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Association between blood neutrophil-to-lymphocyte ratio and severity of coronary artery disease

Evidence from 17 observational studies involving 7017 cases

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Abstract

This study aimed to evaluate the association between blood neutrophil-to-lymphocyte ratio (NLR) and severity of coronary artery disease (CAD), and investigate the diagnostic ability and optimal cut-off value of NLR in predicting severe stenosis in CAD.

A systematic search was conducted in public databases to identify all relevant studies. Weighted mean difference (MD) and 95% confidence interval (CI) were pooled for continuous univariate data, and odds ratios (OR) and 95% CI were calculated for dichotomous multivariate data.

Seventeen studies were included in this meta-analysis with a total of 7017 CAD cases. For continuous univariate data, the cases with the highest stenosis category had a significantly higher NLR level than those with lowest stenosis category (MD: 1.57, 95% CI: 1.06–2.09; n = 17). After further classification according to the Gensini or SYNTAX score, the cases with severe stenosis demonstrated a higher NLR than those with mild stenosis (MD: 2.33, 95% CI: 1.22–3.43; n = 6) and moderate stenosis (MD: 1.92, 95% CI: 0.80–3.04; n = 6). Compared with mild stenosis, NLR was also higher in those with moderate-to-severe stenosis (MD: 1.34, 95% CI: 0.77–1.92; n = 6) and moderate stenosis (MD: 0.52, 95% CI: 0.36–0.68; n = 6). For dichotomous multivariate data, high NLR levels were recognized as an independent predictor for severe stenosis in CAD (OR: 1.50, 95% CI: 1.32–1.72; n = 11). NLR showed a diagnostic ability in predicting severe stenosis in CAD (area under receiver operating characteristics [ROC] curve [AUC]: 0.66, 95% CI: 0.64–0.68; n = 8), with the cut-off ranging from 1.95 to 3.97. Subgroup analysis and sensitivity analysis showed the results were robust. Begg's test detected no significant publication biases.

This study suggested that high blood NLR was associated with the severity of CAD, and it might be useful for predicting severe stenosis in CAD.

Abbreviations: AUC = area under receiver operating characteristics (ROC) curve, CAD = coronary artery disease, CI = confidence interval, ESRD = end-stage renal disease, IQR = interquartile range, LAD = left anterior descending, LCX = left circumflex, MD = mean difference, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle–Ottawa scale, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, OR = odds ratio, Q = quartile, SD = standard error, STE-MI = ST-segment elevation myocardial infarction.

Keywords: coronary artery disease, disease severity, meta-analysis, neutrophil-to-lymphocyte ratio

1. Introduction

Coronary artery disease (CAD) is recognized to be a global health threat, which accounts for a high proportion of mortality worldwide. As a complex inflammatory disease, atherosclerosis plays an important role in the onset and progression of CAD and its complications.[1] It has been found that elevated levels of inflammatory biomarkers are associated with increasing rates of cardiac events in CAD patients.[2] White blood cell (WBC) and its subtypes have been addressed in association with cardiovascular risk. Increased neutrophil count was shown to be associated with the presence and severity of coronary atherosclerosis.[3] High neutrophil levels could increase blood viscosity and hypercoagulability, interact with platelets and endothelium, and induce microvascular injury and reperfusion injury.[4–6] As a representative indicator of inflammation, a high neutrophil-to-lymphocyte ratio (NLR) was recognized as an independent risk factor for the progression of atheromatous plaque lesions, in-stent restenosis, cardiac death after percutaneous coronary intervention or coronary artery bypass surgery, and incidence of cardiac events in acute coronary syndrome (ACS).[7,8]

In recent years, several studies have investigated the association between NLR and CAD. However, most studies focused on the role of NLR in diagnosing CAD, instead of disease severity. Second, few studies failed to adjust the result by multivariate analysis and provide the optimal cut-off value of NLR in predicting severe CAD for further clinical practice. Thus, we conducted this meta-analysis to evaluate the association between NLR and CAD severity using both univariate and multivariate

data, and then investigate the diagnostic ability and optimal cut-off value of NLR in predicting severe stenosis in CAD.

2. Materials and methods

2.1. Search strategy

The databases of PubMed, China Wanfang Database, China SinoMed Database and China Knowledge Resource Integrated Database (CNKI) were searched for relevant studies published up to June 6th, 2018, using the keywords including: "neutrophil" AND "lymphocyte" AND ("coronary" OR "coronary artery" OR "coronary atherosclerosis" OR "heart disease"). Studies in languages other than English or Chinese were excluded. Moreover, we also reviewed the references of related studies and reviews for undetected studies. This study was approved by the ethics committee of Affiliated Heping Hospital of Changzhi Medical College.

2.2. Study selection and exclusion

Two authors (XL and YJ) reviewed the studies independently. The inclusion criteria were as follows: focused on CAD patients; patients were divided into 2 or more groups according to the coronary stenosis severity determined by Gensini or SYNTAX scoring system; The NLR in each group was presented as mean ± standard error (SD) or median (interquartile range [IQR]). The exclusion criteria were as follows: abstracts without full texts, reviews, case reports, and animal studies.

2.3. Data extraction and quality assessment

Two authors (JK and NF) extracted the data by a standardized collection form. All differences were resolved by discussion. In each study, the following information was extracted: first author, publication year, study area, disease type, total cases, scoring system, groups divided by Gensini or SYNTAX score, number of cases per group, number of males per group, average age per group, average NLR per group, effect size, area under ROC curve, and optimal cut-off value. For studies from the same area, we also reviewed the medical center and investigating time to remove duplicate publications. The Newcastle–Ottawa scale (NOS) was used to assess the methodological quality of included studies.[9]

2.4. Statistical analysis

For continuous univariate data, weighted mean differences (MD) and 95% confidence intervals (CI) were pooled by the Inverse Variance method to evaluate the association between NLR levels and CAD severity. If the NLR level was presented as median and interquartile range (IQR), we regarded the median as the mean level, and converted IQR to standard error (SD) by dividing it by 1.35.[10] For dichotomous multivariate data, odds ratios (OR) and 95% CI were pooled by the Mantel–Haenszel method to evaluate the association between NLR levels and severe stenosis in CAD, and the same method was also adopted in integrating the area under receiver operating characteristics (ROC) curve (AUC) and 95% CI.[11] The heterogeneity among studies was estimated by Q test and I^2 statistic.[12] $I^2 > 50\%$ represented substantial heterogeneity, and the summary estimate was analyzed by a random-effects model. Otherwise, a fixed-effects model was applied. Sensitivity analysis was performed to estimate the stability of the meta-analysis by omitting one study at a time during repeated analyses. Subgroup analysis was conducted to assess the effect of confounding factors on the primary result. Publication bias was assessed by using funnel plots and Begg's test. Furthermore, we also conducted meta-regression analysis to evaluate the effect of NLR cut-off values in predicting severe stenosis in CAD.

