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Diagnostic value of neutrophil-lymphocyte ratio in preeclampsia
A PRISMA-compliant systematic review and meta-analysis

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Abstract
Background: Neutrophil-lymphocyte ratio (NLR) is one of the markers of systemic inflammation. Recent studies have associated NLR with diagnosis of preeclampsia (PE). However, due to small sample sizes and different research design, the diagnostic value of NLR in PE patients is not well understood. In this study, we evaluate the potential diagnostic value of NLR in PE.

Methods: We searched PubMed, Embase, Cochrane Library, the Chinese National Knowledge Infrastructure (CNKI) databases, Wanfang data, VIP database and China Biomedical Literature Database systematically for relevant literatures up to May 20, 2018. All analyses were conducted using Meta-DiSc1.4 and Stata 12.0 software. Sensitivity, specificity and other measures of accuracy of NLR for the diagnosis of PE were pooled. Meta-regression was performed to identify the sources of heterogeneity.

Results: This meta-analysis included a total of 7 studies. The pooled sensitivity and specificity were 0.74 (95% CI 0.71–0.76) and 0.64 (95%CI 0.61–0.68), positive likelihood ratio, 2.62 (95%CI1.79–3.84); negative likelihood ratio, 0.34 (95%CI 0.24–0.48); diagnostic odds ratio, 8.44 (95%CI 4–17.78), and area under the curve was 0.82. Meta regression showed that sample size was the main source of heterogeneity. Deeks funnel plot showed that there was no statistical significance for the evaluation of publication bias ($P = .16$).

Conclusion: Current evidence suggests that the diagnostic accuracy of NLR has unsatisfactory specificity but acceptable sensitivity for diagnosis of PE. Further large-scale prospective studies are required to validate the potential applicability of using NLR alone or in combination other markers as PE diagnostic biomarker and explore potential factors that may influence the accuracy of NLR for PE diagnosis.

Abbreviations: AUC = the area under the curve, BMI = Body Mass Index, CBM = China Biomedical Literature Database, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, DOR = diagnostic odds ratio, Fig = Figure, FN = false negative number, FP = false positive number, HCT = hematocrit, NLR = negative likelihood ratio/ Neutrophil-lymphocyte ratio, PE = preeclampsia, PLR = positive likelihood ratio, PLT = platelets, TN = true negative number, TP = true positive number.

Keywords: biomarkers, meta-analysis, pre-eclampsia

1. Introduction

Preeclampsia (PE) is a unique vascular disease during pregnancy, with an incidence of 2% to 8%.[1] It was divided into 2 categories: mild PE and severe PE, causes adverse pregnancy outcomes between maternal and fetus, such as proteinuria, edema, multiple organ failure, fetal growth restriction, even intrauterine death. A World Health Organization survey on maternal mortality shows that the number of deaths due to pregnancy-induced hypertension worldwide is lower than 15%, it is still one of the top three causes of maternal mortality.[2]

There were a lot of researches on the pathogenesis of PE, one of the most recognized was: Inflammatory stimulation results in an abnormal immune response and induces vascular endothelial dysfunction those lead to hypertension.[3–6]

The term "low-grade inflammation" is used to define disease states that have no obvious clinical symptoms but have elevated immune cells and inflammatory factors.[7,8] Neutrophil-lymphocyte ratio (NLR) is one of the markers of systemic inflammation. It has become a research hotspot in recent years, participating in the development of various diseases and related to the prognosis of tumors.[9–14]

In recent years, some studies about the relationship between NLR and PE have been reported, but the conclusions were different due to the different research design, sample size and basic characteristics of the research subjects.[15–17] Meta-analysis is an effective analytical method to overcome the above shortcomings. In the present study, we conducted the meta-analysis using data from multiple studies to explore the diagnostic value of NLR for PE.

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching
(n = 105)

Additional records identified through other sources
(n = 0)

Screening

Records after duplicates removed
(n = 74)

Records screened
(n = 74)

Records excluded
(n = 56)

Eligibility

Full-text articles assessed for eligibility
(n = 18)

Full-text articles excluded, with reasons
(n = 11)

Included

Studies included in qualitative synthesis
(n = 7)

Studies included in quantitative synthesis (meta-analysis)
(n = 7)

