusted HR: 1.793, 95% CI: 1.169–2.515, $P=.012$), NLR (adjusted HR: 1.029, 95% CI: 1.004–1.064, $P=.022$), hs-CRP (adjusted HR: 1.055, 95% CI: 1.019–1.095, $P=.007$), and Gensini score (adjusted HR: 1.006, 95% CI: 1.003–1.010, $P=.001$) are all independent risk factors for long-term MACE in NSTEMI patients (Table 5).

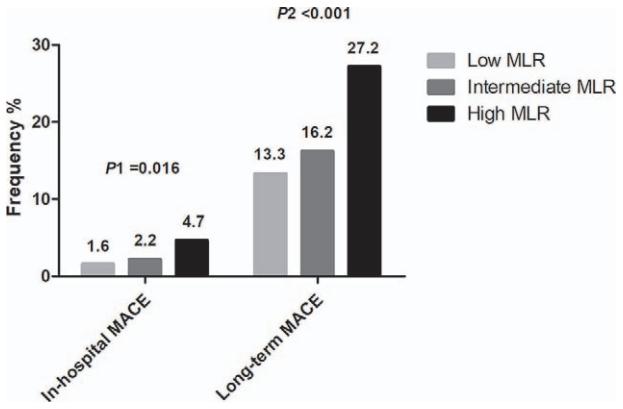

Figure 2. The frequency of in-hospital MACE in patients with NSTEMI based on the tertile of MLR; low MLR <0.23, n=321; intermediate MLR 0.23–0.35, n=322; high MLR >0.35, n=320; P_1, the trend for in-hospital MACE frequency in 3 groups; P_2, the trend for long-term MACE frequency in 3 groups. In-hospital MACE = in-hospital major adverse cardiac event, long-term MACE = long-term major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NSTEMI = non-ST-elevation myocardial infarction.

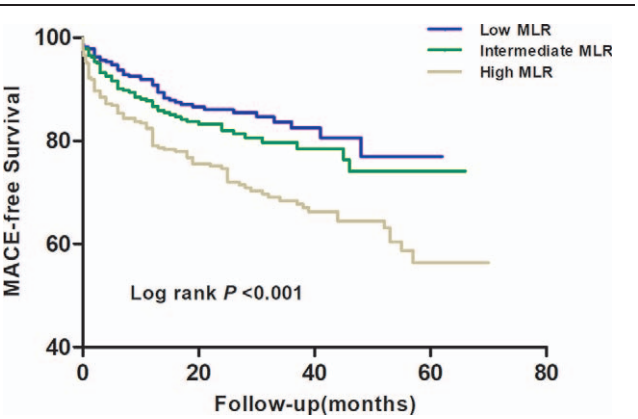

Figure 3. Kaplan–Meier curve analysis for long-term MACE-free survival in patients with NSTEMI based on the tertile of MLR; low MLR <0.23, n=321; intermediate MLR 0.23–0.35, n=322; high MLR >0.35, n=320; the difference between low MLR group and intermediate MLR group, $P_1=.203$; the difference between low MLR group and high MLR group, $P_2<.001$; the difference between intermediate MLR group and high MLR group, $P_3=.004$. MACE = major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NSTEMI = non-ST-elevation myocardial infarction.

3.5. The predictive value of MLR for in-hospital MACE and long-term MACE

ROC curve analysis is applied to test the predictive value of MLR, NLR, and hs-CRP for in-hospital MACE and long-term MACE in patients with NSTEMI (Figs. 4 and 5). Results show that MLR, NLR, and hs-CRP all have significant predictive value for in-hospital MACE and long-term MACE ($P<.05$) (Table 6), and there is no significant difference among the 3 biomarkers of their predictive value for in-hospital MACE ($P_1=.245$) and long-term MACE ($P_2=.486$) (Table 6). MLR has the largest AUC at 0.728 (95% CI: 0.604–0.852, $P=.001$) among all the makers, and a MLR of 0.43 is identified to be an effective cut-off point for predicting in-hospital MACE with a sensitivity of 63.2% and a specificity of 80.8%. Similarly, MLR also has a significant predictive value for long-term MACE in NSTEMI patients with the largest AUC at 0.609 (95% CI: 0.556–0.661, $P<.001$), and the cut-off point is 0.31 with a sensitivity of 57.4% and a specificity of 61.5%.