Statistical analyses were performed using Review Manager 5.2 (RevMan, The Nordic Cochrane Center, The Cochrane Collaboration, 2012), and Begg's test meta-regression analysis was realized with software STATA version 12.0 (StataCorp LP, College Station, TX). P values < .05 were considered statistically significant.

3. Results

3.1. Study characteristics

The search strategy resulted in 586 records: 179 from PubMed, 178 from Wanfang Database, 173 from SinoMed, and 56 from CNKI (Fig. 1). After excluding duplicated and irrelevant records, 17 studies were included in this meta-analysis with a total of 7017 CAD cases (Table 1).[13–29] Eleven studies were conducted in China, and the remaining 6 were performed in Turkey. The medical center and investigating time were reviewed in each included study, and no studies were duplicated. Twelve studies evaluated the severity by Gensini score, while 6 chose SYNTAX score. Liu et al study adopted both scores. Five studies presented NLR levels in the form of median (IQR). Eleven studies investigated the association by multivariate analysis, and eight studies reported the optimal cut-off value of NLR in predicting severe stenosis by ROC analysis. In quality assessment, the included studies had an average score of 7.53 (Table S1, http://links.lww.com/MD/C511).

3.2. NLR levels and CAD severity (the highest stenosis category vs the lowest stenosis category)

All studies divided the cases into groups of different CAD severity according to the Gensini or SYNTAX score. The cases with the highest stenosis category had a significantly higher NLR level than those with lowest stenosis category (MD: 1.57, 95% CI: 1.06–2.09; $I^2 = 97\%$) (Fig. 2). Sensitivity analysis showed the result was robust. Begg's test detected no significant publication bias ($P = .077$, $z = 1.77$) (Fig. S1, http://links.lww.com/MD/C511).

3.3. NLR levels and different CAD severity

The cases were divided into groups by Gensini or SYNTAX score, namely mild stenosis (Gensini score 1–30 or SYNTAX score 1–22), mild-to-moderate stenosis (Gensini score 1–60 or SYNTAX score 1–32), moderate stenosis (Gensini score 31–60 or SYNTAX score 23–32), moderate-to-severe stenosis (Gensini score > 30 or SYNTAX score > 22), and severe stenosis (Gensini score > 60 or SYNTAX score > 32). The cases with severe stenosis had a higher NLR level than those with mild stenosis (MD: 2.33, 95% CI: 1.22–3.43; n = 6, $I^2 = 95\%$; P for Begg's test = .452, $z = 0.75$) (Fig. 3; Fig. S2, http://links.lww.com/MD/C511). The cases with moderate-to-severe stenosis had a higher NLR level than those with mild stenosis (MD: 1.34, 95% CI: 0.77–1.92; n = 6, $I^2 = 88\%$; P for Begg's test = .133, $z = 1.50$) (Fig. 4; Fig. S3, http://links.lww.com/MD/C511). The cases with moderate stenosis had a higher NLR level than those with mild stenosis (MD: 0.52, 95% CI: 0.36–0.68; n = 6, $I^2 = 4\%$; P for Begg's test = 1.000, $z = 0.00$) (Fig. 5; Fig. S4, http://links.lww.com/MD/C511). The cases with severe stenosis had a higher NLR level than those with moderate
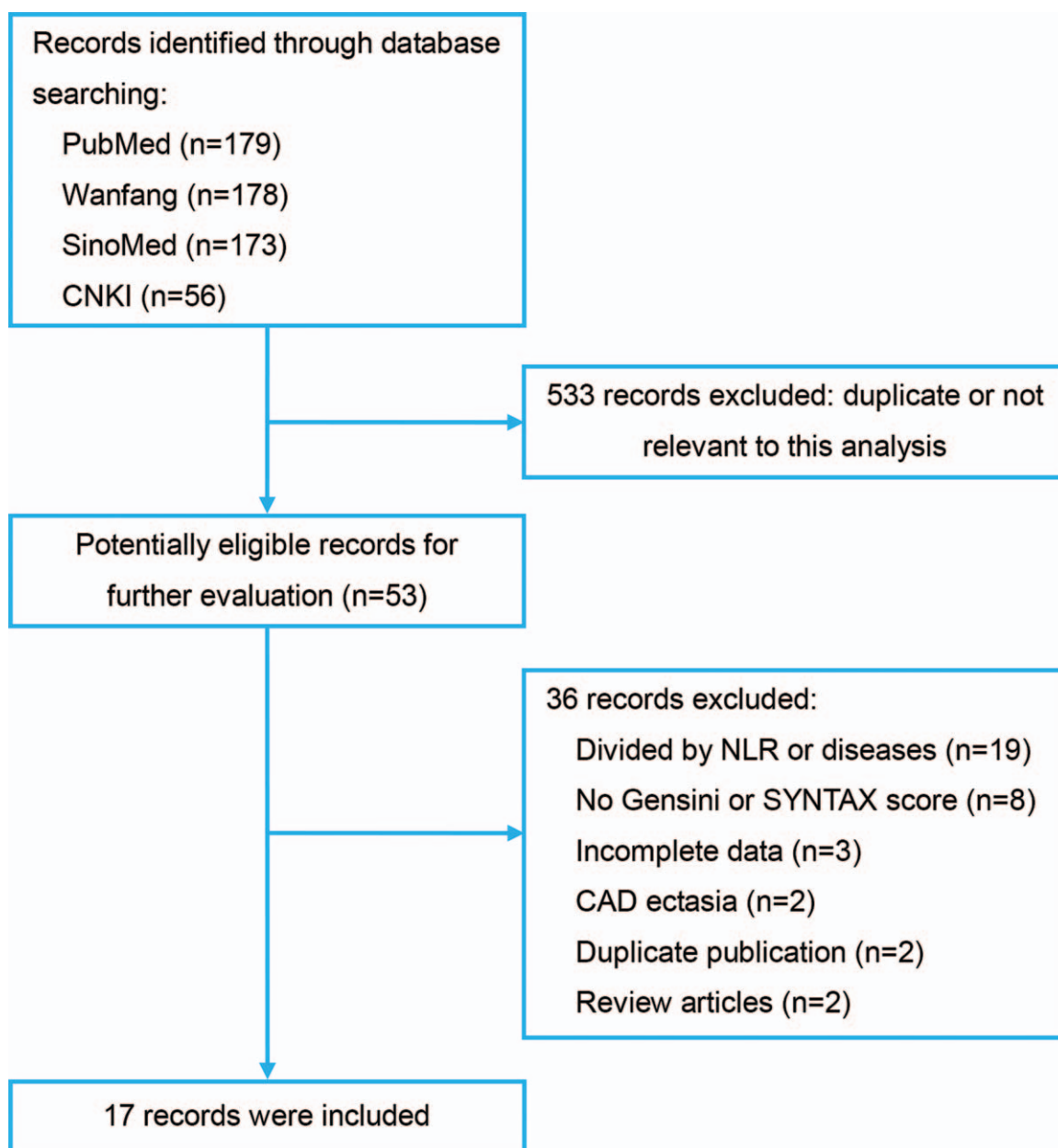
Figure 1. Flowchart of literature search.

stenosis (MD: 1.92, 95% CI: 0.80–3.04; n=6, $I^2=94\%$; P for Begg's test=.133, $z=1.50$) (Fig. 6; Fig. S5, http://links.lww.com/MD/C511). Sensitivity analysis showed the result was robust in each meta-analysis.

