

Neutrophil-to-lymphocyte ratio as a biomarker for predicting the intravenous immunoglobulin-resistant Kawasaki disease

Gang Wu, MD^{a,b}, Peng Yue, MD^{a,b,c}, Fan Ma, MD^{a,b}, Yi Zhang, PhD^{a,b}, Xiaolan Zheng, MD^{a,b,c,*}, Yifei Li, MD^{a,b,*}

Abstract

Background: In recent years, many studies focused on the association between the neutrophil-to-lymphocyte ratio (NLR) and the risk of intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (rKD), with inconsistent results. Therefore, we aimed to investigate the role of NLR as a biomarker in detecting rKD.

Methods: We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure through May 18th, 2019. Meta-disc 1.4 and STATA 15.1 were used to perform this metaanalysis in a fixed/random-effect model.

Results: A total of 7 relevant studies were eligible to analyze pooled accuracy. The overall performance of NLR detection was: pooled sensitivity, 0.66 (95% confidence interval [CI], 0.63 – 0.70); pooled specificity, 0.71 (95%CI, 0.69 – 0.73); and area under the summary receiver operating characteristic curves value (SROC), 0.7956. The meta-regression analysis showed that the type of samples was the sources of heterogeneity. The subgroup analysis suggested that NLR detection after the initial treatment of IVIG had the largest area under curve of SROC in all the subgroups: pooled sensitivity, 0.58 (95%CI, 0.53 – 0.63); pooled specificity, 0.77 (95% CI, 0.75 – 0.79); and SROC, 0.8440.

Conclusions: This is the first meta-analysis demonstrated that NLR might be a biomarker for detecting rKD, especially NLR value after the initial treatment of IVIG. More well-designed researches need to be done to launch the application of NLR for predicting rKD in the clinic.

Abbreviations: AUC = area under curve, CAL = coronary artery lesions, IVIG = intravenous immunoglobulin, KD = Kawasaki disease, NLR = neutrophil-to-lymphocyte ratio, rKD = intravenous immunoglobulin-resistant Kawasaki disease, SROC = summary receiver operating characteristic curves value.

Keywords: biomarker, kawasaki disease, meta-analysis, neutrophil-to-lymphocyte ratio

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^aDepartment of Pediatrics, ^bKey Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, ^cWest China Medical School, Sichuan University, Chengdu, China.

* Correspondence: Yifei Li, Department of Pediatric Cardiology, West China Second University Hospital, Sichuan University, Chengdu, China (e-mail: liyfwcsh@scu.edu.cn); Xiaolan Zheng, Department of Pediatric Cardiology, West China Second University Hospital, Sichuan University, Chengdu, China (e-mail: 349777010@qq.com).

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1. Introduction

Kawasaki disease (KD) is a self-limited systemic vasculitis of unknown cause that is associated with the development of coronary artery lesions (CALs) in children.^[1] KD is currently the most common cause of acquired heart disease in children in many countries.^[2–4] Timely initial treatment with intravenous immunoglobulin (IVIG) has reduced the risk of CAL from 25% to approximately 4%.^[5] Approximately 10% to 20% patients with KD had persistent or recurrent fever after the initial treatment of IVIG, which is defined as IVIG-resistant KD (rKD).^[5] Patients with rKD may be at higher risk of developing CALs than IVIG-responsive patients.^[6,7] The combination of IVIG and other anti-inflammatory therapies as the intensive initial treatment may reduce the occurrence of IVIG resistance or CAL.^[8–12] Therefore, it is important to predict patients with rKD early so that they might benefit from more aggressive treatment.

Japanese researchers have constructed several risk-scoring systems that use general laboratory data to predict IVIG resistance in KD patients' risk scores.^[13–15] However, these risk-scoring systems are not sufficiently accurate for clinical use in countries other than Japan.^[16,17] Better predictive biomarkers must be developed for more widespread use.

Many recent studies focused on the association between the neutrophil-to-lymphocyte ratio (NLR) and the risk of rKD.^[18–20]

However, the results were inconsistent. Therefore, we collected all published case-control studies to gather evidence on the diagnostic performance of the NLR for distinguishing rKD.

2. Materials and methods

2.1. Study protocol

We performed this analysis by a predetermined protocol according to the recommendations of Deeks.^[21] The data collection and reporting followed the preferred reporting items for systematic reviews and meta-analyses statement.^[22] It is a systematic literature research so that ethical approval was not necessary.

2.2. Search strategy

We searched multiple databases, including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure (CNKI) through May 18, 2019, to identify relevant studies. Keyword search terms were ('mucocutaneous lymph node syndrome' OR 'KD OR 'Kawasaki syndrome') AND ('neutrophils' OR 'neutrophil') AND ('lymphocytes' OR 'lymphocyte' OR 'lymphoid'). PubMed database was searched as follows: (mucocutaneous lymph node syndrome [MeSH Terms] OR KD OR Kawasaki syndrome) AND (neutrophils [MeSH Terms] OR neutrophil) AND (Lymphocytes [MeSH Terms] OR Lymphocyte OR Lymphoid) AND (Lymphocytes [MeSH] Terms] OR Lymphocyte OR Lymphoid). Search terms for EMBASE, CENTRAL, and CNKI with corresponding publication numbers can be found in the Supplementary Appendix, <http://links.lww.com/MD/D729>. Languages were limited to English and Chinese.

2.3. Study selection

We preliminarily excluded studies by title and abstract. Then we retrieved potentially relevant studies by full manuscripts and assessed for compliance with inclusion and exclusion criteria.