4. Discussion

MLR, a widely used inflammation maker for the prognosis of cancer, tuberculosis, and autoimmune diseases,[18–21] has also

Table 4

Effects of related variables on in-hospital MACE in univariate and multivariate logistic regression analysis.

	Univariate			Multivariate		
Variable	Unadjusted OR	95% CI	P	Adjusted OR	95% CI	P
Age	1.052	1.015–1.092	.006	1.019	0.965–1.075	.498
Male	0.767	0.320–1.839	.551			
BMI	0.938	0.829–1.061	.307			
Hypertension	1.261	0.561–2.838	.575			
DM	1.251	0.363–2.076	.615			
Dyslipidemia	4.341	1.880–10.024	.001	2.432	0.954–6.741	.068
History of CAD	2.819	1.222–6.504	.015	1.461	1.118–4.301	.006
History of MI	2.087	0.703–6.199	.185			
Smoking index	0.603	0.279–1.303	.198			
Leukocyte	1.114	0.998–1.243	.054	0.962	0.801–1.154	.673
MLR	6.029	1.487–24.446	.002	2.891	1.265–8.354	.026
NLR	1.090	1.039–1.143	.000	1.102	1.012–1.201	.022
hs-CRP	1.221	1.068–1.396	.004	1.207	1.033–1.410	.018
Gensini score	1.019	1.011–1.026	.000	1.018	1.008–1.028	.001

BMI = body mass index, CAD = coronary artery disease, DM = diabetes mellitus, Hs-CRP = serum high-sensitivity C-reactive protein, MI = myocardial infarction, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio.

Table 5

The risk of related variables for long-term MACE in univariate and multivariate Cox proportional hazard regression analysis.

	Univariate			Multivariate		
Variable	Unadjusted HR	95% CI	P	Adjusted HR	95% CI	P
Age	1.027	1.014–1.040	.000	1.016	1.007–1.028	.011
Male	1.058	0.755–1.482	.743			
BMI	1.009	0.972–1.047	.658			
Hypertension	1.496	1.108–2.019	.009	1.161	0.810–1.663	.415
DM	1.119	0.830–1.509	.102			
Dyslipidemia	1.410	1.067–1.862	.016	1.178	0.910–1.511	.058
History of CAD	1.322	1.003–1.742	.047	1.273	0.905–1.789	.166
History of MI	1.109	0.684–1.800	.674			
Smoking index	1.012	0.993–1.022	.113			
Leukocyte	1.033	0.987–1.081	.161			
MLR	3.588	2.081–6.187	.000	1.793	1.169–2.515	.012
NLR	1.039	1.017–1.062	.001	1.029	1.004–1.064	.022
hs-CRP	1.069	1.025–1.116	.002	1.055	1.019–1.095	.007
Gensini score	1.008	1.005–1.011	.000	1.006	1.003–1.010	.001

BMI = body mass index, CAD = coronary artery disease, DM = diabetes mellitus, Hs-CRP = serum high-sensitivity C-reactive protein, MI = myocardial infarction, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio.

been confirmed to be closely related to the cardiovascular events in patients with CAD recently.[22–24] In the present study, we demonstrated that

(1) The NSTEMI patients in high MLR group had worse clinical condition, higher GRACE and TIMI risk scores on admission, more diseased vessels in each coronary artery branch, more severe degree of coronary stenosis, and higher incidence of MACE compared with the patients in low MLR or intermediate MLR groups;
(2) MLR and hs-CRP were both independently correlated with the severity of coronary lesion in patients with NSTEMI, while NLR was not;
(3) MLR was an independent predictor for in-hospital MACE and long-term MACE in NSTEMI patients and had the same good predictive value as the well-known coronary artery inflammatory marker -hs-CRP and NLR.

NSTEMI is one kind of ACS, and increased levels of inflammatory markers have been found in association with the severity of coronary atherosclerosis and prognosis in ACS.[27] Monocytes are the main component of the innate immune system, and are also involved in endogenous inflammatory processes.[7] Monocytes and monocyte-derived macrophages play pivotal roles in the initiation and progression of atherosclerotic disease. Monocytes can migrate from blood to tissues in response to signals and differentiate to inflammatory dendritic cells, macrophages, and foam cells, and then, activate the production of pro-inflammatory cytokines secretion, matrix metalloproteinases, and reactive oxidative species which play key roles in the initiation, formation, and rupture of atherosclerotic plaque.[15,16] Therefore, the increase in the number of peripheral blood monocytes indicates that the monocytes and macrophages raised around the coronary plaque in response to signals can also increased, thus enhancing the inflammatory reaction process, the degree of coronary stenosis and the risk of atherosclerotic plaque rupture. Lymphocytes consisted with T lymphocytes, B lymphocytes and natural killer cells, represent the regulatory pathway of the immune system in contrast. Lymphocytopenia is related to