3.4. NLR levels and severe stenosis in CAD (based on dichotomous multivariate data)

Eleven studies conducted multivariate analyses of the association between NLR levels and severe stenosis in CAD. It was found that high NLR levels were related with severe stenosis in CAD (OR: 1.50, 95% CI: 1.32–1.72; $I^2=81\%$) (Fig. 7). Sensitivity analysis showed the result was robust. Begg's test detected no significant publication bias ($P=.640$, $z=0.47$) (Fig. S6, http://links.lww.com/MD/C511).

3.5. Diagnostic ability of NLR levels in predicting severe stenosis in CAD

Eight studies evaluated the ability of NLR levels in predicting severe stenosis in CAD, and the pool AUC was 0.66 (95% CI: 0.64–0.68; $I^2=24\%$). Sensitivity analysis showed the result was robust. Begg's test detected no significant publication bias ($P=.711$, $z=0.37$) (Fig. 8; Fig. S7, http://links.lww.com/MD/C511).

3.6. The effect of NLR cut-off values in predicting severe stenosis in CAD

Eight studies reported the results of ROC analysis and the corresponding optimal cut-off value of NLR in predicting severe stenosis in CAD. Meta-regression analysis showed the cut-off

Table 1

Characteristics of included studies.

Study	Area	Disease	Total cases	Scoring system	Group	Cases	Male	Age	NLR (%)	OR (95% CI)*	AUC (95% CI)†	Cut-off (%)‡
Li 2013	Beijing, China	NSTE-ACS	226	SYNTAX	1–22	137	64	61.26±9.20	2.07±0.72	—	—	—
					23–32	47	26	62.81±8.86	2.80±0.84	—	—	—
					≥33	42	22	69.33±9.44	4.46±1.42	—	—	—
Sahin 2013	Adana, Turkey	STE–MI	840	SYNTAX	≤11	259	213	55.2±11.5	4±2.9	—	—	—
					11–18	283	195	58.7±12.8	4.8±3.3	—	—	—
					>18	298	214	61.4±11.9	6.5±3.9	—	—	—
Sonmez 2013	Istanbul, Turkey	Stable angina	106	SYNTAX	1–22	62	40	60±10	2.0 (1.5–2.6)	2.1 (1.2–3.8)	0.68 (0.60–0.76)	1.95
					23–32	23	14	64±12	2.4 (1.3–2.6)	—	—	—
					>32	21	15	66±12	2.6 (2.3–3.9)	—	—	—
Chen 2014	Beijing, China	CAD	2976	Gensini	<18	989	689	57.82±9.70	1.89 (1.48–2.50)	1.10 (1.01–1.16)	0.63 (0.59–0.67)	2.04
					18–41	995	729	58.10±9.56	1.94 (1.54–2.66)	—	—	—
					>41	992	785	59.16±10.36	2.10 (1.60–2.78)	—	—	—
Kaya A 2014	Ordu, Turkey	Stable CAD	186	SYNTAX	≤22	72	48	61.0±10.2	2.5±1.08	1.67 (1.25–2.24)	0.72 (0.65–0.80)	2.7
					22–32	50	33	60.9±12.0	2.7±1.38	—	—	—
					>32	64	38	63.2±11.4	4.4±1.2	—	—	—
Kaya H 2014	Diyarbakır, Turkey	CAD	126	Gensini	1–29	63	40	60.4±11.8	2.4±1.2	1.798 (1.348–2.399)	0.730 (0.648–0.813)	2.5
					≥30	63	43	62.4±13.7	4.1±3.0	—	—	—
Zhang 2014	Wuhan, China	CAD	219	Gensini	1–50	142	79	61±10	2.5±1.6	1.246 (1.054–1.471)	0.658 (0.583–0.733)	2.385
					>50	77	59	66±10	3.4±2.0	—	—	—
Zhong 2014	Guangzhou, China	CAD	136	Gensini	1–30	60	34	63.57±10.55	3.23±2.18	—	0.674 (0.594–0.747)	3.966
					31–60	35	24	65.45±15.89	3.48±1.83	—	—	—
					>60	41	30	67.28±12.36	5.33±4.71	—	—	—
Bal 2015	Ankara, Turkey	CAD with ESRD	149	Gensini	Q1	38	20	46.3±12.9	2.47 (2)	—	—	—
					Q2	37	23	52.8±10.7	2.76 (1.6)	—	—	—
					Q3	37	22	56.4±11.9	3.00 (2.1)	—	—	—
					Q4	37	27	58.3±12.1	3.30 (2.6)	—	—	—
Ma 2015	Zhengzhou, China	Unstable angina	124	Gensini	1–30	46	31	59.4±10.8	2.17±0.85	1.55 (1.27–1.76)	—	—
					≥30	78	51	61.2±12.5	3.72±1.55	—	—	—
Song 2016	Zhengzhou, China	ACS	289	Gensini	1–30	59	—	—	2.31±0.71	—	—	—
					31–60	131	—	—	2.83±1.33	—	—	—
					>60	99	–	—	7.54±3.83	—	—	—
Uysal 2016	Aydin, Turkey	CAD	152	Gensini	1–29	70	51	63±10	2.53 (1.92–3.42)	1.450 (1.080–1.945)	0.627 (0.545–0.704)	2.54
					≥30	82	64	65±10	2.87 (2.52–3.56)	—	—	—
Xu 2016	Ningbo, China	Stable CAD	94	SYNTAX	<22	29	22	67.97±8.71	2.01±1.21	2.07 (1.30–3.30)	—	—
					22–33	22	17	65.82±10.50	2.36±1.09	—	—	—
					≥33	43	30	67.12±10.69	3.78±2.91	—	—	—
Bai 2017	Xi'an, China	CAD with chest pain	484	Gensini	1–30	255	165	57.49±10.59	2.81±1.69	1.345 (1.205–1.500)	0.643 (0.594–0.693)	2.32
					>30	229	179	60.91±10.71	4.50±5.88	—	—	—
Pan 2017	Luoyang, China	Unstable angina	124	Gensini	1–30	74	43	61.5±2.4	2.1±0.9	1.548 (1.269–1.762)	—	—
					≥30	50	28	62.1±2.5	3.7±0.7	—	—	—
Xiang 2017	Beijing, China	Young CAD	72	Gensini	1–30	40	37	39.13±4.86	2.82±1.93	2.501 (1.439–4.364)	—	—
					≥30	32	30	38.00±5.40	4.18±1.89	—	—	—
Liu 2018	Wuhan, China	CAD	714	SYNTAX	<7.5	239	135	62.73±10.64	2.47 (1.96)	—	—	—
					7.5–14	247	131	61.96±9.97	2.71 (2.05)	—	—	—
					>14	228	126	62.83±10.38	2.85 (3.00)	—	—	—
			714	Gensini	<20	252	141	62.82±10.69	2.38 (1.76)	—	—	—
					20–40	225	121	61.28±10.03	2.73 (1.77)	—	—	—
					>40	237	130	62.91±10.39	3.02 (3.55)	—	—	—