Criteria for inclusion:

- (1) All patients of KD were confirmed by KD diagnosis criteria;
- (2) Randomized controlled or non-randomized controlled, retrospective or prospective trials evaluating NLR in blood samples;
- (3) Contained the data which can calculate true positive (TP), false positive (FP), false negative (FN), and true negative (TN), such as sensitivity, specificity, and essential sample size;
- (4) All studies had patients with rKD as the experimental group and non-rKD as the control group;
- (5) Blood samples were obtained in the acute phase of KD before or after initial IVIG treatment;
- (6) Full text published in English or Chinese.

Criteria for exclusion:

- (1) Conferences articles, editorials, abstracts, letters, reviews, expert opinions, or case reports without controls;
- (2) No available data to construct a 2 × 2 table;
- (3) Duplicated reports.

2.4. Data collection and assessment of study quality

Two investigators (Xiaolan Zheng, Gang Wu) screened and assessed the eligibility of reports at the title and abstract level

independently following the inclusion and exclusion criteria., and a third reviewer (Yifei Li) determining the divergences according to inclusion or exclusion criteria, and the quality of reports; studies that met all the inclusion criteria were selected for further analysis. The quality assessment of all enrolled studies was independently conducted by 2 investigators (Xiaolan Zheng, Peng Yue) according to the 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) list,^[23] and any disagreement was settled by discussion. All the assessments were only reported in descriptive forms due to a well-conducted study might score poorly once related parts were missing among the methods and results. Finally, 2 investigators (Xiaolan Zheng, Fan Ma) extracted the data which can calculate TP, FP, FN, and TN, such as sensitivity, specificity, and essential sample size.

2.5. Evaluation indicators

The following indicators of NLR were measured: sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curves value (SROC). Sensitivity was represented by the proportion of patients with rKD that was correctly identified by the positive results of NLR. Specificity was represented by the non-rKD cases that were correctly identified by the negative results of NLR. DOR was an independent indicator indicating that patients with positive test results are much more likely to have rKD than patients with negative test results. The higher the DOR, the better the discriminatory ability of the test was.^[24] The SROC was plotted by the combination of sensitivity and specificity, and the area under the curve (AUC) value was then calculated as a global measurement of test performance. The closer the AUC was to 1, the better the test performance.^[25] We used Meta-DiSc 1.4 to check for asymmetry of the SROC curve, and fit an asymmetrical SROC curve if the coefficient *b* is significantly less than or greater than zero.^[26]

2.6. Publication bias

We used stata statistical software (STATA, version 15.1) to obtain a quantitative analysis of all the publication bias according to the Deeks test. An asymmetric distribution of data points in the Deeks plot with a quantified result of $P < .05$ indicated the presence of potential publication bias.^[27]

2.7. Heterogeneity and Meta-regression

Exploring heterogeneity was a critical issue of the analysis. Threshold effect was one of the primary causes of heterogeneity, which arises when differences in sensitivities and specificities occur due to different cut-offs used in different studies to define a positive (or negative) test result^[26]. We used meta-disc 1.4 to compute of Spearman correlation coefficient between the logit of sensitivity and logit of 1-specificity. A strong positive correlation would suggest threshold effect. A curvilinear shape in the SROCs indicated the presence of a threshold effect. If heterogeneity due to threshold effect were present, the accuracy data can be pooled by fitting a SROC curve and summarising that curve by means of the AUC.^[26] Then, studies with inappropriate thresholds will be excluded and the remaining studies will be included for meta-analysis. Heterogeneity of pooling sensitivity and specificity was examined by the X^2 test. Heterogeneity of pooling DOR was examined by the Cochran