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

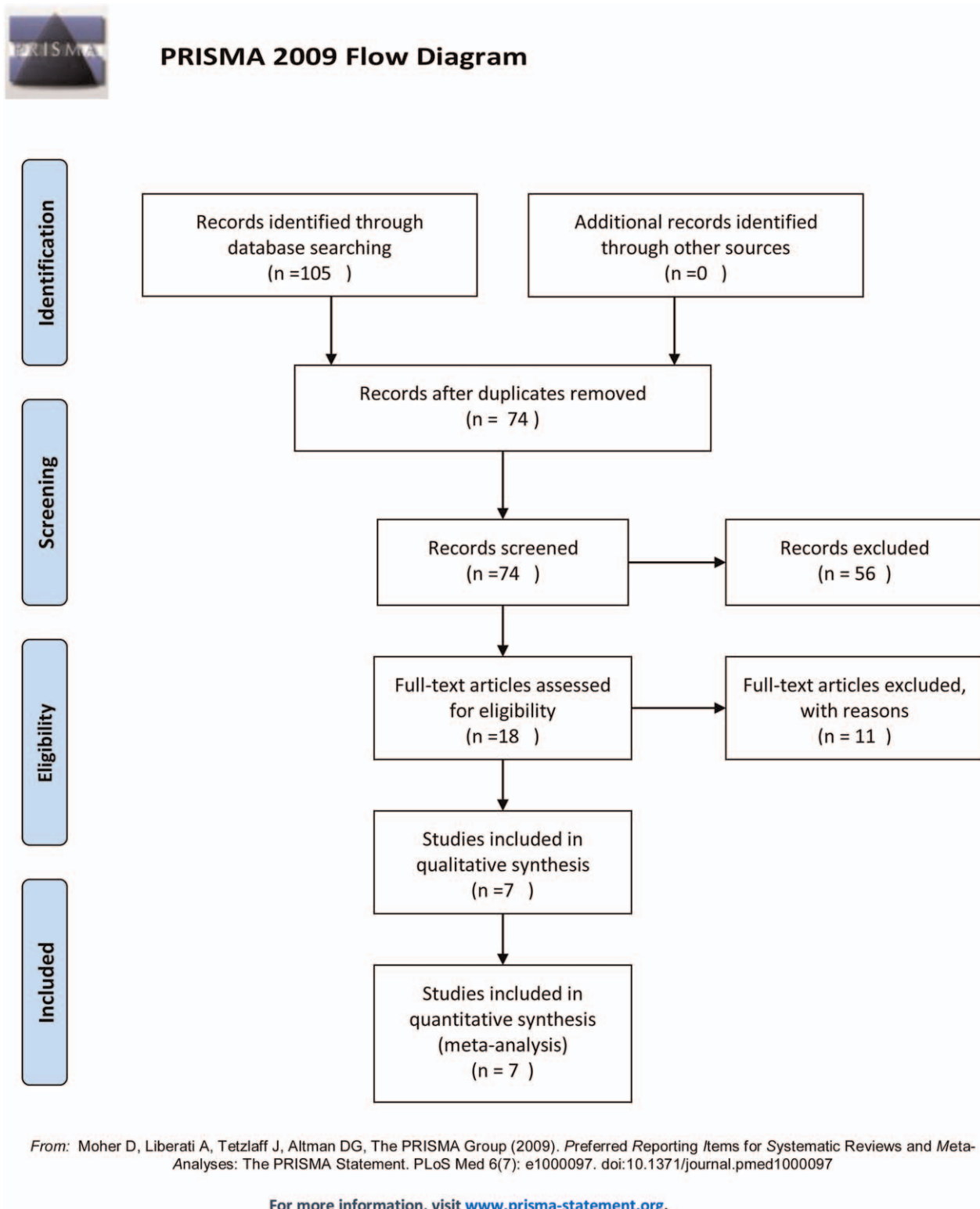For more information, visit www.prisma-statement.org.

Figure 1. Flow chart showing the process for selecting eligible studies in the meta-analysis.

Table 1

Basic characteristics of the included studies.

Studies	Year	Country	Race	Age	NO. of P/C	TP	FP	TN	FN	Criterion	Cutoff
EmelKurtoglu[24]	2014	Turkey	Caucasian	29.2±7.1	130/73	75	55	46	27	ACOG	4.48
Dominique Mannaerts[16]	2017	Belgium	Caucasian	28.91±4.91	59/138	50	9	96	42	ACOG	3.92
Mustafa ylumlu[25]	2014	Turkey	Caucasian	31.6±6.6	54/54	45	9	44	10	ACOG	4.1
Cenk Gezer[26]	2016	Turkey	Caucasian	26.6±6.0	221/209	165	56	147	62	ACOG	3.08
HuseyinAltug Cakmak[27]	2017	Turkey	Caucasian	27±5.0	100/40	93	7	32	8	ACOG	3.5
AySe KirbAS[15]	2015	Turkey	Caucasian	M:29.3±14.3 S: 27.9±4.9	614/320	486	128	124	196	ACOG	4.01
Cao Li[28]	2018	China	Asian	M: 29.2±4. 61 S:29. 5±5. 44	120/60	105	25	35	15	8th edition	3.13