AUC = area under receiver operating characteristics (ROC) curve, CAD = coronary artery disease, CI = confidence interval, ESRD = end-stage renal disease., NLR = neutrophil-to-lymphocyte ratio, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, OR = odds ratio, Q = quartile, SD = standard error, STE-MI = ST-segment elevation myocardial infarction.

* Multivariate analysis of NLR levels in predicting severe stenosis in CAD.
† ROC analysis of NLR levels in predicting severe stenosis in CAD.
‡ Optimal cut-off values determined by ROC curve analysis.

values between 1.95 and 3.97 made no significant effect on the diagnostic ability (OR: 1.03, 95% CI: 0.94–1.13; P = .449) (Fig. 9).

3.7. Subgroup analysis

Subgroup analysis was conducted on the meta-analyses of both continuous univariate data and dichotomous multivariate data to evaluate the effect of confounding factors, including cohort, study size, disease type, NLR presentation, scoring system, and categories. No substantial changes of the primary result were found between subgroups (Table 2).

4. Discussion

Currently, 2 scoring systems of Gensini and SYNTAX basing on coronary angiography were usually used to determine the severity of coronary artery stenosis.[30,31] The Gensini score system defines narrowing of the lumen of the coronary arteries as follows: 1 point for <25% stenosis, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99%, and 32 for total occlusion. Then, the score is multiplied by a factor representing the importance of the lesion's location in the coronary artery system. For the location scores, 5 points were given for left main lesion; 2.5 for proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for the
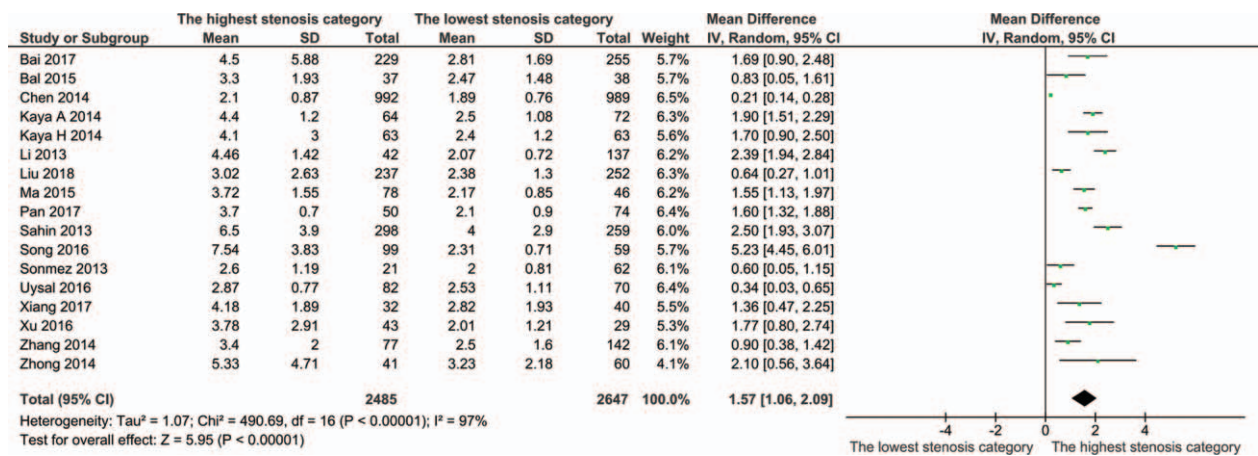
Study or Subgroup	The highest stenosis category Mean	SD	Total	The lowest stenosis category Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bai 2017	4.5	5.88	229	2.81	1.69	255	5.7%	1.69 [0.90, 2.48]
Bal 2015	3.3	1.93	37	2.47	1.48	38	5.7%	0.83 [0.05, 1.61]
Chen 2014	2.1	0.87	992	1.89	0.76	989	6.5%	0.21 [0.14, 0.28]
Kaya A 2014	4.4	1.2	64	2.5	1.08	72	6.3%	1.90 [1.51, 2.29]
Kaya H 2014	4.1	3	63	2.4	1.2	63	5.6%	1.70 [0.90, 2.50]
Li 2013	4.46	1.42	42	2.07	0.72	137	6.2%	2.39 [1.94, 2.84]
Liu 2018	3.02	2.63	237	2.38	1.3	252	6.3%	0.64 [0.27, 1.01]
Ma 2015	3.72	1.55	78	2.17	0.85	46	6.2%	1.55 [1.13, 1.97]
Pan 2017	3.7	0.7	50	2.1	0.9	74	6.4%	1.60 [1.32, 1.88]
Sahin 2013	6.5	3.9	298	4	2.9	259	6.0%	2.50 [1.93, 3.07]
Song 2016	7.54	3.83	99	2.31	0.71	59	5.7%	5.23 [4.45, 6.01]
Sonmez 2013	2.6	1.19	21	2	0.81	62	6.1%	0.60 [0.05, 1.15]
Uysal 2016	2.87	0.77	82	2.53	1.11	70	6.4%	0.34 [0.03, 0.65]
Xiang 2017	4.18	1.89	32	2.82	1.93	40	5.5%	1.36 [0.47, 2.25]
Xu 2016	3.78	2.91	43	2.01	1.21	29	5.3%	1.77 [0.80, 2.74]
Zhang 2014	3.4	2	77	2.5	1.6	142	6.1%	0.90 [0.38, 1.42]
Zhong 2014	5.33	4.71	41	3.23	2.18	60	4.1%	2.10 [0.56, 3.64]
Total (95% CI)			2485			2647	100.0%	1.57 [1.06, 2.09]

Heterogeneity: Tau² = 1.07; Chi² = 490.69, df = 16 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.95 (P < 0.00001)

