



Research article

Diagnostic accuracy of neutrophil lymphocyte ratio and platelet lymphocyte ratio for IVIG-resistance Kawasaki disease: an updated meta-analysis

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Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ABSTRACT

Background: Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are biomarkers for the diagnosis and prognosis of many diseases. However, the diagnostic accuracy of IVIG resistant Kawasaki disease is still unclear. This study aims to evaluate the diagnostic value of NLR and PLR in IVIG resistant Kawasaki disease. Method: We used Pubmed, Embase, Web of

science, CNKI and Google academic database to find all articles that met the inclusion criteria until January 5 2024. Result: After two independent researchers carefully read the title, abstract, and full text, five eligible studies were included in the study analysis, with a total of 3359 children included. The research results showed that the combined sensitivity and specificity were 0.57 (95% CI: 0.48-0.66) and 0.73 (95% CI: 0.67-0.78), respectively; The pooled positive likelihood ratio and Negative likelihood ratio were 2.12 (95% CI: 1.91-2.34) and 0.58 (95% CI: 0.50-0.68), respectively; The pooled DOR was 3.62 (95% CI: 2.99-4.39); The area under the SROC curve (AUC) was 0.71 (95% CI: 0.67-0.75), indicating high diagnostic performance. Conclusion: This study analysis indicates that the PLR+NLR levels in children with Kawasaki disease can serve as an important parameter in the risk scoring system, with relatively high accuracy.

Key words: Neutrophils; Platelets; IVIG resistant Kawasaki disease; Biomarkers

1. Introduction

Kawasaki disease (KD) is an acute febrile illness with systemic vasculitis of unknown etiology affecting predominantly in infants and young children [1]. KD has been acknowledged to be the leading cause of pediatric acquired heart disease and the incidence of coronary aneurysm lesions (CALs) was 25% in untreated children approximately [2]. Although initial therapy with intravenous immunoglobulin (IVIG) for KD can reduce the occurrence of coronary artery aneurysm effectively, approximately 10%-20% of children with KD were resistant to IVIG therapy [3]. These children received the first dose of 2g / kg intravenous immunoglobulin but the fever continued or the typical symptoms of KD appeared in the non-fever stage after 36 hours of treatment [4]. This

phenomenon was defined as IVIG-resistance(rKD). Compared with patients of IVIG responsive, the risk of developing coronary artery disease was significantly increased in Patients with Rkd. Therefore, it is necessary to identify patients with rKD before the initial treatment starting, because an intensive initial therapy may improve the outcomes of patients.

In recent years, several risk-scoring systems have been constructed to predict IVIG resistance in KD patients, such as Kobayashi, Egami, Sano and Nakano scores. However, in the studies of Mohammad Reza Edraki et al and Niloufar Shashaani et al shown that these scoring systems have limited usefulness to predict IVIG resistance in the Iranian population. Sarah Davies et al also demonstrated that the kobayashi score does not predict IVIG resistance in population of UK. Similarly, these risk scoring systems were unable to predict IVIG resistance of Kawasaki disease in Italian and china effectively. In addition, some studies have also reported that several inflammatory cytokines and T-cell surface markers can be used to predict IVIG resistance in KD patients, but the acquisition cost of these biomarkers is too high to be used in widespread clinical screening, compared with conventional laboratory data. Consequently, it is desirable to find effective biomarkers to screen for IVIG resistance without exorbitant expenses.

Leukocytes are the main inflammatory cells in the human body, and the

changes in their numbers reflect the response of the immune system to systemic inflammation. Therefore, the number or proportion of leukocytes and their subsets in peripheral blood is a reliable indicator of inflammatory response. In the past few years, neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been reported as useful diagnostic indicators for cardiovascular disease and cancer. Similarly, kawamura et al used NLR, PLR and their combined indicators to predict the occurrence of IVIG non response in KD children. Recently, many similar studies have also shown the accuracy of combined indicators of PLR and NLR in the diagnosis of rKD. However, the researches could not achieve a convincing result. In order to evaluate the diagnostic performance of combined indicators of PLR and NLR for rKD, we performed this systematic review and meta-analysis to judge whether combined indicators of PLR and NLR can be used as an important parameter of the risk-scoring systems.