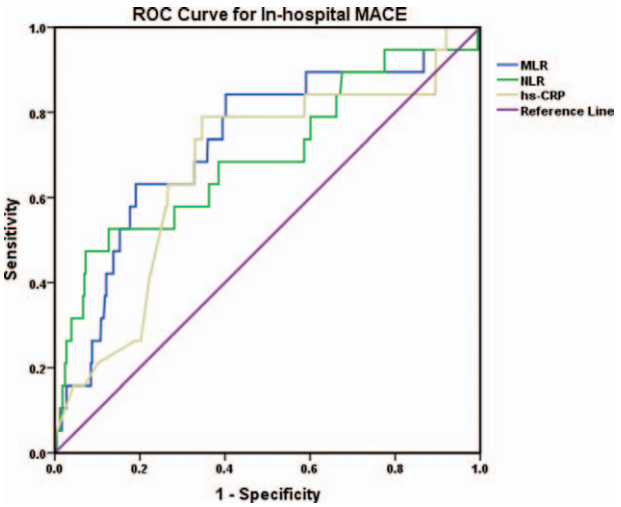

Figure 4. ROC curve analysis of the predictive value of MLR, NLR, and hs-CRP for in-hospital MACE. Hs-CRP = serum high-sensitivity C-reactive protein, In-hospital MACE = in-hospital major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, ROC curve = receiver operating characteristic curve.

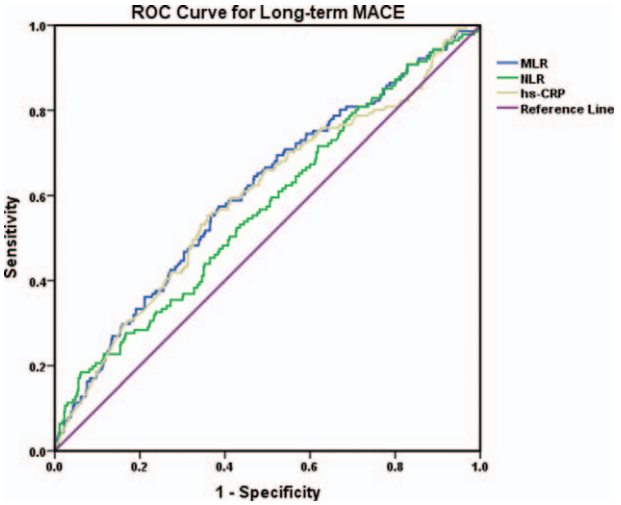

Figure 5. ROC curve analysis of the predictive value of MLR, NLR, and hs-CRP for long-term MACE. Hs-CRP = serum high-sensitivity C-reactive protein, long-term MACE = long-term major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, ROC curve = receiver operating characteristic curve.

major cardiac events for acute chest pain patients, poor outcomes for patients of heart failure with reduced ejection fraction, impaired coronary microcirculation, and cardiac remodeling,[17,28–30] which can be interpreted as the excessive apoptosis of lymphocytes caused by increased catecholamine and cortisol level under stress.[31,32] Thus, the combination of elevated monocytes and low levels of lymphocytes into a single composite marker of inflammation could provide more additive information than either parameter alone, which could reflect the severity of CAD better.

Our study showed that MLR and hs-CRP were both independent correlation variables with the severity of coronary lesion in NSTEMI patients, while NLR was not, which is different from Kurtul's study results.[33] We speculate that the main reason is that Kurtul's study did not include MLR value in their linear regression analysis model, which indirectly indicates that MLR has stronger correlation with the severity of coronary lesion than NLR. Besides, monocytes and monocyte-derived macrophages play more important roles in the initiation and progression of atherosclerotic plaque than neutrophils.[16] Ji et al have also demonstrated that compared to NLR, MLR has better performance to reflect the severity of coronary lesion in CAD patients on the basis of Syntax score in a research including 543 Chinese population, which is consistent with our research findings.[22]