The lowest stenosis category   The highest stenosis category

Figure 2. Meta-analysis of continuous univariate data on neutrophil-to-lymphocyte ratio and severity of coronary artery disease (the highest stenosis category vs the lowest stenosis category).
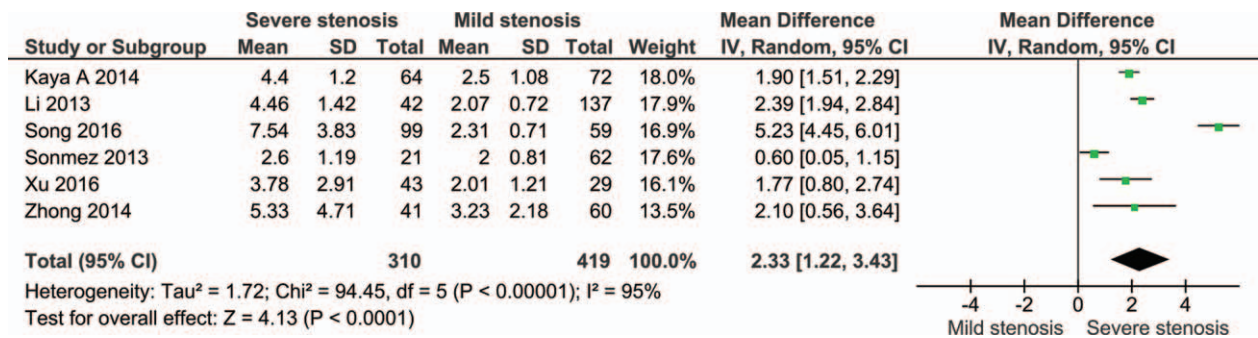
Study or Subgroup	Severe stenosis Mean	SD	Total	Mild stenosis Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kaya A 2014	4.4	1.2	64	2.5	1.08	72	18.0%	1.90 [1.51, 2.29]
Li 2013	4.46	1.42	42	2.07	0.72	137	17.9%	2.39 [1.94, 2.84]
Song 2016	7.54	3.83	99	2.31	0.71	59	16.9%	5.23 [4.45, 6.01]
Sonmez 2013	2.6	1.19	21	2	0.81	62	17.6%	0.60 [0.05, 1.15]
Xu 2016	3.78	2.91	43	2.01	1.21	29	16.1%	1.77 [0.80, 2.74]
Zhong 2014	5.33	4.71	41	3.23	2.18	60	13.5%	2.10 [0.56, 3.64]
Total (95% CI)			310			419	100.0%	2.33 [1.22, 3.43]

Heterogeneity: Tau² = 1.72; Chi² = 94.45, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.13 (P < 0.0001)

Mild stenosis   Severe stenosis

Figure 3. Meta-analysis of continuous univariate data on neutrophil-to-lymphocyte ratio and severity of coronary artery disease (severe stenosis vs mild stenosis).
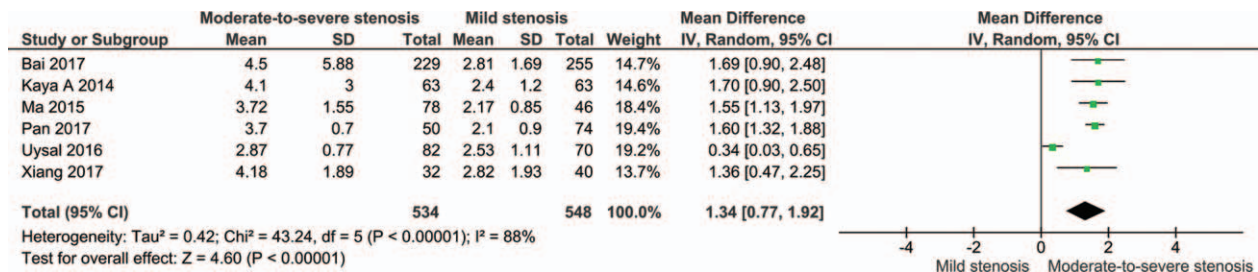
Study or Subgroup	Moderate-to-severe stenosis Mean	SD	Total	Mild stenosis Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bai 2017	4.5	5.88	229	2.81	1.69	255	14.7%	1.69 [0.90, 2.48]
Kaya A 2014	4.1	3	63	2.4	1.2	63	14.6%	1.70 [0.90, 2.50]
Ma 2015	3.72	1.55	78	2.17	0.85	46	18.4%	1.55 [1.13, 1.97]
Pan 2017	3.7	0.7	50	2.1	0.9	74	19.4%	1.60 [1.32, 1.88]
Uysal 2016	2.87	0.77	82	2.53	1.11	70	19.2%	0.34 [0.03, 0.65]
Xiang 2017	4.18	1.89	32	2.82	1.93	40	13.7%	1.36 [0.47, 2.25]
Total (95% CI)			534			548	100.0%	1.34 [0.77, 1.92]

Heterogeneity: Tau² = 0.42; Chi² = 43.24, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.60 (P < 0.00001)

Mild stenosis   Moderate-to-severe stenosis

Figure 4. Meta-analysis of continuous univariate data on neutrophil-to-lymphocyte ratio and severity of coronary artery disease (moderate-to-severe stenosis vs mild stenosis).
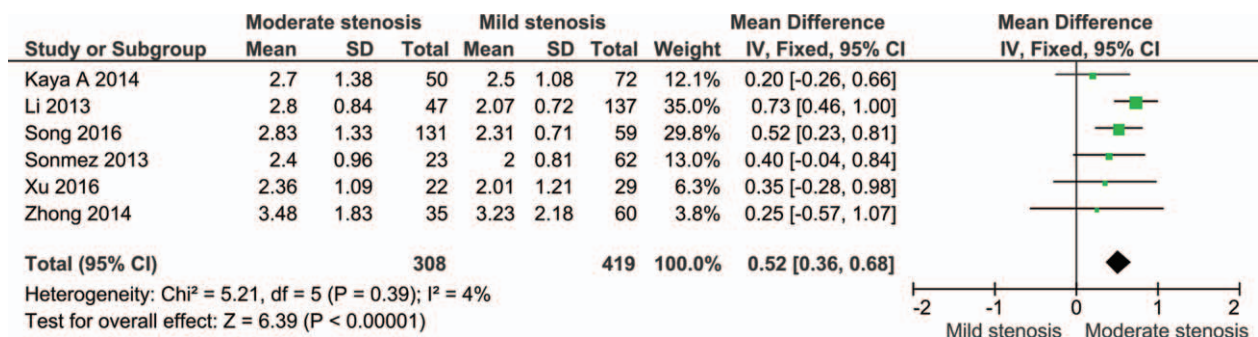
Study or Subgroup	Moderate stenosis Mean	SD	Total	Mild stenosis Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kaya A 2014	2.7	1.38	50	2.5	1.08	72	12.1%	0.20 [-0.26, 0.66]
Li 2013	2.8	0.84	47	2.07	0.72	137	35.0%	0.73 [0.46, 1.00]
Song 2016	2.83	1.33	131	2.31	0.71	59	29.8%	0.52 [0.23, 0.81]
Sonmez 2013	2.4	0.96	23	2	0.81	62	13.0%	0.40 [-0.04, 0.84]
Xu 2016	2.36	1.09	22	2.01	1.21	29	6.3%	0.35 [-0.28, 0.98]
Zhong 2014	3.48	1.83	35	3.23	2.18	60	3.8%	0.25 [-0.57, 1.07]
Total (95% CI)			308			419	100.0%	0.52 [0.36, 0.68]

