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A meta-analysis on first-trimester blood count parameters—is the neutrophil-to-lymphocyte ratio a potentially novel method for first-trimester preeclampsia screening?

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Objective: Meta-analysis focusing on the role of first-trimester neutrophil-to-lymphocyte ratio (NLR) in the prediction of preeclampsia.

Data sources: PubMed, Scopus, Web of Science, Cochrane Library, and Embase databases were queried from inception up to December 31, 2022.

Study eligibility criteria: The study included all types of original research that was conducted in humans and values of NLR were measured during the first trimester, among patients who later developed preeclampsia, compared to the values of control groups.

Study appraisal and synthesis methods: Two reviewers independently performed data abstraction and quality appraisal, and disagreements were resolved by consensus and, if necessary, by the opinion of a third reviewer. During the analysis, PRISMA and MOOSE guidelines were followed. All statistical analyses were made with *R*.

Results: For the research on the predictive role of NLR values in the first trimester for preeclampsia, a total of 6 studies were selected for analysis, covering 2,469 patients. The meta-analysis revealed a 95% confidence interval (CI) for the effect size of 0.641 to 1.523, with a prediction interval of 0.027 to 2.137.

Conclusion: Based on the analysis, NLR is a promising biochemical marker for future pieces of research that try to find new screening methods for first-trimester preeclampsia. We encourage other researchers to examine NLR's predictive value combined with other markers in preeclampsia screening, this way being able to find new and affordable protocols for first-trimester preeclampsia screening.

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KEYWORDS

NLR, neutrophil-to-lymphocyte ratio, first trimester, pre-eclampsia, preeclampsia screening

1 Introduction

Preeclampsia is a pregnancy-specific disorder, and it was defined for decades by the new onset of hypertension and proteinuria. According to the latest guidelines such as NICE (National Institute for Health and Care Excellence) and ISSHP (International Society for the Study of Hypertension in Pregnancy) proteinuria is not mandatory for the diagnosis of preeclampsia: according to NICE -preeclampsia is characterized by the onset of new hypertension after 20 weeks of pregnancy, accompanied by one or more newly emerging features: these features may include substantial proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications, or hematological complications (1, 2). By the definition of - ISSHP, which closely resembles NICE's definition—pre-eclampsia is diagnosed when new-onset hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg) occurs after 20 weeks of pregnancy, accompanied by at least one additional symptom or group of symptoms, which may include: proteinuria; dysfunction of other maternal organs (such as liver, kidney, central nervous system); hematological abnormalities; uteroplacental dysfunction (e.g., intrauterine growth restriction—IUGR, and/or abnormal Doppler ultrasound results concerning uteroplacental circulation) (3). Preeclampsia affects 2–8% of pregnant women and is one of the leading causes of maternal and neonatal morbidity and mortality in the world, particularly in low-income countries (4–6). According to WHO, in developing countries, 16% of maternal deaths are attributed to hypertensive disorders, and the reduction of maternal mortality is a global goal (7, 8). Despite its significant impact on obstetrics and healthcare in general, preeclampsia has remained an enigmatic field of medicine. However, recently, new preventive and screening methods have been tested (9).

The early identification of patients at high risk for preeclampsia can be crucial for achieving significantly improved maternal and perinatal outcomes. This involves providing closer surveillance, considering prophylactic use of low-dose aspirin therapy, administering antihypertensive medications, and opting for earlier induced delivery (10, 11).

Since inflammatory reactions are suggested behind the pathomechanism of preeclampsia (12–16) in recent years publications have been evaluating the role of white blood cells both in clinical studies and animal models in the prediction of preeclampsia (17, 18). The distribution of white blood cells can be monitored through the neutrophil-to-lymphocyte ratio (NLR), which has been found to be a useful marker for inflammatory diseases such as systemic lupus erythematosus (SLE), spondyloarthritis, psoriasis, psoriatic arthritis, various types of tumors, and Takayasu arteritis (TA) (19–25). There have also been studies that evaluated the role of NLR in pregnancy-related diseases (26, 27). Moreover, in recent years, several meta-analyses have been published that found elevated NLRs in blood samples from mothers who experienced preeclampsia (28, 29).