PRISMA 2009 Flow Diagram

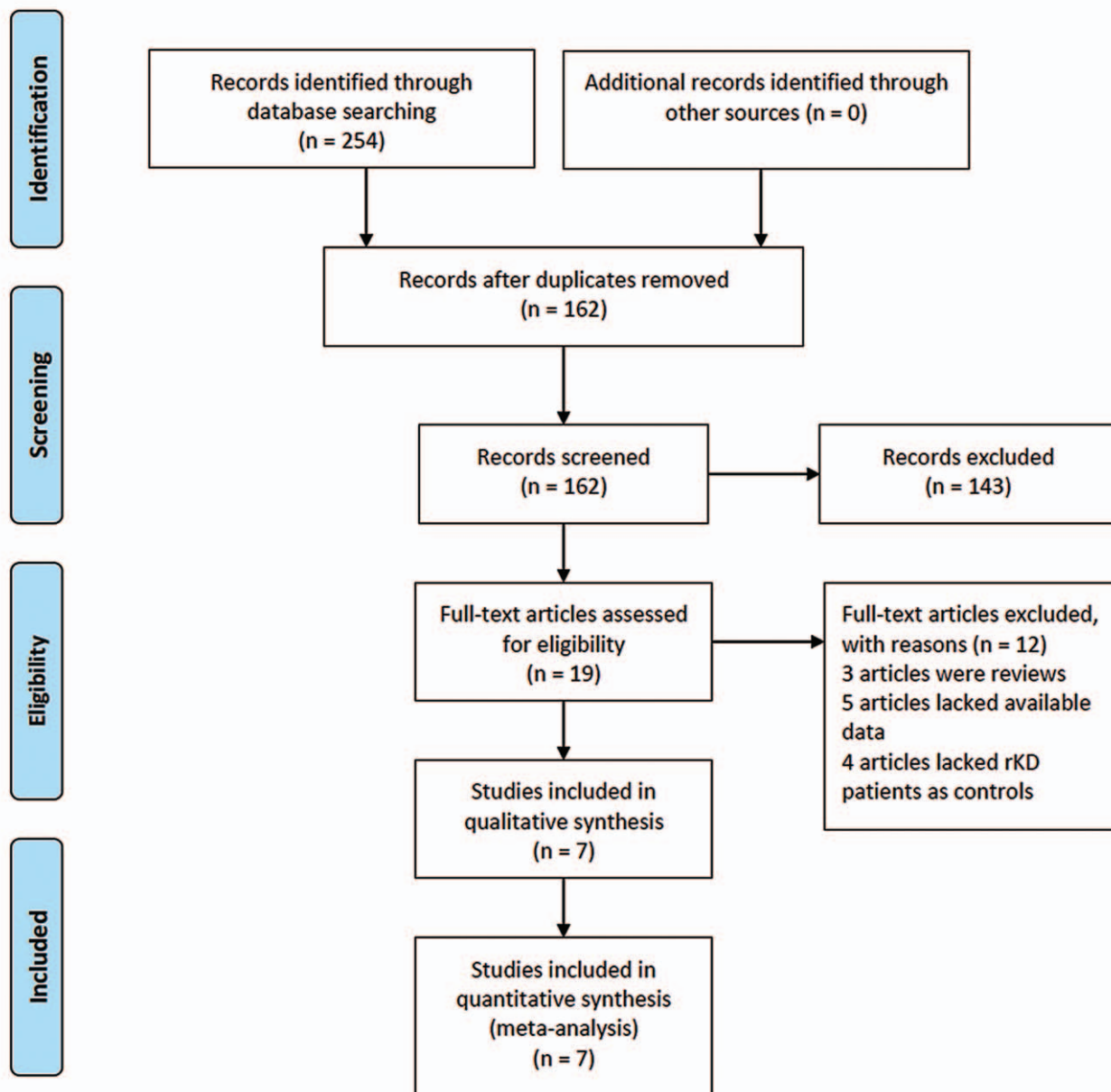


Figure 1. Flow diagram of the study selection process. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

Q test. Heterogeneity was considered as statistically significant when $P < .05$. The I^2 test was also performed in every pooling analysis in order to quantitatively estimate the proportion of total variation across studies, which was attributable to heterogeneity rather than chance. Results utilized random effects model when I^2 was higher than 50%, which was considered as evidence of high heterogeneity.^[28] Furthermore,

we carried out the meta-regression analysis using STATA 15.1 to identify the potential factors that might cause the heterogeneities other than threshold effect. The meta-regression could determine the correlation between the potential factors and the existing heterogeneities. A significant difference with a P value $< .05$ indicated that the factor should have a dramatic impact on the homogeneity.

Table 1
Characteristics of studies in meta-analysis.

No.	First author	Yr	Country	Design	Diagnostic criteria	Sample size of rKD/ non-rKD	Mean age of rKD/ non-rKD (month)	Indicators for predicting rKD	Indicators acquisition time	cut-off of NLR	AUC	sensitivity	specificity
1	Ha KS	2015	Korea	retrospective	AHA	222/365	34.2/34.0	NLR	before IVIG	5.49	0.67	0.39	0.86
								NLR	after IVIG	1.26	0.73	0.52	0.87
2	Kawamura Y	2016	Japan	retrospective	JKDRC	85/320	34/25	NLR	before IVIG	3.83	0.75	0.84	0.59
								NLR	after IVIG	1.27	0.86	0.9	0.72
								NLR+PLR	before IVIG	3.83	N/R	0.71	0.69
								NLR+PLR	after IVIG	1.27	N/R	0.32	0.88
3	Takeshita S	2017	Japan	retrospective	JKDRC	93/344	24.0/13.2	NLR+PLR	before IVIG	3.83	N/R	0.72	0.67
4	Yuan YD	2017	China	retrospective	AHA	31/373	24.0/20.4	NLR	before IVIG	4.36	0.78	0.85	0.63
								NLR	after IVIG	1.45	0.82	0.86	0.62
5	Cho HJ	2017	Korea	retrospective	AHA	23/173	31.2/32.4	NLR	before IVIG	5	0.797	0.739	0.775
6	Chantasiwan N	2018	Thailand	retrospective	AHA	26/191	28.8/39.1	NLR+HCT+ PLT+AST	before IVIG	3.2	0.796	0.808	0.668
7	Chen Y	2019	China	retrospective	AHA	11/81	8.2/7.6	NLR	before IVIG	2.51	0.692	0.545	0.84

AHA = American Heart Association, AST = aspartate transaminase, AUC = area under the curve, HCT = haematocrit, IVIG = intravenous immunoglobulin, JKDRC = Japan Kawasaki Disease Research Committee, N/R = not report, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PLT = platelet count, rKD = intravenous immunoglobulin-resistant Kawasaki disease.

2.8. Sensitivity analysis

We used STATA 15.1 to conducted sensitivity analysis for every study to determine the influence of individual trials on the results.

2.9. Statistical analysis

We used Meta-Disc Version 1.4 to perform the data analysis and threshold analysis. Besides, publication bias, meta-regression analysis, and sensitivity analysis were conducted by STATA Version 15.1 (Stata Corporation, College Station, Texas). We utilized the fixed effects model for homogenous results analysis, while the random effects model was utilized for the heterogeneous ($I^2 > 50\%$) results analysis. The data were presented using a forest map.

3. Results

3.1. Search results

Initially, 254 potentially relevant papers were retrieved by the aforementioned search method, and 19 articles were considered interesting after review of the titles and abstracts. However, 3 reviews were excluded after reading the complete articles, 5 studies lacked available data to construct a 2×2 table, and 4 articles lacked rKD patients as controls. Finally, 7 studies [18–20,29–32] were included in the meta-analysis. The process of study selection is illustrated in Figure 1.