Heterogeneity: Chi² = 5.21, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 6.39 (P < 0.00001)

Mild stenosis   Moderate stenosis

Figure 5. Meta-analysis of continuous univariate data on neutrophil-to-lymphocyte ratio and severity of coronary artery disease (moderate stenosis vs mild stenosis).
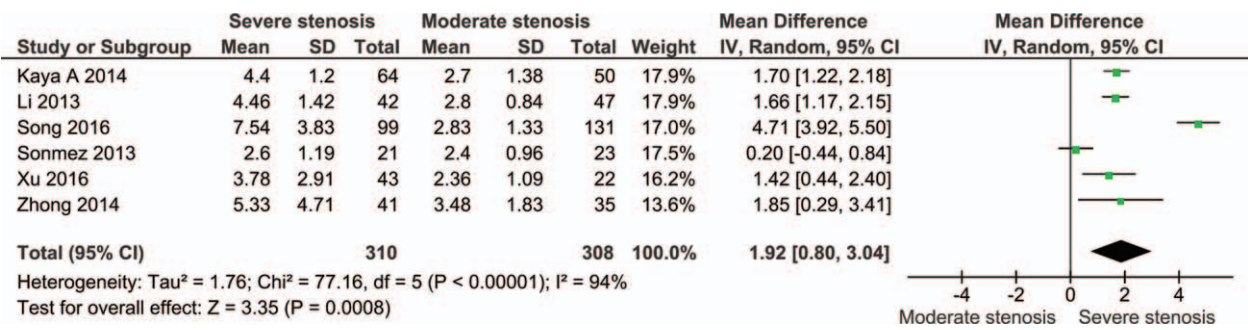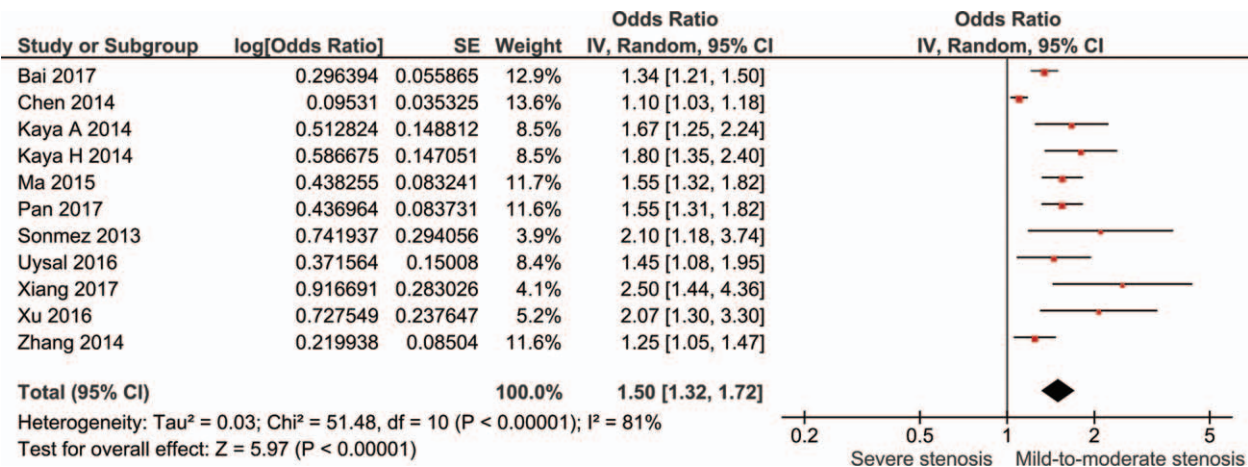
Study or Subgroup	Severe stenosis Mean	SD	Total	Moderate stenosis Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kaya A 2014	4.4	1.2	64	2.7	1.38	50	17.9%	1.70 [1.22, 2.18]
Li 2013	4.46	1.42	42	2.8	0.84	47	17.9%	1.66 [1.17, 2.15]
Song 2016	7.54	3.83	99	2.83	1.33	131	17.0%	4.71 [3.92, 5.50]
Sonmez 2013	2.6	1.19	21	2.4	0.96	23	17.5%	0.20 [−0.44, 0.84]
Xu 2016	3.78	2.91	43	2.36	1.09	22	16.2%	1.42 [0.44, 2.40]
Zhong 2014	5.33	4.71	41	3.48	1.83	35	13.6%	1.85 [0.29, 3.41]
Total (95% CI)			310			308	100.0%	1.92 [0.80, 3.04]

Heterogeneity: Tau² = 1.76; Chi² = 77.16, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 3.35 (P = 0.0008)

Figure 6. Meta-analysis of continuous univariate data on neutrophil-to-lymphocyte ratio and severity of coronary artery disease (severe stenosis vs moderate stenosis).

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Bai 2017	0.296394	0.055865	12.9%	1.34 [1.21, 1.50]
Chen 2014	0.09531	0.035325	13.6%	1.10 [1.03, 1.18]
Kaya A 2014	0.512824	0.148812	8.5%	1.67 [1.25, 2.24]
Kaya H 2014	0.586675	0.147051	8.5%	1.80 [1.35, 2.40]
Ma 2015	0.438255	0.083241	11.7%	1.55 [1.32, 1.82]
Pan 2017	0.436964	0.083731	11.6%	1.55 [1.31, 1.82]
Sonmez 2013	0.741937	0.294056	3.9%	2.10 [1.18, 3.74]
Uysal 2016	0.371564	0.15008	8.4%	1.45 [1.08, 1.95]
Xiang 2017	0.916691	0.283026	4.1%	2.50 [1.44, 4.36]
Xu 2016	0.727549	0.237647	5.2%	2.07 [1.30, 3.30]
Zhang 2014	0.219938	0.08504	11.6%	1.25 [1.05, 1.47]
Total (95% CI)			100.0%	1.50 [1.32, 1.72]

Heterogeneity: Tau² = 0.03; Chi² = 51.48, df = 10 (P < 0.00001); I² = 81%
Test for overall effect: Z = 5.97 (P < 0.00001)

Figure 7. Meta-analysis of dichotomous multivariate data on neutrophil-to-lymphocyte ratio and severe stenosis in coronary artery disease.

mid-segment LAD and LCX; 1 for the distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; 0.5 for the second diagonal and second obtuse marginal branches. CAD cases were usually divided into groups of different severity according to the Gensini score: low stenosis (1–30), moderate stenosis (31–60) and severe stenosis (>60).