The fact that laboratory findings are widely affordable and accessible even in developing countries (30, 31) and neutrophil and lymphocyte counts are usually part of routine laboratory tests (32) are other reasons why NLR would provide beneficial predictive value in preeclampsia.

2 Object

This current meta-analysis aims to evaluate the role that first-trimester NLR values can play in preeclampsia screening.

3 Methods

3.1 Eligibility criteria, information sources, search strategy

The data for the meta-analysis were collected by two independent researchers from PubMed, Scopus, Web of Science, Cochrane Library, and Embase databases. Disagreements were resolved through consensus and, if necessary, by the opinion of a third reviewer. The database searches were conducted until December 31, 2022, without any additional time restrictions. Language restrictions were not applied.

For the preparation and planning of this analysis, a PRISMA checklist and the MOOSE method were utilized (33, 34).

3.2 Study selection

For this research, the keywords "NLR" supplemented with "preeclampsia" were used. Each search was conducted across five online medical databases: PubMed, Cochrane Library, Scopus, Embase, and Web of Science. During the screening process, the research group aimed to select studies that reported NLR values in the first trimester of pregnancy in women who later developed preeclampsia. These values were compared to control groups consisting of women who remained normotensive and free of obstetrical complications during their pregnancies.

3.3 Data extraction

From the studies collected for further review, the following data were extracted: the study objective; the number of mild preeclamptic patients included in the study; the number of severe preeclamptic patients included in the study; the total number of preeclamptic patients included in the study; the number of control (healthy, normotensive) pregnant patients; the time of data collection (trimester, weeks); NLR values of mild preeclamptic patients and their corresponding standard deviations; NLR values of severe preeclamptic patients and their corresponding standard deviations; NLR values of preeclamptic patients and their corresponding standard deviations; NLR values of healthy, normotensive patients (control group) and their corresponding standard deviations; and *p*-values. Additionally, both researchers collected the articles' titles, authors, publication years, publishers, and DOIs.

3.4 Assessment of risk of bias

The Newcastle–Ottawa scale (NOS) (35) was used to assess the quality of the included studies. The quality assessment was conducted independently by two authors, with any disagreements resolved

through consensus or, if necessary, by involving a third author. The NOS evaluates articles based on three main factors: the selection of study groups, the comparability of groups, and the ascertainment of exposure, assigning scores ranging from 0 to 9. A score of 0 represents the worst possible quality, while 9 indicates the best possible quality. Studies scoring 0–4 stars are considered low quality, while those receiving 5 or more stars are deemed moderate to high quality. According to the authors, all the included articles received 6 or more stars on the NOS.

3.5 Data synthesis

Mean difference (MD) with a 95% confidence interval (CI) was used to express the effect size. To calculate the mean difference the number of patients, the mean, and standard deviation (SD) of the variable of interest for the "preeclampsia" and "without preeclampsia" (i.e., control) groups were extracted from the studies. The mean difference is calculated as the mean of the "preeclampsia" group minus the mean of the "without preeclampsia" group. In some cases (highlighted with * in the forest plots) means and SDs were given for moderate and severe preeclampsia subgroups separately and we combined them using established formulae https://training.cochrane.org/handbook/archive/v6.1/chapter-06#section-6-5-2-1 (36).

As we anticipated considerable between-study heterogeneity, a random-effects model was used to pool effect sizes. The inverse variance weighting method was used to calculate the pooled mean difference. Hartung-Knapp adjustment (37, 38) was applied as the study number and sample sizes were relatively small. To estimate the heterogeneity variance measure (tau squared), a restricted maximum-likelihood estimator was applied with the Q profile method (39). Additionally, between-study heterogeneity was described by Higgins and Thompson's (I squared) statistics (40). Forest plots were used to graphically summarize the results. The confidence interval of each individual study was calculated based on the t-distribution. Additionally, where applicable, we reported prediction intervals (i.e., the expected range of effects of future studies) of results following the recommendations of IntHout et al. (41).