2. Materials and Methods

2.1. Literature Search

To identify eligible studies, a search was conducted in the electronic databases PubMed, EMBASE, web of science, China National Knowledge Infrastructure (CNKI) and Wan fang from their inception to January 5, 2024, without Language restrictions. Two independently

investigators searched these databases for all RDW and NS related studies with the following combination of terms: (Mucocutaneous Lymph Node Syndrome[MeSH Terms]) OR (Kawasaki Syndrome) OR (Lymph Node Syndrome, Mucocutaneous) OR (Kawasaki Disease) OR (KD) AND (PLR) OR (platelet-to-lymphocyte ratio) OR (Blood Platelets[MeSH Terms]) OR (Blood Platelet) OR (Platelet, Blood) OR (Platelets, Blood) OR (Thrombocytes) OR (Thrombocyte) OR (Platelets) OR (Platelet) AND (Lymphocytes[MeSH Terms]) OR (Lymphocyte) OR (Lymphoid) AND (NLR) OR (Neutrophil-to-lymphocyte ratio) OR (Neutrophils) OR (Neutrophil[MeSH Terms]) AND (Lymphocytes[MeSH Terms]) OR (Lymphocyte) OR (Lymphoid). In addition, manual search was Performed by the perusal of the reference sections of all the relevant reviews or Included literature. If different articles contain the same study, the one with a larger number of cases will be selected.

2.2. Inclusion Criteria

All studies meeting following criteria were included: ① cohort study, case-control study or cross-sectional study. ② pediatric patients confirmed to be with KD by KD diagnosis criteria. ③ control group was composed of non-rKD , and patients with rKD as the experimental group. ④ All studies provide the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) directly or indirectly.

2.3. Exclusion Criteria

All studies meeting following criteria were excluded: ①the content of the study is irrelevant to Kawasaki disease or rKD. ②unavailability of the original data. ③the pediatric patients in the control group may have other diseases other than KD or the specific health status is not specified. ④review, letters, expert opinions, duplicate publications. Two independent investigators screened the literature according to inclusion and exclusion criteria after reading the title, abstract or full text. Articles with different opinions among investigators will be discussed to decide whether to include them.

2.4. Quality Assessment and Data Extraction

Two investigators extracted the following data from all Included studies independently: first author, year of publication, sample size, age of participants, sex, number of cases and controls, diagnostic criteria of KD, and cut-off value of PLR+NLR, TP, FP, TN and FN. QUADAS-2 Scale was used to evaluate the quality of all enrolled studies. Disagreements between the two investigators were settled by discussion.

2.5. Statistical Analysis

We performed a meta-analysis to estimate the perform of PLR+NLR in diagnosis of rKD. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio (DOR) and 95% confidence intervals (CIs) were pooled. The summary receiver operating

characteristic (SROC) curve was also conducted based on the sensitivity and specificity. The area under the curve (AUC) close to 1 indicated that RDW has a good diagnostic performance [5]. Spearman correlation analysis was used to analyze the threshold effect, and $P < 0.05$ indicated a significant threshold effect [6]. Heterogeneity among studies was mainly assessed using I^2 statistic and Cochrane's Q statistic. $I^2 = 100\% \times (Q - df) / Q$. The heterogeneity was considered statistically significant when the $P < 0.05$ in the Q test and/or $I^2 > 50\%$, and then a random effects model was used for pooling the data; otherwise, a fixed effects model was used. We conducted the meta-regression analysis and subgroup analysis to identify the potential factors that might cause the heterogeneities. Sensitivity analysis was performed by excluding each study at a time to evaluate the influence of individual studies on the overall results of the meta-analysis. Deeks test were used to evaluate the publication bias of the included studies and the quantified result of $P < 0.05$ was considered a significant publication bias [7]. RevMan (5.3) software, Metadisc1.4 software and STATA (16.0) software were used for data analysis, and $P < 0.05$ was defined as being statistically significant.

3. Results

3.1. Search Results

We identified 179 studies by the initial search from above databases.

After removing the duplicates and irrelevant literature, the full texts of the remaining 27 studies were evaluated. Preliminary screening excluded 22 studies (Fifteen studies lacked diagnostic tests of PLR+NLR; Five studies did not provide available data; Two Reviews). Finally, 5 eligible studies were selected for meta-analysis. The process of the study selection is shown in Fig.1.