The SYNTAX score is also an angiographic tool used in grading the severity of CAD. Each coronary lesion with a diameter stenosis > 50% in vessels > 1.5 mm is scored separately and added together to provide the cumulative score
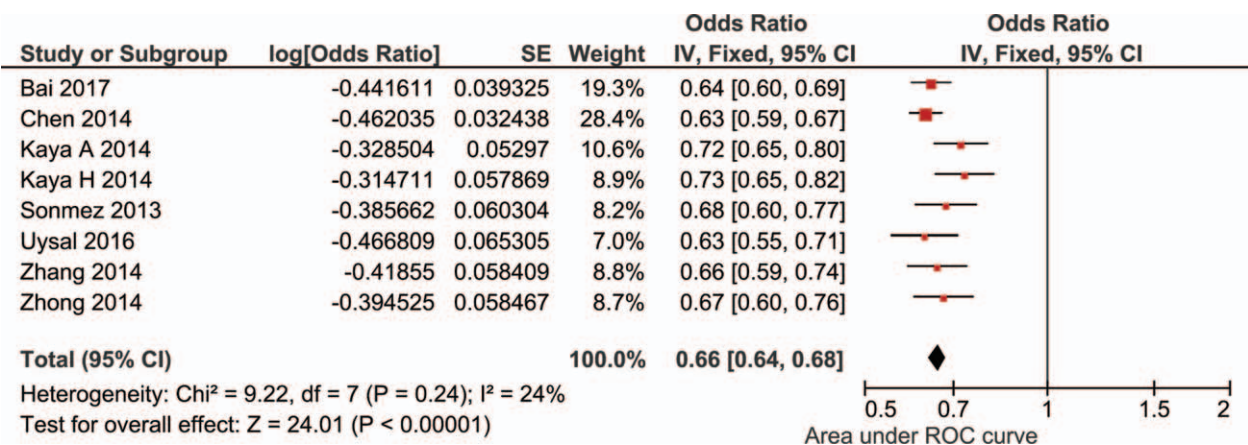
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Bai 2017	−0.441611	0.039325	19.3%	0.64 [0.60, 0.69]
Chen 2014	−0.462035	0.032438	28.4%	0.63 [0.59, 0.67]
Kaya A 2014	−0.328504	0.05297	10.6%	0.72 [0.65, 0.80]
Kaya H 2014	−0.314711	0.057869	8.9%	0.73 [0.65, 0.82]
Sonmez 2013	−0.385662	0.060304	8.2%	0.68 [0.60, 0.77]
Uysal 2016	−0.466809	0.065305	7.0%	0.63 [0.55, 0.71]
Zhang 2014	−0.41855	0.058409	8.8%	0.66 [0.59, 0.74]
Zhong 2014	−0.394525	0.058467	8.7%	0.67 [0.60, 0.76]
Total (95% CI)			100.0%	0.66 [0.64, 0.68]

Heterogeneity: Chi² = 9.22, df = 7 (P = 0.24); I² = 24%
Test for overall effect: Z = 24.01 (P < 0.00001)

Figure 8. Meta-analysis of diagnostic ability of neutrophil-to-lymphocyte ratio in predicting severe stenosis in coronary artery disease.
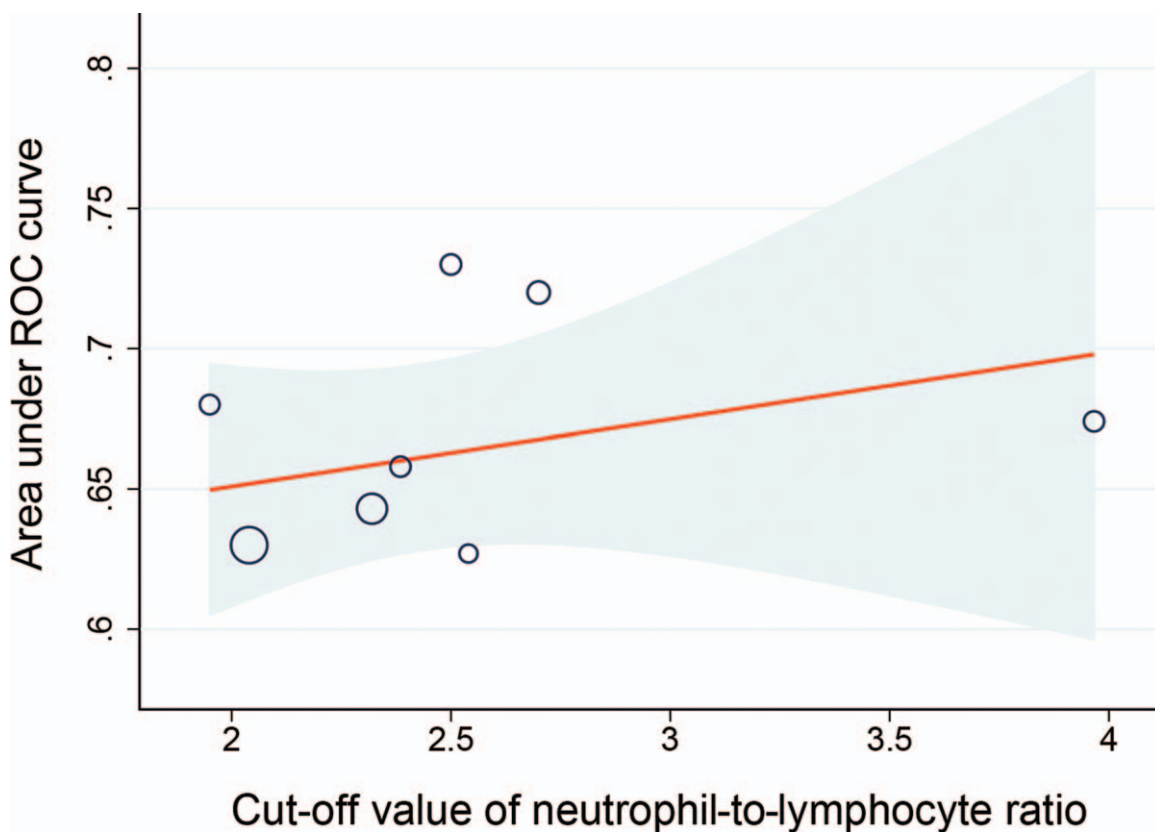
Figure 9. Meta-regression analysis of cut-off values of neutrophil-to-lymphocyte ratio in predicting severe stenosis in coronary artery disease.