Outlier and influence analyses were carried out following the recommendations of Harrer et al. (42) and Viechtbauer and Cheung (43). Publication bias was assessed with Egger's test (at a significance level of 10%) (44)—however, results should handled critically due to the small number of studies.

All statistical analyses were made with *R* software (45) using the meta package (46) for main calculations, and the dmetar package (47) for influential analysis.

4 Results

4.1 Study selection

4.1.1 Study selection for evaluating NLR's predictive role in preeclampsia

For the research, the keywords "NLR" and "preeclampsia" were combined, and searches were conducted in 5 online medical databases (PubMed, Cochrane Library, Scopus, Embase, Web of Science). In total, 324 articles were found, and 134 remained after removing duplicates. An additional 103 articles were excluded because they were irrelevant to the conducted research. In our meta-analysis, we aimed to find clinical studies that utilized first-trimester NLR values as predictive markers of preeclampsia. We excluded studies that were not clinical (e.g., systematic reviews, meta-analyses), letters to other publications, and clinical studies that focused on NLRP3 (NOD-, LRR-, and pyrin domain-containing protein) 3 values in pre-eclamptic women, studies which were results for our searches because they used negative likelihood ratio which's short form is also NLR and the studies which were clinical but did not use first trimester NLR findings. The remaining 31 pieces of research were selected for detailed screening and out of these 25 got excluded because the samples were not collected during the first trimester (23 studies), only a part of the patients' samples were collected during the first trimester and the researchers did not publish the data separately (1 study) or first trimester NLR values were presented but the research's focus was not on preeclampsia prediction (1). The PRISMA flow diagram was conducted regarding strictly The PRISMA 2020 statement: an updated guideline for reporting systematic reviews (34) (Figure 1). Of the remaining 6 (48–53) pieces of research the data (the NLR values in the control and preeclampsia groups and their standard deviations) got extracted for the meta-analysis.

4.2 Study characteristics

In our study, we included overall 6 studies, the number of preeclampsia patients, the number of the control groups, the ages of the patients (both mean and standard deviation) and the BMIs of the patients (both mean and standard deviation), gestational age at delivery (both mean and standard deviation), are presented on Table 1.

4.3 Risk of bias

As mentioned above, publication bias was assessed with Egger's test (at a significance level of 10% due to the small study number).

4.3.1 Bias in NLR research

Although Egger's test p-value is 0.2132, the meta-analysis contains few studies therefore Egger's test may lack the statistical power to detect bias or it could give a false "positive" result.

4.4 Synthesis of results

4.4.1 NLR results

A total of 6 studies were selected for analyses covering a total of 2,469 patients.

On average, the effect size is 1.082. The 95% confidence interval of the effect size is 0.641 to 1.523, which tells us that the mean effect size in the universe of comparable studies could fall in this range.

The between-study heterogeneity expressed as I^2 value is 0.765 (95% CI, 0.473–0.895), which tells us that 76.5% of the variance in observed effects reflects variance in true effects rather than sampling error. The variance of true effects T^2 is 0.12 and the standard deviation of true effects T is 0.34.