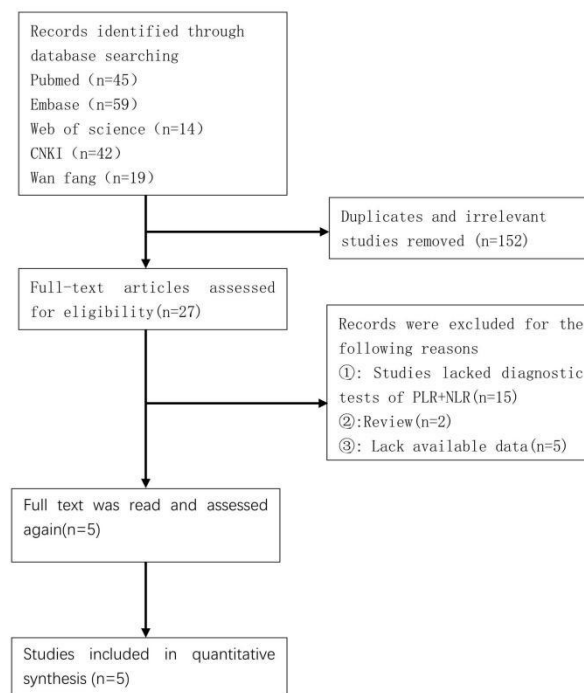


Figure 1. The process of the study selection

3.2. Characteristics of the Included Studies and Quality Assessment

A total of 5 eligible articles containing 8 studies were selected for meta-analysis, involving a total of 3359 children, 657 of whom had IVIG-resistant KD. These included two prospective and six retrospective observational studies. Two studies used the American Heart Association

(AHA) diagnostic criteria [6]. Three studies used the Japan Kawasaki Disease Research Committee (JKDRC) diagnostic criteria [8]. The author, publication year, country, sample size, sensitivity, specificity and other detailed characteristics of eligible studies were presented in Table 1. The methodological quality of the included studies was evaluated according to QUADAS-2 Scale, and the results were shown in Fig.2.

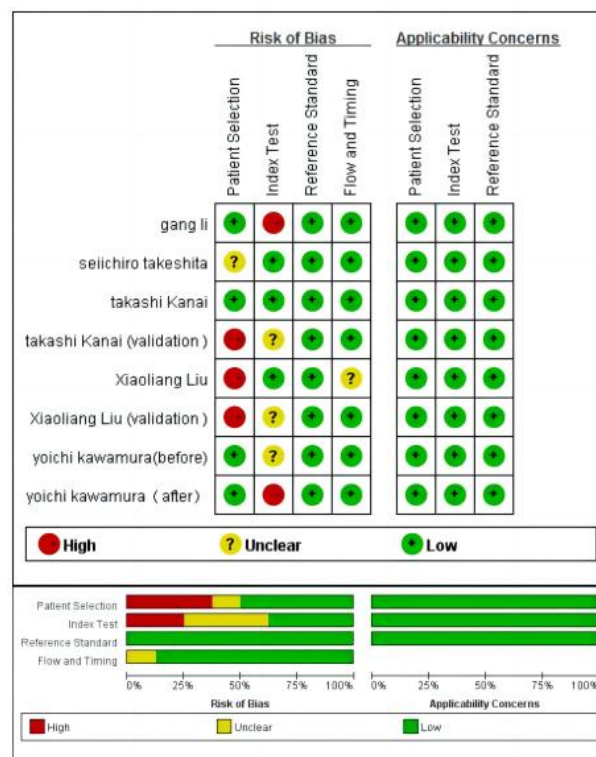


Figure 2. The methodological quality of the included studies

Table 1 The characteristics of the included studies

author	year	Country	Type of study	Diagnostic criteria	Sample size	M/F	Indicators for predicting rKD	Indicators acquisition time	Sensitivity	specificity	Diagnostic accuracy	AUC (95% CI)
Xiaoliang Liu	2020	China	prospectively	AHA	101/441	322/220	PLR+ NLR	After IVIG therapy	0.48	0.73	0.68	0.62
Xiaoliang Liu	2020	China	prospectively	AHA	23/143	NA	PLR+ NLR	After IVIG therapy	0.61	0.75	0.68	NA
yoichi kawamura	2016	Japan	retrospectively	JKDRC	85/320	234/171	PLR+ NLR	Before IVIG	0.71	0.69	0.69	NA

before)								therap y After IVI G therap y Before IVI G therap y Before IVI G therap y Before IVI G therap y Before IVI G therap y				
yoichi kawamura (after)	20 16	Japa n	retrospect ively	JKDR C	85/3 20	234/ 171	PLR+ NLR		0.32	0.88	0.76	NA
takashi Kanai	20 20	Japa n	retrospect ively	JKDR C	117/ 403	284/ 236	PLR+ NLR		0.58	0.73	0.70	NA
takashi Kanai	20 20	Japa n	retrospect ively	JKDR C	79/2 53	190/ 142	PLR+ NLR		0.54	0.72	0.69	NA
seiichiro takeshita	20 17	Japa n	retrospect ively	JKDR C	93/3 44	250/ 187	PLR+ NLR		0.72	0.67	0.68	NA
gang li	20 20	Chin a	retrospect ively	AHA	159/ 798	570	PLR+ NLR		0.68	0.6344	NA	0.6 91