Table 2

Subgroup analysis of neutrophil-to-lymphocyte ratio and severity of coronary artery disease.

	Univariate analysis [*]			Multivariate analysis [†]		
Subgroup	Num	MD (95%CI)	I^2 (%)	Num	OR (95%CI)	I^2 (%)
Cohort						
Asian	11	1.73 (1.02–2.45)	97	7	1.43 (1.22–1.67)	84
Caucasian	6	1.31 (0.54–2.07)	93	4	1.67 (1.42–1.96)	0
Study size						
<200	10	1.32 (0.88–1.76)	86	8	1.62 (1.48–1.78)	0
>200	7	1.91 (0.85–2.96)	98	3	1.22 (1.06–1.40)	80
Disease type						
Stable CAD	3	1.41 (0.48–2.34)	86	3	1.82 (1.45–2.29)	0
Unstable CAD	2	1.58 (1.35–1.82)	0	2	1.55 (1.38–1.74)	0
Others	12	1.62 (0.95–2.29)	97	6	1.38 (1.18–1.62)	81
NLR presentation						
Mean±SD	12	2.04 (1.55–2.54)	89	8	1.53 (1.36–1.71)	54
Median (IQR)	5	0.41 (0.19–0.64)	57	3	1.36 (1.00–1.87)	74
Scoring system [‡]						
Gensini	12	1.46 (0.88–2.03)	96	8	1.43 (1.24–1.65)	83
SYNTAX	6	1.58 (0.78–2.38)	94	3	1.82 (1.45–2.29)	0
Score categories						
2	7	1.27 (0.78–1.77)	86	4	1.59 (1.10–2.31)	83
≥3	10	1.79 (0.95–2.64)	98	7	1.48 (1.33–1.64)	50

CAD = coronary artery disease, CI = confidence interval, IQR = inter-quartile range, MD = mean difference, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, SD = standard error.

[*] Continuous univariate data of the highest Gensini/SYNTAX score category vs the lowest Gensini/SYNTAX score category.

[†] Multivariate analysis of NLR levels in predicting severe stenosis in CAD.

[‡] Liu et al study (2018) used both Gensini and SYNTAX scores.

which is prospectively calculated using the score algorithm on the baseline diagnostic angiogram. Cases with a score of 1 to 22 were usually regarded as mild stenosis, while 23 to 32 for moderate stenosis and > 32 for severe stenosis.

In the present study, we demonstrated the independent association between NLR levels and CAD severity. Some studies divided the cases into different severity groups according to the tertiles of the Gensini or SYNTAX score. The cases with the highest category had a higher NLR levels than those with the lowest category. When adopting the same classification criteria, the NLR levels still increased with the disease severity. As for multivariate data, the association existed. NLR showed a diagnostic ability in predicting severe stenosis in CAD (AUC: 0.66, 95% CI: 0.64–0.68), with the cut-off ranging from 1.95 to 3.97. We thought NLR might be a useful biomarker in predicting CAD severity. For the CAD cases with a NLR level of more than 1.95 to 3.97, physicians should pay more attention, especially after exclusion of infectious diseases.

Several studies also evaluated the association using different criteria to classify the CAD severity. In Arbel et al study (n = 3005), CAD severity was divided into 4 categories according to the number of diseased vessels (0, 1, 2, 3), and the patients were divided into 3 groups according to the NLR value (<2, 2–3 and > 3).[32] Patients with NLR > 3 had more advanced obstructive CAD (P<.001) and worse prognosis, with a higher rate of major CVD events during up to 3 years of follow-up (P=.01). In the studies of both Iranirad et al (n = 500) and Datta et al (n = 110), patients grouped by NLR levels had a significant different distribution in the number of diseased coronary vessels.[33,34] In Demir et al[35] study, NLR levels were significantly higher in the group of chronic coronary total occlusion (n = 75) than in the group with coronary stenosis > 50% (n = 75) (P<.001). In Ates et al[36] study (n = 684), NLR was found to be an independent predictor of critical coronary plaques detected by multi-detector computed tomography (MDCT) (P<.001). The criteria based on the number of diseased vessels or maximum stenosis in single vessels could not reflect the disease severity systematically. However, the 2 most popular criteria of Gensini score and SYNTAX score considered the effects of lesion location, stenosis in single vessels and the number of diseased vessels, which could assess the CAD severity systematically and quantitatively. Thus, we adopted studies with these 2 criteria, and the meta-analysis showed a consistent result with the studies using other criteria, indicating that high blood NLR was associated with the CAD severity. Furthermore, NLR was also reported with the ability in diagnosing CAD.[37–39]

The inflammatory process played a key role in pathogenesis of atherosclerosis, and multiple studies have demonstrated a strong correlation between various inflammatory biomarkers and CAD.[40] Furthermore, NLR is a combination of 2 independent inflammatory biomarkers.[41] Neutrophils could reflect the ongoing nonspecific inflammation, and lymphocytes acted as a marker of the regulatory pathway. A higher NLR level suggested a higher inflammatory level.[42] Thus, NLR could reveal more information that was not evident from the total leukocyte count. The NLR was also associated with arterial stiffness and coronary calcium score.[43] Unlike other inflammatory biomarkers and bioassays, NLR was an inexpensive and easily available marker that provided an additional level of risk scores in predicting the severity of coronary artery stenosis. NLR levels were also associated with the severity of multiple infectious and inflammatory diseases.[44–46] This indicated NLR might not be a specific biomarker in the diagnosis of certain diseases, but it was a good indicator of disease severity. In other words, it might be more meaningful among the patients who have been diagnosed as CAD. After excluding the etiology of infection, inflammation and cancers, physicians should pay more attention to the CAD patients with high NLR levels.[47,48]

This meta-analysis had several strengths. First, to the best of our knowledge, this is the first meta-analysis to evaluate the association between NLR and CAD severity. Second, the estimates based on univariate and multivariate data were pooled respectively, which made the results more reliable. Third, AUC was also pooled to evaluate the diagnostic ability of NLR in predicting severe stenosis in CAD, and the effect of cut-off values was also considered. Fourth, sensitivity analysis and Bgger' test were conducted to estimate the stability of pooled results and potential publication bias. However, several limitations in this study should be considered. First, the number of cases and controls in part studies was relatively small. Second, the obvious heterogeneity between studies was observed. For this, we conducted both sensitivity analysis and subgroup analysis to evaluate the stability of pooled results.

5. Conclusions

In conclusion, this study suggested that high-blood NLR was associated with the severity of CAD, and it might be useful for predicting severe stenosis in CAD.

Author contributions

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Visualization: Yanli Ji.
Writing – original draft: Xiaoli Li, Ning Fang.
Writing – review & editing: Ning Fang.

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