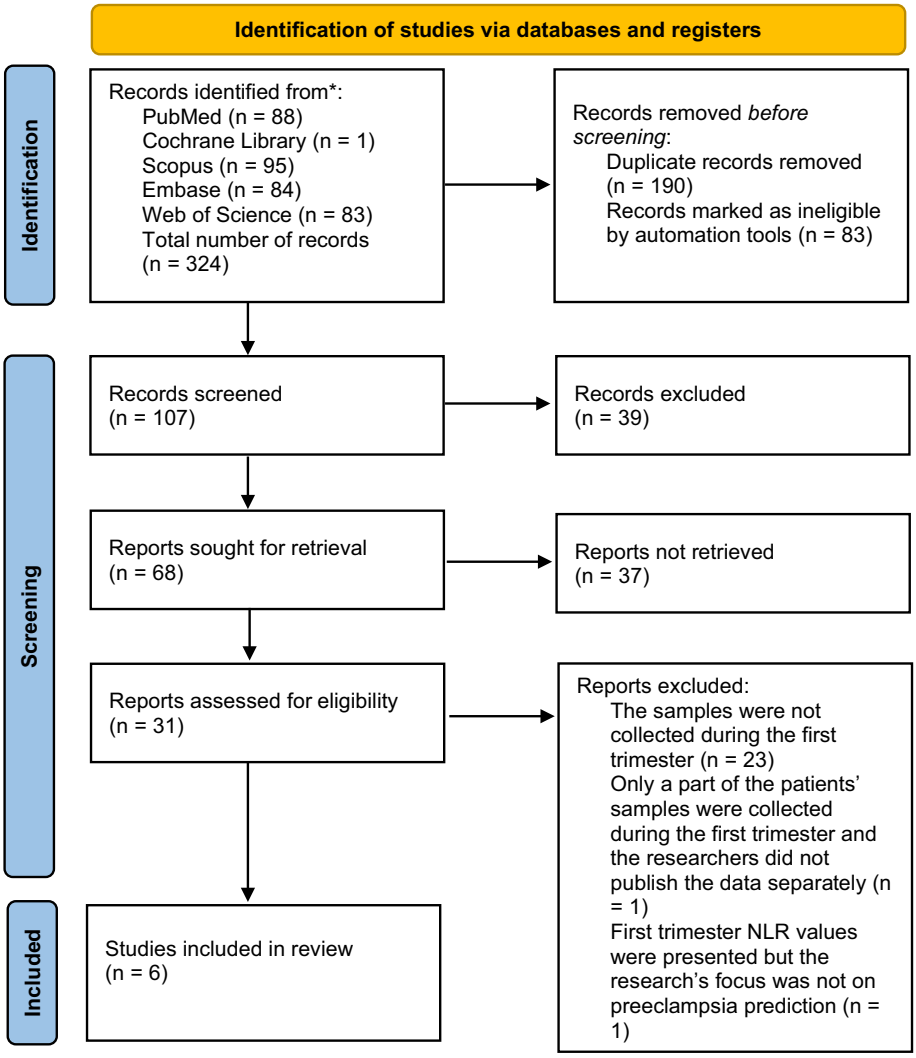

FIGURE 1
Selection of the studies for the analysis of NLR values' predictive role in first-trimester preeclampsia.

The prediction interval is 0.027 to 2.137. Based on that we would expect in some 95% of all populations comparable to those in the analysis, the true effect size will fall in this range (Figure 2).

5 Comment

5.1 Principal findings

NLR's prediction interval fell in the range of 0.027 to 2.137, and the 95% confidence interval of the effect size is 0.641 to 1.523, all the evaluated studies found elevated levels of NLR in mothers who later during their pregnancies developed preeclampsia.

5.2 Comparison with existing literature

5.2.1 The possible explanation behind the elevation of NLR in preeclampsia

Recent studies show that IL-6, IL-8, and IL-17 play an important role in preeclampsia and the production of neutrophil (55–58). One of IL-8's most important roles is the attraction of neutrophils to the inflamed areas, they play a role in neutrophil recruitment to the endometrium (this way contributing to preeclampsia development), and IL-8 also stimulates neutrophil degranulation (59–62). While IL-6 is linked to genes that stimulate the proliferation, maturation, and activation of neutrophils (63–67). Levels of IL-17A are elevated in preeclampsia and it stimulates the expression of neutrophil chemokines in vascular smooth muscle, IL-17A also increases the levels of G-CSF and GM-CSF which both increase the production of neutrophils (57, 68, 69).

5.2.2 The neutrophil-to-lymphocyte ratio in clinical research

NLR is more and more getting at the center of new studies: while in the PubMed database for the search "neutrophil-to-lymphocyte ratio" there are 65 results from 2012, this number was 1,669 in 2022.

NLR is also studied as a predictive biomarker in COVID-19 (70–72): Fernandes et al. (73) found that NLR levels are higher in COVID-19 patients who needed invasive mechanical ventilation than the control group of COVID-19 patients who did not require invasive mechanical ventilation.

TABLE 1 Studies included in the meta-analysis.