AHA: American Heart Association; JKDR: Japan Kawasaki Disease Research Committee; M/F: Male/Female; rKD: IVIG-resistant KD; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; AUC: area under the curve; NA: not available

3.3. Pooled Analysis of Diagnostic Value of NLR+PLR

We conducted a meta-analysis of eight studies to analyzed diagnostic performance of the NLR+PLR in detecting rKD. A random effects model was used to analysis the results of these studies. Q-test was used to evaluated the heterogeneity among the included studies. The pooled sensitivity and specificity were 0.57 (95%CI:0.48-0.66) with significant heterogeneity ($P<0.001$, Cochran-Q = 49.00, I^2 = 85.71%) and 0.73 (95%CI:0.67-0.78) with noticeable heterogeneity ($P<0.001$, Cochran-Q = 76.33, I^2 = 90.83%), respectively (Fig.3A). The pooled positive likelihood ratio and Negative likelihood ratio were 2.12 (95%CI:1.91-2.34) with no significant heterogeneity ($P=0.39$, Cochran-Q = 7.43, I^2 = 0.00%) and 0.58 (95%CI:0.50-0.68) with significant heterogeneity($P<0.001$, Cochran-Q=29.83, I^2 =76.53%) (Fig.3B). The pooled DOR was 3.62 (95% CI:2.99-4.39) with significant

heterogeneity($P < 0.001$, Cochran- $Q = 46.12$, $I^2 = 84.82\%$). From the SROC, AUC was 0.71 (95% CI:0.67-0.75), suggesting that RDW has a high diagnostic perform. The Spearman correlation coefficients was 0.762, P value was $0.028 < 0.05$, indicating that there was conspicuous threshold effect among the included studies.

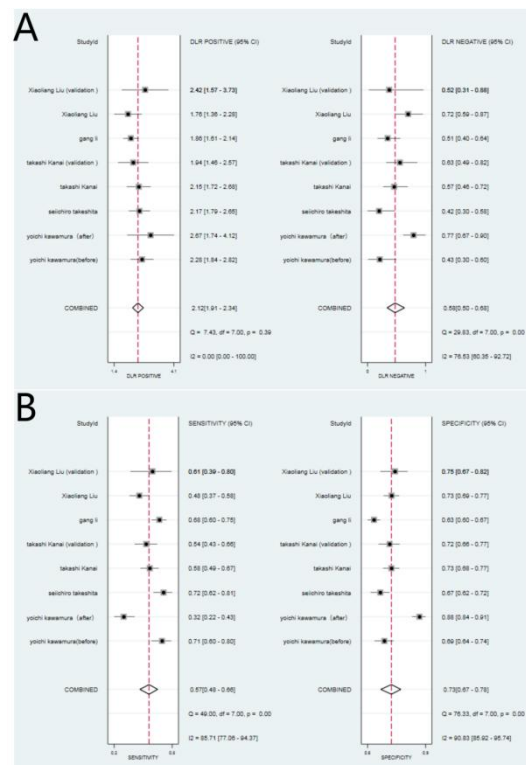


Figure 3. The Pooled Analysis of Diagnostic Value of NLR+PLR. A, The pooled sensitivity and specificity; B, The pooled positive likelihood ratio and Negative likelihood ratio.

3.4. Publication Bias

Deeks' test was used to evaluate the publication bias of the included studies. Each dot plots in these graphs represented a study. The distance between each dot and the vertical line indicated bias in each study.

Symmetrical distribution indicated there was no publication bias. According to the results of deek's funnel plot (Fig.4), P value was $0.64 > 0.05$, indicating that there was no significant publication bias among the included articles.