3.2. Study characteristics

The 7 published reports enrolled a total of 2338 children: 491 rKD patients and 1847 non-rKD patients. All included studies were retrospective trials. All patients were treated with IVIG (single dose 2 g kg^{-1}) in the acute phase of KD. Five reports [18,29–32] used the American Heart Association (AHA) diagnostic criteria.^[1] Two studies [19,20] used the Japan Kawasaki Disease Research Committee (JKDRC) diagnostic criteria.^[33] Although KD patients with persistent or recurrent fever after the first IVIG treatment was defined as rKD patients in all studies, the duration of persistent or recurrent fever was inconsistent in the definitions. Two studies defined persistent or recurrent fever as lasting 24 hours,^[19,20] 2 studies defined persistent or recurrent fever as lasting 36 hours,^[29,31] and 3 studies defined persistent or recurrent fever as lasting 48 hours.^[18,30,32]

Three studies [18,19,29] reported the diagnostic performance of the NLR for rKD before and after the first IVIG treatment, and the remaining 4 studies [20,30–32] just evaluated the diagnostic performance of the NLR before IVIG treatment. One study [19] reported the diagnostic performance of NLR alone and in combination with the platelet-to-lymphocyte ratio (PLR). Four studies [18,29,30,32] reported the diagnostic performance of the NLR only, and 2 studies [20,31] reported the diagnostic performance of the NLR in combination with other indicators, such as the PLR, haematocrit, platelet count (PLT), and aspartate transaminase (AST). There were 2 reports from China, 2 reports from Japan, 2 reports from Korea, and 1 report from Thailand. The total KD sample size of 3 studies was much smaller ($n < 400$)

Table 2
QUADAS criteria of included studies.

No.	Spectrum composition	Selection criteria	Reference standard	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Reference standard execution	Test review bias	Reference standard review bias	Clinical review bias	Uninterruptible test results	Withdrawals
1	+	+	+	+	+	+	+	+	+	+	+	+	+	?
2	+	+	+	+	+	+	+	+	+	?	+	+	?	+
3	+	+	+	?	+	+	+	+	+	+	+	+	+	?
4	+	+	+	?	+	+	+	+	+	+	+	+	+	?
5	+	+	+	+	+	+	+	+	+	?	+	+	+	?
6	+	+	+	?	+	+	+	+	+	?	+	+	+	?
7	+	+	+	+	+	+	+	+	+	?	+	?	+	+

QUADAS = quality assessment of diagnostic accuracy studies.