FN = false negative, FP = false positive, M = mild preeclampsia, NO. of P/C = number of patients / control, S = severe preeclampsia, TN = true negative, TP = true positive.
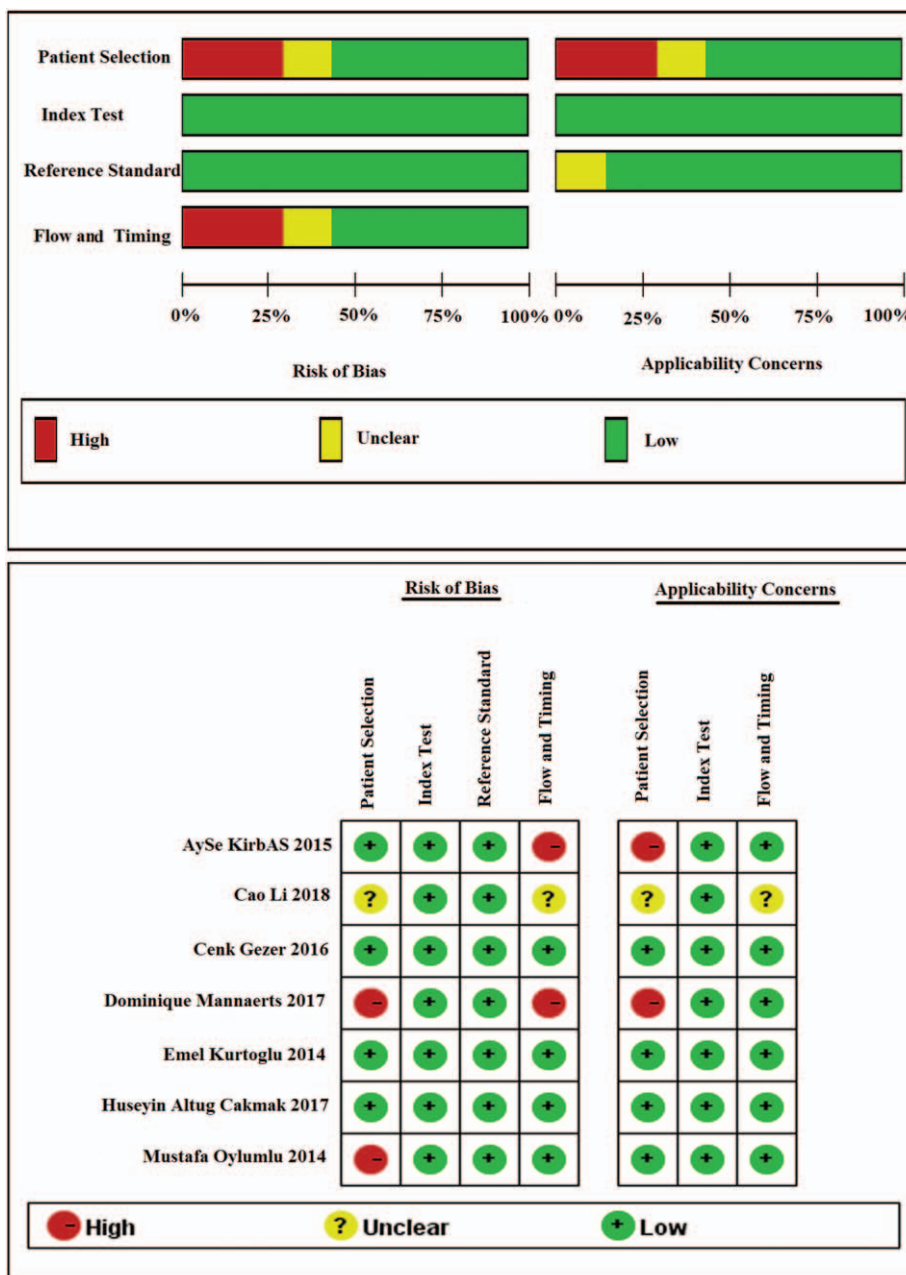

Figure 2. Quality as assessment of the studies selected for the meta-analysis (QUADAS-2).

2. Materials and methods

2.1. Study search

The present study was conducted following the criteria of Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA).[18] We conducted a literature search using PubMed, The Cochrane Library, EMbase, Chinese National Knowledge Infrastructure (CNKI), Wanfang Medical Network, VIP (VIP), and China Biomedical Literature Database (CBM) without language limitation. The search time limitation was from the establishment of the database to May 31, 2018. The index words were as follows: "pre-eclampsia" "neutrophil-to-lymphocyte" "neutrophil-lymphocyte" "NLR" "Neutrophil/lymphocyte ratio". All searches used a combination of subject words and free words. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database.

Ethical approval was not necessary under the ethical committee of The People's Hospital of China Three Gorges University, since this study was a meta-analysis of previous literature works, which informed consents had been obtained by the previous clinical researchers.

2.2. Study selection

The included studies had to fulfill the following selection criteria:

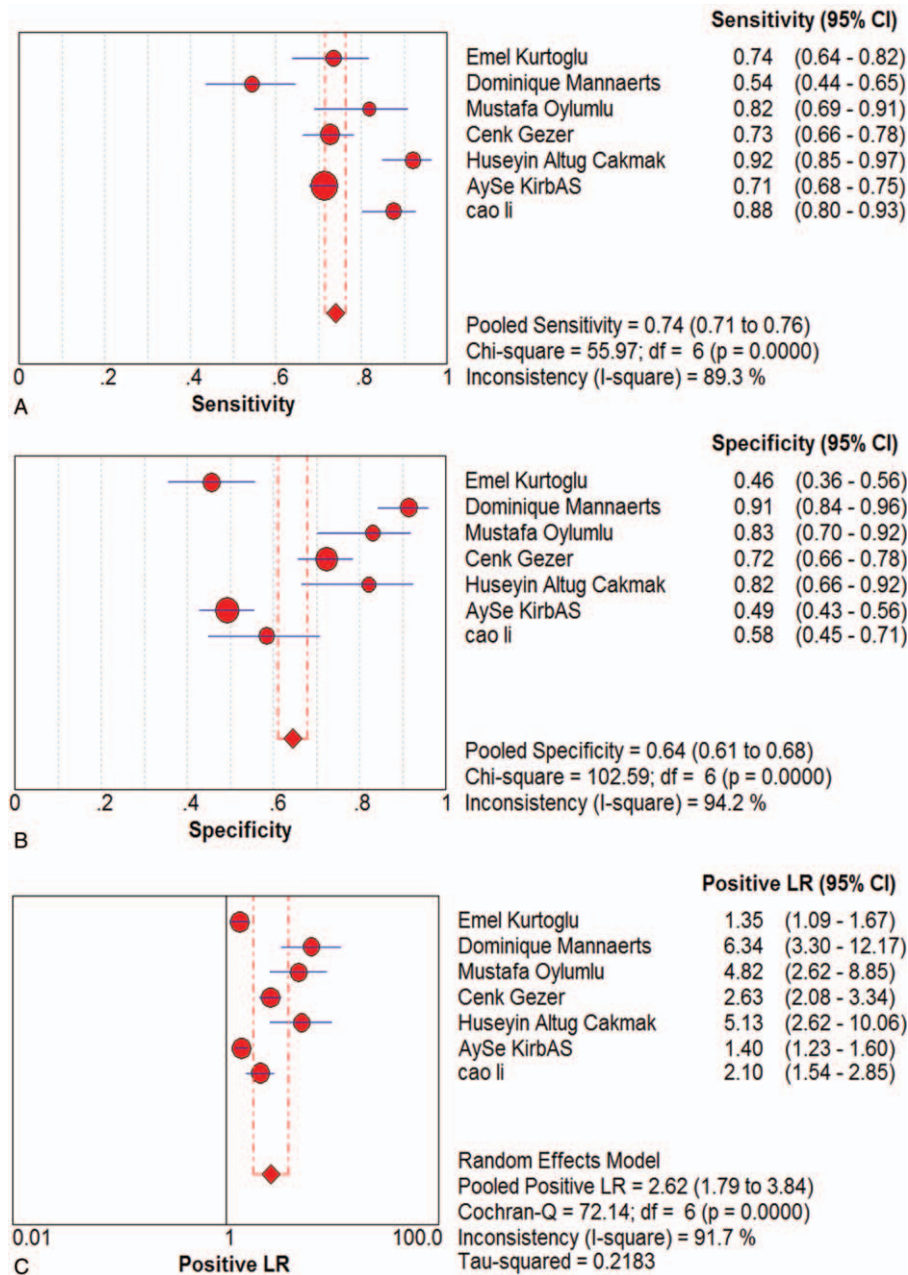(1) evaluated diagnostic accuracy of NLR for PE;

Figure 3. The indicator of effect. Forest plot of estimated sensitivity (A) specificity (B) positive likelihood ratio (C) negative likelihood ratio (D) diagnostic odds ratio (E) for quantitative analysis of Neutrophil-Lymphocyte Ratio in the diagnosis of preeclampsia.
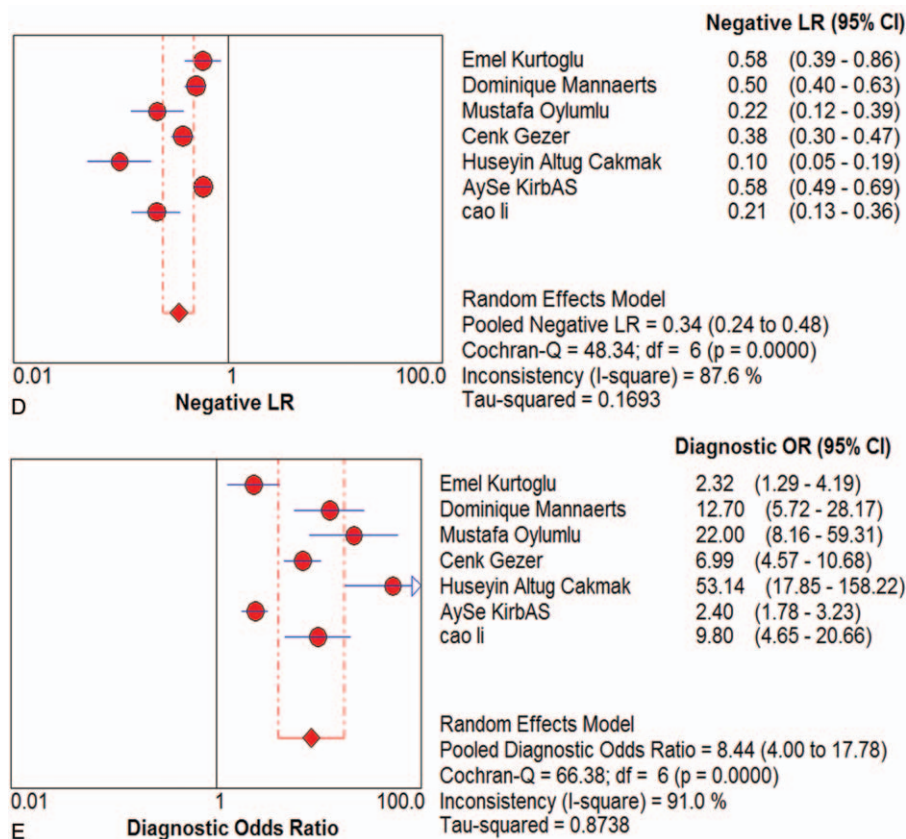
Figure 3. (Continued)

(2) Meet the following diagnostic criteria: the 8th edition of Obstetrics and Gynecology[19] or The American College of Obstetricians and Gynecologists (ACOG).[20] After reading the two diagnostic criterions carefully, we found both were the same standard. Such as: a systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg, measured twice in 4-hour intervals while resting, after the 20th gestational week, as well as 300 mg proteinuria detected in a 24-hour urine sample. Finally, ACOG criteria was chosen as standard for this study.