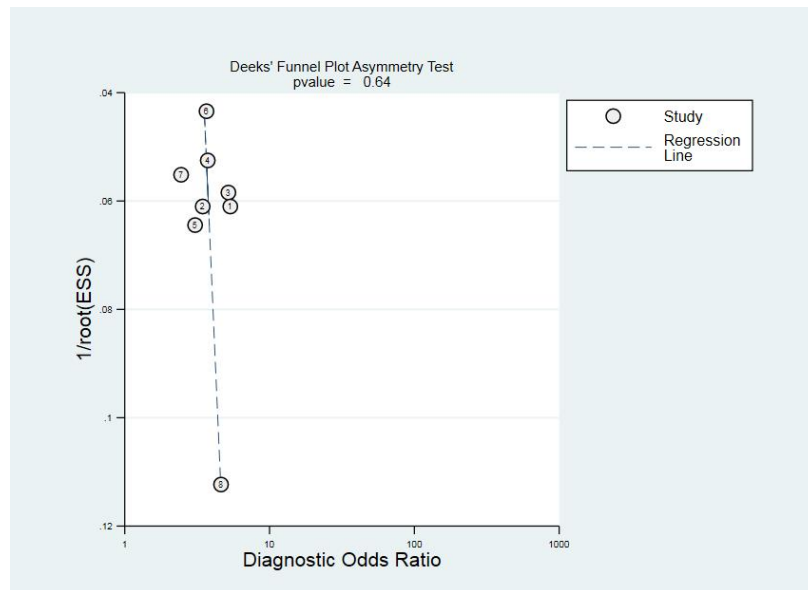


Figure 4.The deek's funnel plot of publication bias

3.5. Sensitivity Analysis

Sensitivity analysis was conducted to investigate the influence of included studies, using STATA 16 for meta-analysis random-effects estimates. Sensitivity analysis revealed that no individual study significantly affected the pooled performance of PLR+NLR, indicating the reliability of the results.

3.6. Meta-regression Analysis

In order to identify the source of heterogeneity, a meta regression analysis was performed to explore potential sources of heterogeneity

(methodological heterogeneity, clinical heterogeneity, and statistical heterogeneity). The type of research design, country, diagnostic criteria of KD, sample size, which might be potential sources of heterogeneity, were analyzed by the meta regression method of single factor. The meta-regression revealed the country made not contribution to the homogeneity, $P = 0.263$, $t = 1.24$, 95%CI (-0.2256-0.6859) . Similarly, the results demonstrated that the type of research design (prospectively and retrospectively) was not a dramatic impact factor on the homogeneity of the studies ($P=0.165$, $t=1.58$, 95% CI (-0.1960- 0.9094)). The diagnostic criteria of KD (AHA and JKDRC) was not a dramatic impact factor, $P = 0.263$, $t = 1.24$, 95%CI (-0.2256-0.6859). The total sample size ($n<500$ and $n \geq 500$) also was not a dramatic impact factor, $P = 0.222$, $t = 1.36$, 95%CI (-0.1974-0.6934) . According to the results of meta-regression, the above factors were not the main sources of heterogeneity.

3.7. Subgroup Analysis

The size of the sample size may affect the results of the experiment. Therefore, this subgroup analysis was based on total sample size to evaluate the diagnostic performance of NLR+PLR. A random effects model was used to analysis the results of these studies. The pooled sensitivity (95% CI) and specificity (95% CI) of the total sample size ($N \leq 500$) group were 0.58(95%CI: 0.53-0.63) and 0.74(95%CI: 0.72-0.76). The pooled DOR was 4.22(95%CI: 3.27-5.44). From the SROC, $AUC \pm$

SE was 0.7385 ± 0.0203 . The pooled sensitivity (95% CI), specificity (95% CI), DOR and AUC \pm SE of the total sample size ($N > 500$) group were $0.59(95\%CI: 0.54-0.64)$, $0.68(95\%CI: 0.66-0.71)$, $3.29(95\%CI: 2.54-4.25)$ and 0.7046 ± 0.0216 , respectively. After then, the second subgroup analysis was stratified by country. They are divided into two subgroups, China and Japan. The pooled sensitivity (95% CI), specificity (95% CI), DOR and AUC \pm SE of group with Japanese were $0.58(95\%CI: 0.53-0.62)$, $0.74(95\%CI: 0.72-0.76)$, $4.06(95\%CI: 3.24-5.08)$ and 0.7331 ± 0.0188 , respectively. The pooled sensitivity (95% CI), specificity (95% CI), DOR and AUC \pm SE of group with Chinese were $0.60(95\%CI: 0.54-0.66)$, $0.68(95\%CI: 0.65-0.70)$, $3.23(95\%CI: 2.34-4.44)$ and 0.7007 ± 0.0224 , respectively.

4. Discussion

Our meta-analysis demonstrated the value of NLR+PLR in the diagnosis of rKD by analyzing 5 included observational studies. The pooled sensitivity was 0.57 (95%CI:0.48-0.66, specificity was 0.73 (95%CI:0.67-0.78) , DOR was 3.62 (95% CI:2.99-4.39) and the area under the SROC curve (AUC) of RDW was 0.71. These results indicate that NLR+PLR has good diagnostic accuracy and high diagnostic efficiency as a biomarker. KD is an important risk factor for acquired heart disease in children, and its therapeutic effect is closely related to the occurrence

and development of coronary artery aneurysm in children. Because IVIG treatment of rkd is usually ineffective, early diagnosis of rkd is very important. Although several risk-scoring systems [9,10]. have been commonly used to predict IVIG resistance in KD patients in Japan, their diagnostic performance in different populations is inconsistent or satisfactory. Recently, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been reported to be useful as diagnostic indicators of rkd.

An elevated neutrophil count in response to inflammation and infection. It is reported [11,12] that in the acute phase of KD, with the production of oxygen intermediates, neutrophil elastase and myeloperoxidase, the number and function of neutrophils are significantly increased, which may lead to coronary vascular injury and aneurysm formation possibly. platelet count also play a major role in systemic infection and inflammation. Platelet and neutrophils are essential in immune response and may affect the development of thrombotic and inflammatory diseases. Similarly, lymphocytes perform the regulatory function of the immune system. Some studies [13,14] have also shown that low lymphocyte count is associated with poor prognosis in patients with myocardial infarction and chronic heart failure. In recent years, more and more attention has been paid to some simple hematological parameters, such as PLR and NLR. Binnaz Celik et al [15] demonstrated that acute appendicitis

pediatric patients with higher NLR and PLR levels might be more likely to develop a complication. Baodong Qin et al [16] also found that NLR and PLR could reflect inflammatory response and disease activity in SLE patients. It can be seen that PLR and NLR are closely related to various inflammatory diseases. Therefore, we conducted this meta-analysis to evaluate their combined diagnosis performance.

At the same time, we analyzed the publication bias and sensitivity of the included articles. According to the results, there was no significant publication bias, and the pooling results were stable and reliable. But, significant heterogeneity was found in the pooled sensitivity and specificity. In order to explore the source of heterogeneity, we conducted meta regression analysis and subgroup analysis. The results of meta-regression analysis showed that the type of research design, country, diagnostic criteria of KD and sample size were not the main causes of heterogeneity. In the subsequent subgroup analysis, the included studies were divided into two groups according to the sample size ($N \leq 500$ and $N > 500$ group). Similarly, the second subgroup analysis was stratified by country. But, there was no significant difference among the results of two groups, both with Significant heterogeneity. Therefore, we considered that the above factors are not the main reasons for the heterogeneity of the results. Spearman correlation coefficient showed that there was a significant threshold effect which may have contributed to

high heterogeneity in this meta-analysis. In addition, the small sample size of the included study, quality of included studies and methodological differences in type of study may also contribute to the heterogeneity. As far as we know, this is the first meta-analysis to evaluate the diagnostic performance of the NLR+PLR for rKD.

Our meta-analysis also has the following limitations. First, the number of included studies was small. Although a total of 8 studies were analyzed, the results of subgroup analysis and regression analysis should be treated cautiously and conservatively due to the limitation of quantity. Second, all studies were conducted in Asian populations. Because of the influence of racial differences, our results may have different effects in the process of application in other regions. Third, the higher statistical heterogeneity of the included studies may affect our results. A large part of the heterogeneity comes from the threshold effect. Due to the different cut-off values, the numerical value of each research result may be affected which may lead to inaccurate application of the results. Although, these deficiencies existed, the current research results were reliable and decisive, and can be used as an effective tool for clinical diagnosis.

5. Conclusion

This biomarker is a simple and inexpensive biomarker, which can be obtained in blood routine examination without extra blood sample and

cost. Our meta-analysis showed that PLR+NLR can be used as an important parameter of the risk-scoring systems with a relatively high accuracy. Due to the small number of included literatures and significant heterogeneity among studies, it should be more cautious and conservative to use PLR + NLR alone to explain the diagnosis of rkd. In addition, it is necessary to carry out further large sample studies, so as to explore the appropriate cut-off value and more accurately evaluate the predictive value of this marker.

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