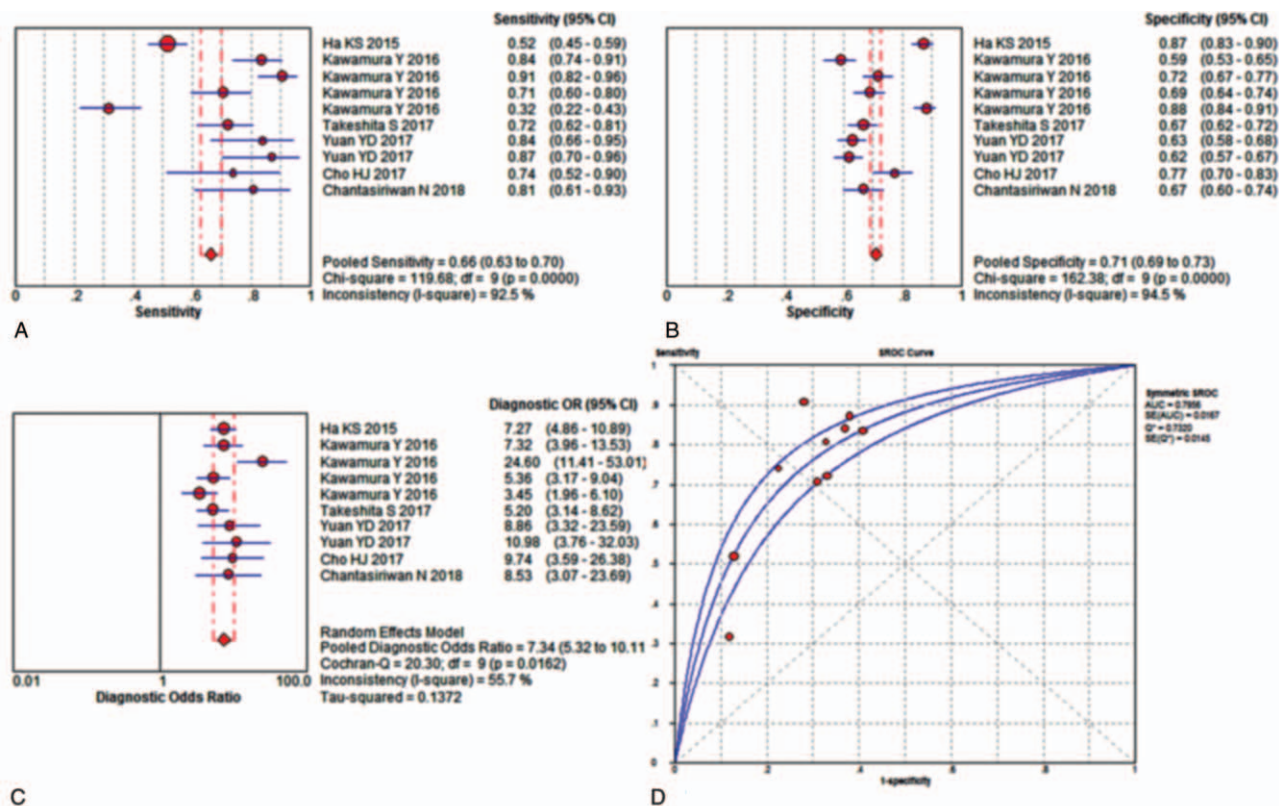


Figure 2. Performance of NLR detection for the diagnosis of rKD. (A) Pooled sensitivity. (B) Pooled specificity. (C) Overall DOR. (D) The SROCs for all datasets. The point estimates from each study are shown as solid squares. The pooled estimates are shown as a solid diamond. Effect sizes were pooled by random-effect models. Each square in the SROC represents 1 study. Sample size is indicated by the size of the square. Error bars represent 95% CIs. CI = confidence interval, DOR = diagnostic odds ratio, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, rKD = intravenous immunoglobulin-resistant Kawasaki disease, SROC = summary receiver operating characteristic curves value.

compared to the remaining 4 studies (n ≥400). The basic characteristics of the included studies are shown in Table 1.

3.3. Study quality

The quality assessment of the included studies was accomplished according to the QUADAS list of questions, and the results are shown in Table 2.

3.4. Diagnostic accuracy of NLR

First, we analyzed all of the included studies for the overall diagnostic performance of the NLR in detecting rKD. However, the Spearman correlation coefficient was 0.779 (P < .05) which suggests that a threshold effect was present. Because the coefficient *b* was significantly less than or greater than zero (P = .02), we fitted an asymmetrical SROC curve, and the calculated AUC value was 0.7899 ± 0.0141 (Supplementary Figure 1, <http://links.lww.com/MD/D730>). A review of the baseline data revealed that the cut-offs of the NLR before IVIG in 5 studies were approximately 4 but not in 2 studies (Table 1). Therefore, these 2 studies were excluded, and the remaining studies were included to analyze the overall diagnostic performance of the NLR in detecting rKD. The Spearman correlation coefficient was 0.624 (P > .05), which suggested no threshold effect. The pooled sensitivity was 0.66 (95% CI, 0.63 - 0.70) with significant heterogeneity (P < .001, X² = 119.68, I² = 92.5%) (Fig. 2A). The pooled specificity was

0.71 (95% CI, 0.69 to 0.73) with noticeable heterogeneity (P < .001, x² = 162.38, I² = 94.5%) (Fig. 2B). The pooled DOR was 7.34 (95% CI, 5.32 - 10.11) with significant heterogeneity (P = .016, Cochran Q = 20.30, I² = 55.7%) (Fig. 2C), and the SROC value was 0.7956 ± 0.0167 (Fig. 2D).

Next, we performed a meta-regression analysis to identify the potential factors underlying the heterogeneities other than the threshold effect. A review of the baseline data and the original data that produced the procedure, the type of samples (the NLR alone and the NLR in combination with other indicators), countries (Korea, Japan, China, and Thailand), total KD sample sizes (n < 400 and n ≥ 400), specimen acquisition time (before IVIG and after IVIG), KD diagnostic criteria (AHA and JKDRC), and the duration of persistent or recurrent fever in the definitions of rKD (24 hours, 36 hours, and 48 hours) were taken into account in the meta-regression to determine the origins of the heterogeneities. The results (Fig. 3) demonstrated that the type of samples was a dramatic impact factor on the homogeneity of the enrolled studies (P = .03, t = -2.54, 95% CI (0.2851, 0.9423)) (Fig. 3A). Country was not a dramatic impact factor on the homogeneity (P = .78, t = 0.29, 95% CI (0.6344, 1.8005)) (Fig. 3B). The total KD sample size was also not a dramatic impact factor on the homogeneity (P = .66, t = -0.48, 95% CI (0.2447, 2.5145)) (Fig. 3C). The meta-regression also found that specimen acquisition time was not a dramatic impact factor (P = .62, t = 0.51, 95% CI (0.5189, 2.7984)) (Fig. 3D). The diagnostic criteria of KD did not dramatically impact the results