	Study ID	Sample size		Age		BMI		Gestational age at delivery	
		Preeclampsia	Control	Preeclampsia	Control	Preeclampsia	Control	Preeclampsia	Control
1	Gezer et al. (51)	209	221	26.6 ± 6	25.8 ± 4.9	25.7 ± 3.7	25.2 ± 4.1	35.8 ± 3.02	39.37 ± 1.16
2	Hale et al. (53)	214	240	28.7 ± 3.4	27.5 ± 3.5	22.9 ± 3.2	22.7 ± 3.5	37.6 ± 1.1	40.5 ± 1.5
3	Kirbas et al. (50)	614	320	Severe PE: 29.3 ± 14.3, mild PE: 27.9 ± 4.9	27.0 ± 5.0	Severe PE: 23.7 ± 3.6, mild PE: 22.9 ± 3.1	22.7 ± 3.6	Severe PE: 33.0 ± 3.5, mild PE: 37.5 ± 2.1	40.6 ± 1.6
4	Oğlak et al. (49)	201	100	Severe PE: 28.7 ± 6.8, mild PE: 28.3 ± 7.4	27.4 ± 6.1	NR	NR	NR	NR
5	Bulbul et al. (48)	161	161	30.91 ± 6.47	30.08 ± 6.04	28.00 ± 2.62	26.73 ± 2.97	36.4 ± 2.9	38.2 ± 1.9
6	Mannaerts et al. (54)	14	14	29 (no SD presented)	31 (no SD presented)	26.7 ± 3.4	28.0 ± 3.6	NR	NR

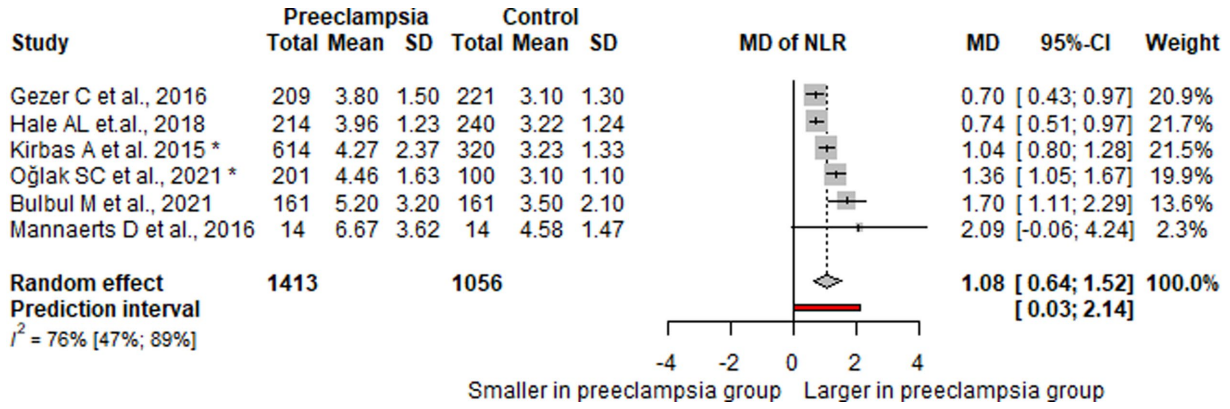

FIGURE 2
Forest plot of NLR values.

NLR was studied in pregnant COVID-19 patients as well (74, 75): Aydin Güzey et al. (76) evaluated 254 cesarean sections with COVID-19 and found elevated levels of NLR among the symptomatic patients. Our research group also presented a case report where we found elevated NLR in a preeclamptic COVID-19 patient (77). Our research group additionally conducted a case–control study, which included 45 pregnant patients with COVID-19. Statistical analyses revealed that NLR values were notably elevated in patients who succumbed to fatal COVID-19 compared to those who survived the disease (78).

Even though Lurie et al. (79) published their results as early as 1998 of growing neutrophil counts and declining lymphocyte counts in preeclamptic patients, they did not try to evaluate the quotient of these data in PE screening. The first study on NLR's predictive role in preeclampsia was published in 2015 by Kurtoglu et al. (80) and since then a handful of other studies were published evaluating NLR's role in all the 3 trimesters (54, 81, 82).