(3) Clearly reporting sensitivity, specificity with 95% confidence interval or can calculate from 2 × 2 tables.

(4) Duplicate documents of the same author or the same research institution, with closer publication.

(5) the full-text article was available.

Studies with the following characteristics were excluded:

(1) Unsuitable publication types: case reports, meetings, abstracts, reviews.

(2) Animal experiments or non-clinical reports studies.

(3) Incomplete data without original text.

(4) Studies that overlapped the included studies (such as studies from the same study group, institution, and with the same results).

2.3. Quality assessment and data extraction

Two reviewers (Wen-Fei Zheng, Jing-Qiong Zhan) independently screened the literature, extracted the data, including: author, year, country, ethnicity, sample size, diagnostic criteria, outcome indicators (sensitivity, specificity, true positive number (TP), false positive number (FP), false negative number (FN), true negative number (TN)). Missing data were supplemented by contacting authors as much as possible. Quality assessment included in the study was based on the QUADAS-2 scale.[21] Two reviewers independently evaluated the quality of the literature, in case of conflict, a third reviewer was consulted, and disagreement was settled through multilateral discussion.

2.4. Statistical analysis

Meta-disc 1.4 software (Cochrane Colloquium, Barcelona, Spain) and Stata 12.0 (Stata Corporation, College Station, USA) software were used for Statistical analysis. The sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were summarized. The area under the curve (AUC) was used for evaluating the overall accuracy. In addition, the threshold effect was assessed by the Spearman correlation coefficient (between the logic of sensitivity and logic of 1-specificity), a value of P less than .05 indicated significant threshold effect. The heterogeneities between studies were detected by chi-square and I^2 test. $P \leq .05$ or an $I^2 \geq 50\%$ indicated the existence of significant heterogeneity.[22] Meta-regression analyses and subgroup analysis were used to explore the potential sources of heterogeneity. Deeks' funnel plot was performed to explore the possibility of publication bias, $P < .01$ was considered representative of significant statistical

publication bias.[23] All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

3. Results

3.1. Document screening process and results

A total of 130 related articles were obtained in the initial inspection. According to inclusion and exclusion criteria, 31 studies were excluded due to duplication, 56 studies were excluded as irrelevant study. After reading full-text articles, 11 studies were excluded for lacking necessary data. At last, 7 studies were determined to be eligible for meta-analysis (Fig. 1).

3.2. Inclusion of research basic characteristics and methodological quality evaluation

The basic characteristics of the study are shown in Table 1. In these 7 studies,[15,16,24–28] including 1298 cases of pre-eclampsia pregnant women (with or and) 894 cases of normal blood pressure pregnant women. All studies were published between 2014 and 2018. The methodological quality assessment is shown in Figure 2. The included studies basically met the criteria for quality assessment of diagnostic accuracy.

3.3. Diagnostic accuracy

Seven studies were included and the random effects model was used to evaluate the overall effect of NLR in the diagnosis of PE Figure (Fig. 3). The combined sensitivity and specificity were 0.74

(95% CI 0.71–0.76) (Fig. 3A) and 0.64 (95% CI 0.61–0.68) (Fig. 3B). In addition, the PLR was 2.62 (95% CI 1.79–3.84) (Fig. 3C), the negative likelihood ratio was 0.34 (95% CI 0.24–0.48) (Fig. 3D), the DOR was 8.44 (95% CI 4–17.78) (Fig. 3E). The SROC curve for the studies was shown in Figure 4, AUC was 0.82. The above results indicated that NLR had a moderate diagnostic value for the diagnosis of PE. Through the test of post-test probability calculation, it was further shown that NLR could improve the diagnostic value of pre-eclampsia, as shown in Figure 5.

3.4. Subgroup analysis and meta-regression analysis

I^2 test showed obvious heterogeneity among the 7 studies (sensitivity: $I^2 = 89.3\%$, specificity: $I^2 = 94.2\%$, DOR: $I^2 = 91\%$, $P < .01$). The threshold effect was the primary cause of heterogeneity. The spearman correlation coefficient was 0.179 ($P = .702$), indicating that there was no threshold effect and the heterogeneity caused by other reasons. To further explore the source of heterogeneity, subgroup analysis was performed based on ethnicity, sample size (total number of samples >200 and total sample size <200), cutoff values (>4 and <4). In the racial subgroup, there was only 1 study on Asian populations, we found that studies on Asian populations group had a better overall accuracy as compared with that of those on non-Asian populations, with sensitivity of 0.88 vs 0.65, specificity of 0.58 vs 0.57, PLR of 2.1 vs 1.36, NLR of 0.38 vs 0.30, RR of 9.8 vs 1.96, only NLR was poor, 0.21 vs 0.71, respectively. Further-
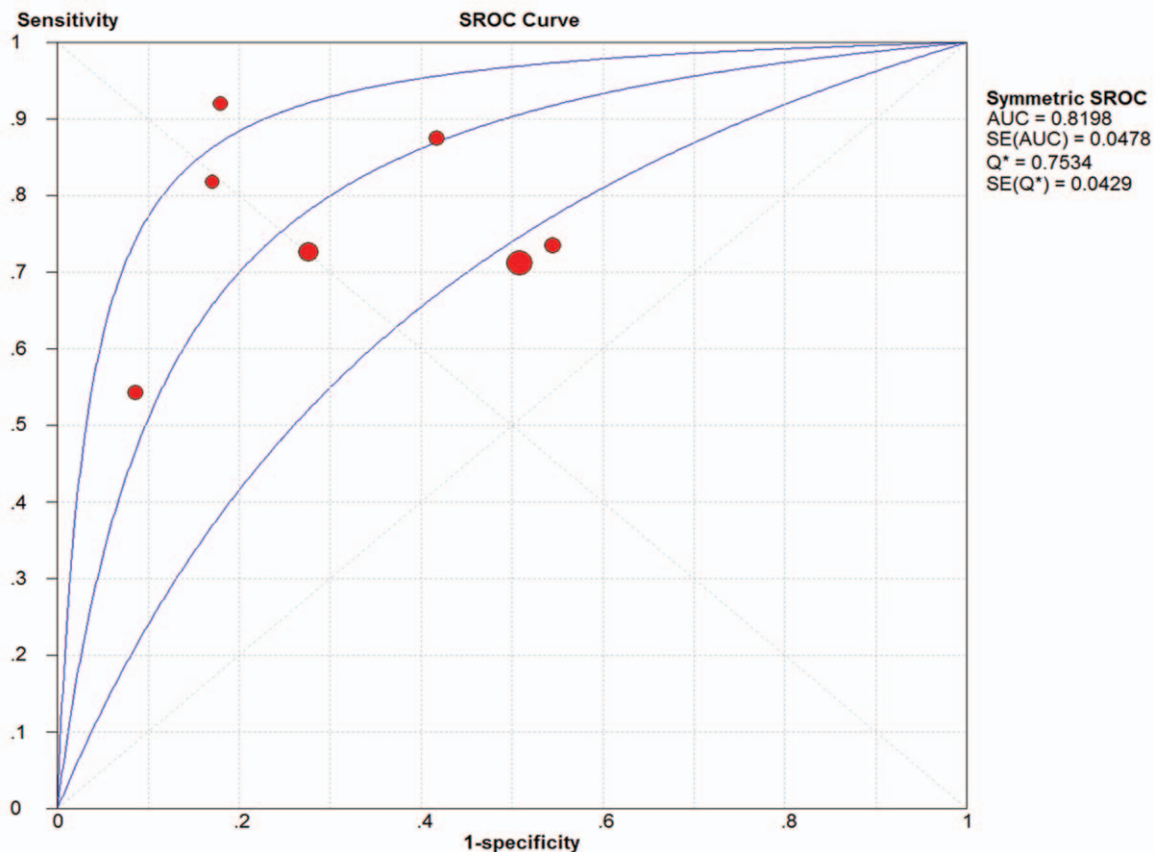

Figure 4. The SROC curve for quantitative analysis of Neutrophil-Lymphocyte Ratio in the diagnosis of preeclampsia.
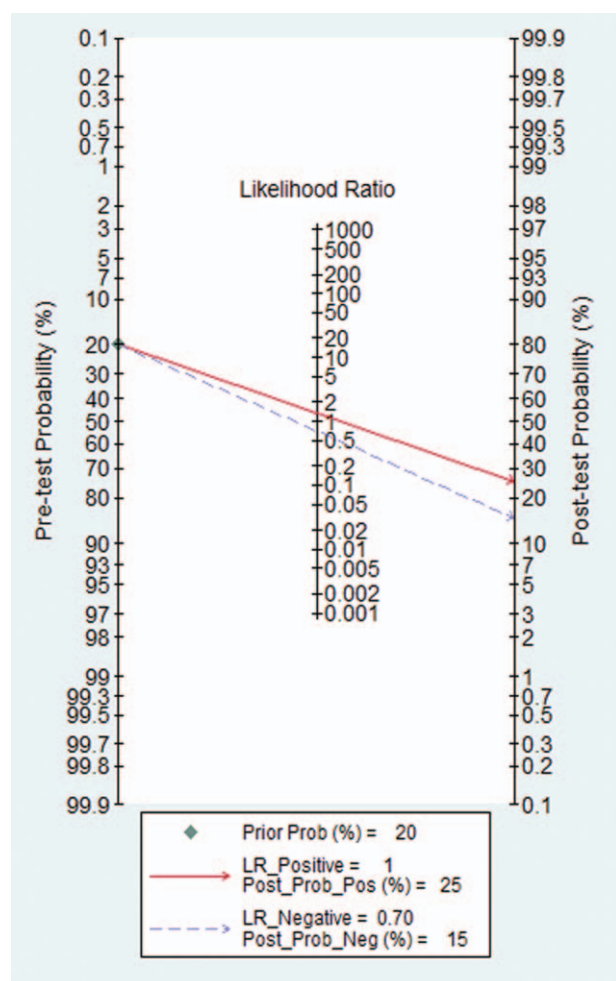
Figure 5. The Fagan for assessment of Neutrophil-Lymphocyte Ratio diagnostic probability.

more, the larger sample size group had a better specificity, PLR, negative likelihood ratio, risk ratio and AUC than smaller. In addition, we also found that the cutoff value of NLR (>4 or <4) cannot indicate the accuracy well, the group of NLR>4 only had a bit better sensitivity, PLR and risk ratio, but a poor of specificity, negative likelihood ratio and AUC.

To explore probable sources of the heterogeneity, we utilized a meta-regression analysis to assess covariates used in the seven studies. We found sample size maybe a source of heterogeneity, race, country and published date of articles did not influence on heterogeneity. The pooled data about Subgroup analysis and meta-regression analysis are shown in Tables 2 and 3, respectively.

3.5. Publishing bias

The publication bias was visually displayed by using Deek's funnel plots. P value was .16, which indicated there was no publication bias (Fig. 6)

4. Discussion

The present systematic review and meta-analysis of 7 studies including 1298 cases of pre-eclampsia pregnant women, and or

with 894 cases of normal blood pressure pregnant women investigated the potential of NLR for identification of PE. In recent years, NLR has attracted more attention as a marker of systemic inflammatory response. A previous study confirmed[29,30] that NLR had a certain value for the prediction and prognosis in some cancers and cardiovascular diseases. There are so many methods to predict the diagnose of PE, including traditional prediction, biophysical prediction and serum marker prediction.[31–34] There are abundant studies about serum markers, such as Liu's study[35] about the relationship between body mass index (BMI), hematocrit (HCT), platelets (PLT), miR-210 and PE in early pregnancy show the AUCs were 0.69, 0.67, 0.73, and 0.75, respectively. The AUC of the above indicators in the second trimester were 0.71, 0.81, 0.65, and 0.81, respectively. Jin et al[36] used a combined detection of homocysteine + triglyceride + lipoprotein B + age + BMI (Hcy + TG + Apo-B + folic acid + age + BMI) to predict the PE, and the AUC was 0.77. Gan et al[34] showed that PE can be predicted by miR-210 and miR-155, AUC was 0.75 and 0.703, respectively. All of these studies have shown that some serologic markers are valuable in predicting PE, but none of them are acknowledged and reliable.

The present study showed that NLR had a good diagnostic value for the diagnosis of PE, the AUC is 0.82. Unfortunately, less research has been done to compare NLR and other conventional markers, so we could not clarify whether the individual or combined NLR can improve the diagnostic accuracy of PE. The pooled sensitivity and specificity of NLR were 0.74 (95% CI 0.71–0.76) and 0.64 (95% CI 0.61–0.68), respectively, revealing the quantitative analysis of NLR has an acceptable sensitive but a poor specificity for diagnosis of PE. The likelihood ratio is an independent indicator to assess the authenticity, which can simultaneously reflect sensitivity and specificity. When the PLR is >10 or the negative likelihood ratio is <0.1, the probability of diagnosing or excluding a certain disease is significantly increased,[37] Likelihood ratio is more clinically significant than SROC curve and DOR value. In our study, the PLR and the negative likelihood ratio were 2.62 (95% CI 1.79–3.84) and 0.34 (95% CI 0.24–0.48), respectively. The results showed that the diagnostic accuracy of NLR in PE patients was nearly 3 times of the healthy patients, but with 34% error rate. These results indicated that the likelihood ratio obtained in Meta-analysis may be poor stability and accuracy. Moreover, when the odds ratio is equal to 1, indicate a test cannot distinguish between patients with a disease or not. The DOR value of our study is 8.44 (95% CI 4–17.78), indicated that NLR had a certain accuracy in the diagnosis of patients with PE. According to Fagan's analysis, we knew that the post-test probability of PLR can be increased by 25% when the pre-test probability was 20%, the negative likelihood ratio was reduced to 15%. The above results showed that there was a good diagnostic value of NLR for PE.

Heterogeneity is an important part of the meta-analysis. The I^2 test in our study showed a high degree of heterogeneity among the seven studies included. The threshold effect is a main source of heterogeneity, the spearman correlation coefficient of this study was 0.179. ($P = .702$), indicating that heterogeneity was caused by not a threshold effect but other reasons. To explore the potential sources of heterogeneity, we conducted a meta-regression of the country, publication time, sample size, and ethnicity. The results showed that sample size was the heterogeneity source of the study, the test of P value was .021. In addition, publication bias is not significant, indicating that our meta-analysis results were reliable.
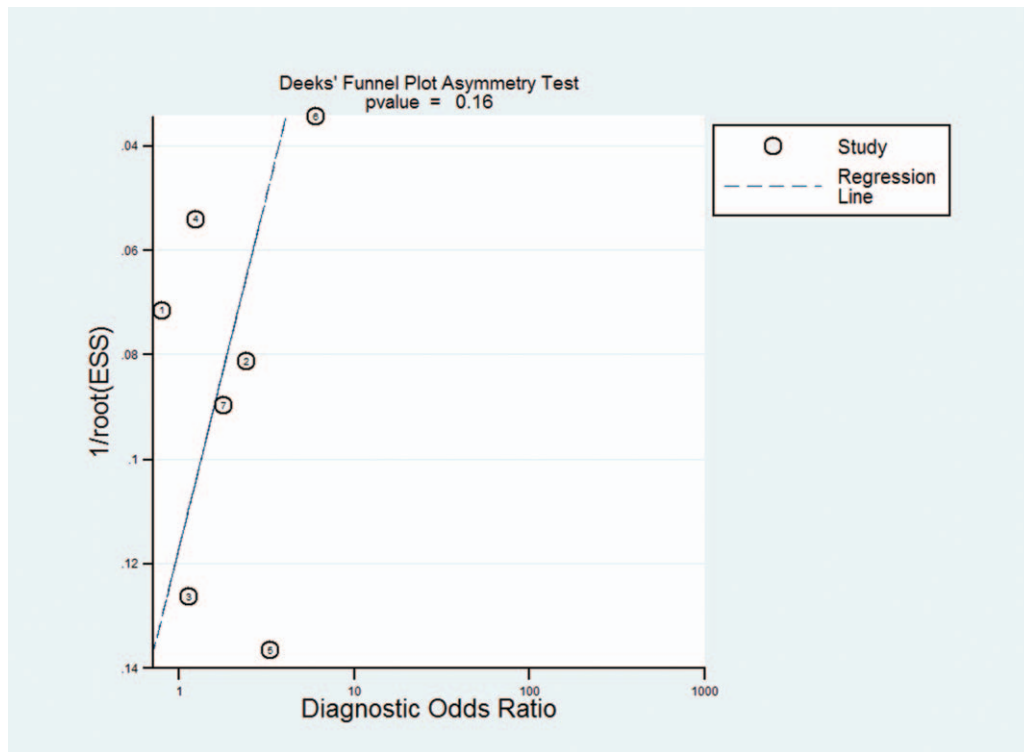
Figure 6. The Deeks' funnel plot for the assessment of potential publication bias of the included studies.

Table 2

Subgroup analysis results.

Variables	NO.	Sen (95% CI)	Spe (95% CI)	PLR (95% CI)	NLR (95% CI)	RR (95% CI)	AUC
Total	7	0.74 (0.71–0.76)	0.64 (0.61–0.68)	2.62 (1.79–3.84)	0.34 (0.24–0.48)	8.44 (4.0–17.78)	0.82
Race							
Asian	1	0.88 (0.80–0.93)	0.58 (0.45–0.71)	2.10 (1.54–2.85)	0.21 (0.13–0.36)	9.8 (4.65–20.66)	–
non-Asian	6	0.65 (0.63–0.68)	0.57 (0.53–0.61)	1.36 (0.95–1.94)	0.71 (0.46–1.09)	1.96 (0.86–4.44)	0.61
Size							
Total <200	4	0.70 (0.67–0.72)	0.54 (0.50–0.59)	1.28 (0.76–2.15)	0.70 (0.32–1.52)	1.84 (0.5–6.75)	0.58
Total >200	3	0.59 (0.54–0–63)	0.60 (0.51–0.69)	1.3 (1.04–1.62)	0.75 (0.61–0.93)	1.99 (1.28–3.08)	0.61
Cutoff							
>4	3	0.74 (0.71–0.77)	0.55 (0.5–0.6)	1.27 (0.69–2.36)	0.7 (0.29–1.72)	1.81 (0.4–8.23)	0.57
<4	4	0.57 (0.53–0.61)	0.57 (0.50–0.63)	1.24 (1.03–1.50)	0.78 (0.65–0.94)	1.75 (1.1602.65)	0.60

NLR = negative likelihood ratio, NO. = number of studies, PLR = positive likelihood ratio, RR = risk ratio, Sen = sensitivity, Spe = specificity.

There are still some limitations in our study:

(1) NLR is a new indicator of systemic inflammation, and the numbers of document included were limited in this meta-analysis. Some defects exist in robustness.
(2) Five of the 7 studies were from Turkey and one from China, involved English and Chinese, so selective bias for specific populations or languages may exist.
(3) Some data (such as TP, FP, TN, FN) were obtained not directly from the original articles but indirectly calculated by AUC, which may affect the accuracy of the diagnosis.
(4) The sample size included affected the results in a way.
(5) The time of test NLR is different, some in first trimester, some are not. Time span is different, it is difficult to do subgroup analysis, which may be a factor of heterogeneity.

Table 3

Meta-regression analysis results.

covariate	Conversion rate	Standard error	95% confidence interval	P value
Race	0.0376371	0.3113968	−0.7628339 0.838108	.909
Published date	0.0121353	0.0746976	−0.1798809 0.2041515	.877
Country	−0.0111107	0.1492318	−0.3947232 0.3725018	.944
Sample size	0.000802	0.000218	0.0001968 0.0014073	.021[*]

[*] P < .05, the difference was statistically significant.

5. Conclusion

In summary, NLR has an acceptable sensitivity as a diagnostic marker for PE, but not better specificity. Prospective studies with larger sample will be needed in the future to verify the potential applicability of NLR alone or combination with other markers for PE.

Author contributions

Conceptualization: Wenfei Zheng
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Formal analysis: Wenfei Zheng, Aihua Chen.
Methodology: Huaijie Yang.
Writing – original draft: Wenfei Zheng.
Writing – review & editing: Rashmisha Maharjan.

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