With the improvement of medical level, more and more attention has been paid to the prognosis of NSTEMI patients. The FAST-MI Program has shown that the 6-month mortality of acute myocardial infarction patients has decreased considerably over the past 20 years, and the mortality of STEMI patients continued to decline until 2015, whereas the mortality in patients with NSTEMI appears stable since 2010.[34] Thus, the risk stratification and management of patients with NSTEMI in early phase are very crucial for improving the prognosis of these patients. Recently, Wang et al have demonstrated that lymphocyte/monocyte is an independent predictor for major adverse cardiac and cerebrovascular events in STEMI patients in a research including 306 patients,[24] so we speculated that whether MLR is also a predictor for MACE in NSTEMI patients. In the present study, we found that MLR was an independent predictor for in-hospital and long-term MACE in patients with NSTEMI, and the MLR's predictive value for the MACE was as good as that of the well-known coronary artery inflammatory marker -hs-CRP and NLR. Similarly, a newly published research also reported that MLR was an independent predictor for long-term MACE in a retrospective cohort population of 678 NSTEMI patients.[35]

MLR is more specific and efficient than NLR in evaluating the severity of coronary lesion, and more routine, stable, immediately obtainable, and inexpensive than hs-CRP in predicting in-hospital and long-term MACE in patients with NSTEMI. Therefore, MLR has a great clinical practical value, and could be considered as a new indicator for early risk stratification in patients with NSTEMI.

In addition, we have observed that low MLR group tended to have higher value of BMI, HbA1c%, TC, and TG than that of the other 2 groups ($P < .05$) in the present study. Obesity may produce systemic inflammatory condition, and the macrophage infiltration in adipose tissue is a central event leading to the metabolic complications of obesity. Accordingly, we consider that the relatively obese patients with low MLR are the result of increased migration of monocytes from the intravascular compartment to adipose tissues due to an increase chemotactic and adhesion molecule activities in the adipose tissues of the obese patients.[36,37]

There are several limitations in this study. First, this was a single-center study with a relatively small patient population. Further large multicenter studies involving larger numbers of patients will be required to determine the relationship of MLR with NSTEMI. Second, this study was a observational study without interventions. The benefits of anti-inflammatory therapy for NSTEMI patients are still unclear. Therefore, prospective interventional studies of NSTEMI patients in a large-scale population are necessary. Third, other inflammatory markers such as tumor necrosis factor-alpha, monocyte chemotactic

Table 6

ROC curve analysis of the predictive value of MLR, NLR, and hs-CRP for in-hospital MACE and long-term MACE.

Variable	AUC	95% CI	Sensitivity, %	Specificity, %	Cut-off point	*P*
In-hospital MACE						
MLR	0.728	0.604–0.852	63.2	80.8	0.43	.001
NLR	0.696	0.556–0.836	52.6	87.3	8.23	.004
hs-CRP	0.673	0.544–0.801	78.9	65.4	6.84	.010
Long-term MACE						
MLR	0.609	0.556–0.661	57.4	61.5	0.31	.000
NLR	0.571	0.518–0.625	52.5	57.2	4.33	.009
hs-CRP	0.596	0.542–0.650	55.3	64.1	5.59	.000

The difference of predictive value among MLR, NLR, and hs-CRP for in-hospital MACE, $P_1 = .245$; the difference of predictive value among MLR, NLR, and hs-CRP for long-term MACE, $P_2 = .486$.
AUC = area under curve, Hs-CRP = serum high-sensitivity C-reactive protein, In-hospital MACE = in-hospital major adverse cardiac event, Long-term MACE = long-term major adverse cardiac event, MLR = monocyte/lymphocyte ratio, NLR = neutrophil/lymphocyte ratio, ROC curve = receiver operating characteristic curve.

protein-1, and interleukin-6, were not measured in the study, so we could not evaluate their addictive effects on the severity of CAD and the MACE of NSTEMI patients in analysis models.

5. Conclusion

In conclusion, MLR is independently correlated with the severity of coronary lesion in NSTEMI patients and has better performance to reflect the severity of coronary lesion than NLR. MLR is also an independent predictor for in-hospital and long-term MACE in patients with NSTEMI. Therefore, MLR, an efficient, routine, immediately obtainable and inexpensive inflammatory biomarker, may be considered as a useful indicator for early risk stratification of NSTEMI patients, so that we can provide more aggressive therapeutic approach, intensive care and close follow-up for high-risk patients.

Author contributions

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Resources: Xiawei Dang.
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Supervision: Danjun Zhu.
Validation: Danjun Zhu.
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Writing – review and editing: Danjun Zhu, Gang Tian.

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