It is important to mention Kang's et al. (29) meta-analysis from 2019, which found that NLR levels are higher in symptomatic preeclamptic patients compared to control groups. Their meta-analysis also suggests that NLR values can be used to evaluate disease severity. Despite the existence of this prior meta-analysis, our work provides valuable insights as we aimed to evaluate NLR values in the first trimester, before the onset of preeclampsia. Therefore, our study assesses the potential role of NLR values in the screening of preeclampsia. Furthermore, our meta-analysis was justified because, nearly 4 years after their study, numerous new clinical studies have emerged investigating NLR in relation to preeclampsia. However, to the best of our knowledge, there is still no meta-analysis that specifically evaluates the role of this laboratory marker purely in preeclampsia prediction.

5.2.3 Preeclampsia's first-trimester detection, its importance

As preeclampsia is a relatively common clinical syndrome of the human pregnancy, with a prevalence of 2–8% (5), its only definitive treatment currently the termination of the pregnancy: the delivery of the placenta and the neonate (83) and remains one of the leading

causes of maternal- and neonatal morbidity (84) it is eager to find more and more accurate screening methods and therapies.

Large cohort studies and meta-analyses indicate that the main risk factors for preeclampsia development are obesity, antiphospholipid antibody syndrome, chronic hypertension, pregestational diabetes, the use of assisted reproductive technology, nulliparity, and irregular antenatal visits (85–87).

In the screening of preeclampsia, the evaluation of maternal characteristics (maternal age, weight, height, ethnicity, and smoking), medical (chronic hypertension, diabetes, family history of preeclampsia), and obstetrical history (prior pregnancies affected by preeclampsia) is key in the risk calculation of preeclampsia (88, 89). The two most frequently used guidelines that aim to stratify risk using maternal risk factors and characteristics are the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) (1, 90). However, the use of risk factors for first-trimester preeclampsia screening performs with poor sensitivity (91).

Another important basis of preeclampsia screening is the usage of Doppler ultrasound, in which case MAP (mean arterial pressure) and uterine artery pulsatility index (UtA-PI) are measured (88, 92).

Biochemical markers are also widely used in preeclampsia's first-trimester screening: abnormal serum levels of placental growth factor (PlGF), pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), Inhibin A, soluble-endoglin (sEng), and soluble Flt-1 (sFlt-1) are all associated with higher risks of preeclampsia (93–96).

While these methods and the combination of them keep improving it is still urgent to find new markers (possibly ones that can be applied in developing countries as well) to supplement and to make better the currently existing protocols which are key to the reduction of maternal mortality (7, 97).

As a result of our meta-analysis, we found, that to the list of useful biochemical markers, higher levels of NLR can be added: according to the studies used in our analysis, this marker is elevated in first-trimester preeclampsia, moreover, NLR is also easily and widely accessible. However, we maintain that further research should evaluate the usage of the above-mentioned biochemical and biophysical markers combined with NLR, to find more and more beneficial and affordable screening methods.

5.2.4 Preventive medication for preeclampsia

We evaluated NLR's first-trimester predictive role because we maintain that novel and more accurate screening methods could help obstetricians to detect preeclampsia earlier and consequently, start the treatment or the preventive treatment earlier.

In preeclampsia prevention, the most widely used medication is low-dose aspirin therapy (98, 99). However, there is a growing skepticism against aspirin use in preeclampsia prevention: Lin et al. found that 100 mg of aspirin per day, initiated from 12 to 20 gestational weeks until 34 weeks of gestation, did not reduce the incidence of preeclampsia in pregnant women with high-risk factors (100).

Consequently, new studies are experimenting with other treatments in preeclampsia prevention: Cruz-Lemini et al. (101) published a meta-analysis on low-molecular-weight heparin therapy in women at high risk of preeclampsia. They found that LMWH therapy significantly reduces the risk of preeclampsia and other placenta-mediated complications if the treatment is started before the 16th gestational week.

Our research group's earlier meta-analysis highlighted that pravastatin therapy started before the 20th gestational week reduces preeclampsia development. The therapy is also beneficial for neonates, as it reduces the number of neonates born with IUGR, neonatal admissions to intensive care units, and the occurrence of preterm deliveries (102).