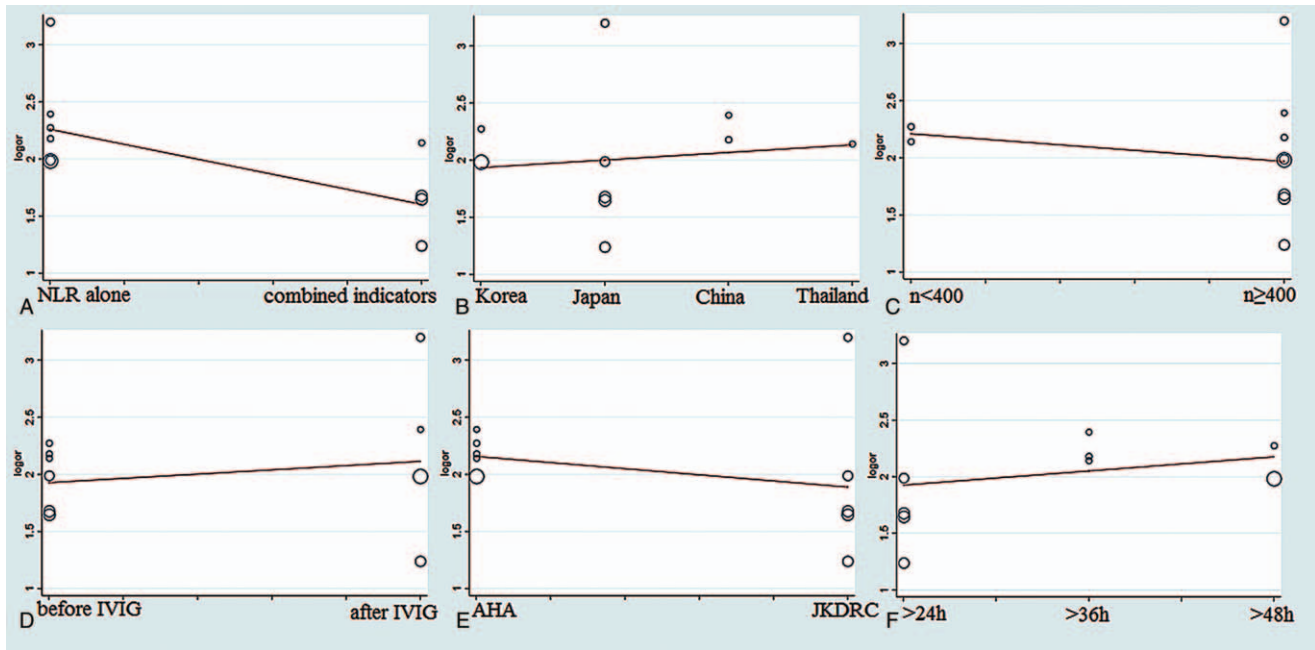


Figure 3. The meta-regression of the enrolled studies. (A) For the type of samples, the meta-regression detected it was a dramatic impact on the homogeneity of the enrolled studies, $P=.03$, $t=-2.54$, 95%CI (0.2851, 0.9423). (B) For the countries, the meta-regression did not find it was a dramatic impact on the homogeneity of the enrolled studies, $P=.78$, $t=0.29$, 95%CI (0.6344, 1.8005). (C) For the total KD sample sizes, the meta-regression did not detect it was a dramatic impact on the homogeneity of the enrolled studies, $P=.64$, $t=-0.48$, 95%CI (0.2447, 2.5145). (D) For the specimen acquisition time, the meta-regression did not detect it was a dramatic impact on the homogeneity of the enrolled studies, $P=.62$, $t=0.51$, 95%CI (0.5189, 2.7984). (E) For the diagnostic criteria of KD, the meta-regression did not detect it was a dramatic impact on the homogeneity of the enrolled studies, $P=.47$, $t=-0.76$, 95%CI (0.3388, 1.7256). (F) For the duration of persistent or recurrent fever in the definitions of rKD, the meta-regression did not detect it was a dramatic impact on the homogeneity of the enrolled studies, $P=.59$, $t=0.57$, 95%CI (0.6812, 1.8836). AHA=American Heart Association, CI=confidence interval, IVIG=intravenous immunoglobulin, JKDRC=Japan Kawasaki Disease Research Committee, NLR=neutrophil-to-lymphocyte ratio, or=odds ratio, rKD=intravenous immunoglobulin-resistant Kawasaki disease.

($P=.47$, $t=-0.76$, 95% CI (0.3388, 1.7256)) (Fig. 3E), and the duration of persistent or recurrent fever in the definitions of rKD was not a dramatic impact factor ($P=.59$, $t=0.57$, 95% CI (0.6812, 1.8836)) (Fig. 3F).

3.5. Subgroup analysis

We performed subgroup analyses according to the sample type (the NLR alone and the NLR in combination with other indicators) and the specimen acquisition time (before IVIG and after IVIG). All of the results are shown in Table 3 and

Supplementary Figures 2 to 5, <http://links.lww.com/MD/D731>. The subgroup analyses suggested that the subgroup NLR alone had a larger AUC of SROC than the subgroup NLR in combination with other indicators: pooled sensitivity, 0.70 (95% CI, 0.65–0.74); pooled specificity, 0.69 (95% CI, 0.67–0.72); and SROC, 0.8217 ± 0.0196 (Supplementary Figure 2, <http://links.lww.com/MD/D731>). The subgroup after IVIG had a larger AUC of SROC than the subgroup before IVIG: pooled sensitivity, 0.58 (95% CI, 0.53 – 0.63); pooled specificity, 0.77 (95% CI, 0.75 – 0.79); and SROC, 0.8440 ± 0.0206 (Supplementary Figure 5, <http://links.lww.com/MD/D731>).

Table 3
Subgroup analysis results of included studies.

	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	SROC (AUC±SE)
Total	0.66 (0.63–0.70)	0.71 (0.69–0.73)	7.34 (5.32–10.11)	0.7956±0.0167
I^2/P^2	< .001/92.5%	< .001/94.5%	.02/55.7%	–
Type of samples				
NLR alone	0.70 (0.65–0.74)	0.69 (0.67–0.72)	9.45 (7.30–12.24)	0.8217±0.0196
I^2/P^2	< .001/92.9%	< .001/95.1%	.14/40.1%	–
NLR in combination with other indicators	0.61 (0.55–0.66)	0.73 (0.71–0.76)	5.01 (3.83–6.56)	0.7568±0.0206
I^2/P^2	< .001/93.0%	< .001/94.6%	.43/0.0%	–
Specimen acquisition time				
Before IVIG	0.76 (0.72–0.81)	0.66 (0.64–0.68)	6.44 (4.98–8.34)	0.7647±0.0238
I^2/P^2	.26/22.6%	.001/75.7%	.75/0.0%	–
After IVIG	0.58 (0.53–0.63)	0.77 (0.75–0.79)	8.66 (3.98–18.84)	0.8440±0.0206
I^2/P^2	< .001/96.4%	< .001/96.9%	< .001/82.7%	–

AUC=area under the curve, CI=confidence interval, DOR=diagnostic odds ratio, IVIG=intravenous immunoglobulin, NLR=neutrophil-to-lymphocyte ratio, SE=standard error, SROC=summary receiver operating characteristic curves value.

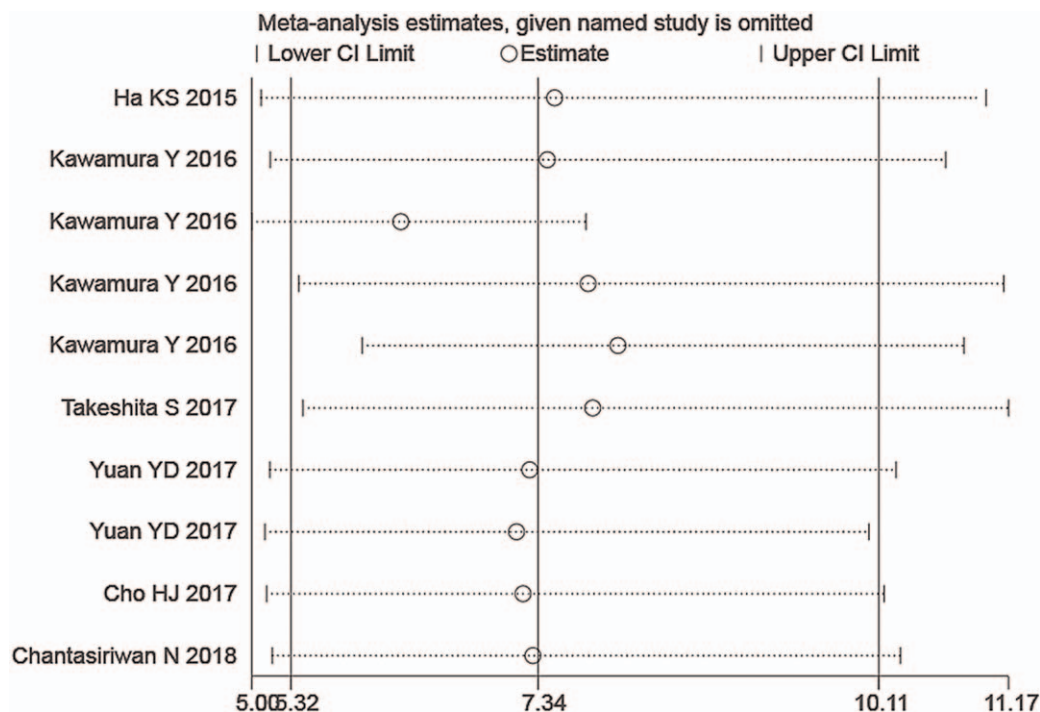


Figure 4. Sensitivity analysis of the individual trials on the results of NLR. Not any single study was detected to incur undue weight in the analysis. NLR = neutrophil-to-lymphocyte ratio.

3.6. Sensitivity analysis

We used STATA 15.1 for meta-analysis random-effects estimates to systematically and qualitatively analyze the sensitivity across included studies. We did not detect any significant impact from any single research study and confirmed the results of the overall performance of the NLR (Fig. 4).

3.7. Publication bias

We used Deeks funnel plot asymmetry test to evaluate the publication bias of the included studies. Each dot in these plots represents 1 study. The distance between each dot and the vertical line suggested bias in each study. The absence of any asymmetric distribution suggested no publication bias. The asymmetric distribution indicated that publication bias existed. Deeks tests revealed no significant publication bias among the included evaluation pooled results of the overall performance of NLR ($P = .60$, 95% CI, -17.3403 to 27.9277) (Fig. 5).

4. Discussion

rKD was significantly associated with coronary events and major adverse cardiac events.^[34] The early prediction of rKD may enable clinicians to use more aggressive treatment to prevent the occurrence of CAL. We performed this meta-analysis to assess the diagnostic accuracy of the NLR for the detection of rKD and found that the overall diagnostic sensitivity and specificity of the NLR for diagnosis rKD were 0.66 and 0.71, respectively. The AUC of SROC was 0.7956. These findings suggest that the NLR may be used as a biomarker for detecting rKD.

The meta-regression analysis indicated that the type of sample had a dramatic impact on the homogeneity of the enrolled studies ($P = .03$, Fig. 3A). The subgroup analysis found that the NLR

alone had the higher diagnostic accuracy compared to the NLR in combination with other indicators. Several risk-scoring systems (Kobayashi, Egami, and Sano scoring systems) are mainly composed of various laboratory indicators that use general laboratory data, such as total bilirubin (TB), neutrophils, C-reactive protein (CRP), serum sodium, PLT, AST, and alanine aminotransferase (ALT) (13–15). These risk-scoring systems are limited by regions and are not suitable for global promotion. Clinicians need more convenient and feasible indicators to predict rKD. Previous studies^[35–38] have shown that many laboratory indicators, such as TB, ALT, CRP, albumin, and N-terminal pro-brain natriuretic peptide (NT-proBNP), are associated with rKD. However, there is no useful single biomarker in existence. In 2016, Baek et al^[39] performed a meta-analysis and found that laboratory predictive factors for rKD included higher TB, polymorphonuclear leukocyte, pro-brain natriuretic peptide, AST, ALT, CRP, lower sodium and albumin. Two years later, Li et al^[40] performed a meta-analysis and indicated that increased erythrocyte sedimentation rate, decreased hemoglobin and PLT might be risk factors for predicting rKD. Neither meta-analysis assessed the diagnostic accuracy of the indicators, and neither analysis mentioned the NLR. Our study is the first meta-analysis to assess the diagnostic accuracy of the NLR in detecting rKD.

To allow clinicians to implement medical measures earlier, it is better to predict rKD earlier. Therefore, we performed a subgroup analysis by the specimen acquisition time. Although the NLR after initial treatment of IVIG had a larger AUC than before IVIG, the gap between the 2 was not large (0.8440 vs 0.7647, respectively). Due to the small number of studies included in both groups, there was inevitably some bias in the results. More research is needed to confirm the results.

The NLR was recently reported to be a powerful indicator of systemic inflammation, sepsis, and cardiovascular diseases.^[41–43]

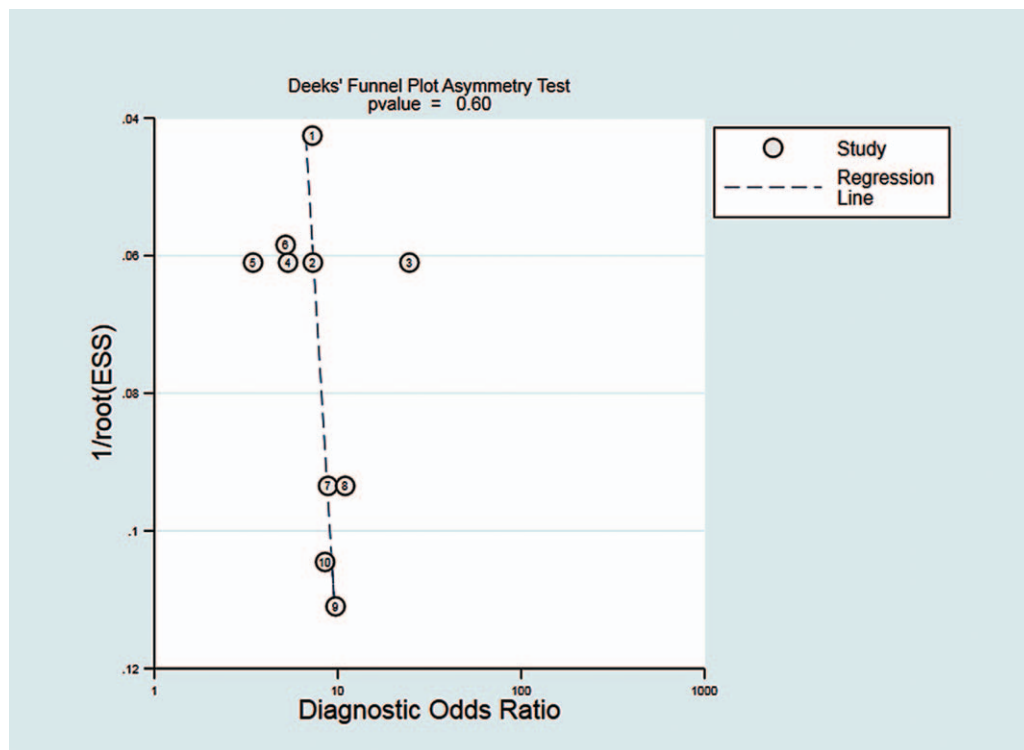


Figure 5. Deeks funnel plot for the assessment of potential publication bias. The funnel graphs plot the square root of the effective sample size ($1/\text{ESS}^{1/2}$) against the DOR. Each circle represents each study in the meta-analysis. Asymmetry of the circle distribution between regression lines indicates potential publication bias. This funnel plot indicates no publication bias with a P value $> .05$. DOR=diagnostic odds ratio, ESS=effective sample size.

Neutrophil counts reflect ongoing inflammation, and lymphocyte counts are a marker of immune regulatory response.^[32] The NLR is a combination of neutrophils and lymphocytes, and it may be used as a marker of balance between inflammation and immune regulation.^[41] We found that rKD patients had a significantly higher NLR than nonrKD patients in all of the studies included in our meta-analysis, which indicates that rKD patients might have a more severe inflammatory course. However, the immunological basis of IVIG resistance is not clear, partially because the mechanism of action of IVIG is poorly understood.^[5] Host genetic factors, such as polymorphisms in the Fc gamma receptors, may play a role in IVIG response and resistance.^[44,45]

A previous study^[46] suggested the NLR as a useful marker to predict CAL in patients with KD. However, there was only 1 study^[18] that reported a similar conclusion in all of the included studies. Therefore, we did not perform an analysis of the value of NLR in predicting CAL. More studies are needed to clarify the diagnostic value of NLR in predicting CAL.

There are several limitations of this meta-analysis. First, the number of included studies was small ($n=7$), and all of the studies were performed in Asian populations, which means that these results may not generalize to other populations. Second, fewer than ten studies were included in this study, and the results of meta-regression and subgroup analyses must be treated with caution.

In conclusion, despite these limitations, this report is the first meta-analysis to show that the NLR could be used as a biomarker for detecting rKD, especially the NLR value after the initial treatment of IVIG. More well-designed research must be conducted to launch the application of the NLR for predicting rKD in the clinic.

Author contributions

Conceptualization: Xiaolan Zheng, Yifei Li.

Data curation: Xiaolan Zheng, Gang Wu, Yifei Li.

Formal analysis: Gang Wu, Xiaolan Zheng, Peng Yue, Fan Ma.

Investigation: Gang Wu, Xiaolan Zheng, Yi Zhang, Yifei Li.

Methodology: Yi Zhang, Fan Ma.

Project administration: Yifei Li.

Software: Xiaolan Zheng, Fan Ma.

Supervision: Xiaolan Zheng, Yifei Li.

Validation: Xiaolan Zheng, Yifei Li.

Visualization: Xiaolan Zheng, Yifei Li.

Writing – original draft: Xiaolan Zheng.

Writing – review & editing: Yifei Li.

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