Calcium, magnesium, and vitamin D supplementation may also be useful in preeclampsia prevention (103–107).

As there are more and more medications that are proven to be effective in preeclampsia prevention it would be key to find more screening methods that would help doctors to detect the risk of preeclampsia earlier and define which patients would need to take preventive medications: this is another reason why we think that first-trimester NLR values in preeclampsia screening should be furtherly evaluated.

5.2.5 The importance of finding cost-effective screening methods

Preeclampsia, even in the 21st century in developed countries remains one of the leading causes of maternal mortality (108–111) and it also puts a large financial burden on health care systems: in 2012, the cost of preeclampsia within the first 12 months of delivery was $2.18 billion in the United States ($1.15 billion for infants and $1.03 billion for mothers) (112). While preeclampsia is a huge and unsolved problem even in developed countries, developing countries are affected more severely (7, 113–117).

In developing countries, it is key to find cost-effective ways the screening and treatment of diseases, but the price is an important aspect in developed countries also.

As NLR is proven to be a cost-effective, relatively accessible biomarker of several diseases (118–121), and the results of our analysis also highlight it as a promising addition to first-trimester preeclampsia screening methods, we maintain that elevated levels of NLR in preeclampsia screening should be evaluated in further clinical studies.

5.3 Strengths and limitations

We are pleased to present our work as the first meta-analysis or systematic review examining the role of NLR in predicting preeclampsia during the first trimester of pregnancy. While previous meta-analyses (28, 29) have explored NLR in preeclampsia prediction, our study uniquely focuses on evaluating first-trimester laboratory findings. We believe that our analysis offers valuable insights into the potential utility of these values for screening preeclampsia during the first trimester. Consequently, our study contributes to a more structured understanding of this area and may serve as a foundation for future clinical investigations, both prospective and retrospective, into the use of NLR in first-trimester preeclampsia screenings.

However, we acknowledge that despite our study's significant contribution to the field, its primary limitation lies in the small number of eligible studies and patients included. Owing to this limited pool, we faced challenges in estimating the prediction interval of true study effect sizes with a high degree of certainty.

Additionally, the limited number of studies prevented us from thoroughly evaluating publication bias or conducting outlier and influential analyses.

6 Conclusions and implications

As the presented statistics show the effect size (1.082), the 95% confidence interval of the effect size (0.641 to 1.523), the standard deviation of true effects (0.34), and the prediction interval (0.027 to 2.137) all fall in a range that lets us conclude that NLR can have a role in first-trimester preeclampsia screening.

We encourage other researchers to examine NLR in cohort studies and randomized clinical studies, alone and combined with other screening methods to find new screening protocols for preeclampsia early on, in the first trimester during pregnancy, this way allowing prophylactic preeclampsia treatment to start earlier.

We maintain that because of the circumstances mentioned in the part "Discussions" it is desired to experiment with screening methods that are: (a) can help to detect preeclampsia early during pregnancy (b) are applicable in low-resource settings-based on our analysis NLR fulfills both criteria.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

BM: Conceptualization, Investigation, Writing – original draft. DV: Formal analysis, Investigation, Software, Validation, Visualization, Writing – original draft. LN: Formal analysis, Investigation, Writing – original draft. BK: Supervision, Writing – review & editing. ZK: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. SV: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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.

Publisher's note

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Glossary

NLR	Neutrophil-to-lymphocyte ratio
ACOG	American College of Obstetricians and Gynecologists
NICE	National Institute for Health and Care Excellence
SLE	Systemic lupus erythematosus
TA	Takayasu arteritis
DOI	Digital object identifier
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
MAP	Mean arterial pressure
UtA-PI	Uterine artery pulsatility index
PAPP-A	Pregnancy-associated plasma protein A
PlGF	Placental growth factor
AFP	Alpha-fetoprotein
hCG	Human chorionic gonadotropin
uE3	Unconjugated estriol
sEng	Soluble-endoglin
sFlt-1	Soluble Flt-1
LMWH	Low-molecular-weight heparin
IL	Interleukin
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor