


SYSTEMATIC REVIEW

The combination of NLR and MEOWS as a potential modality for detecting the severity of preeclampsia: A systematic review

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Article Info	ABSTRACT
<p>Received Apr 20, 2023 Revised Jul 5, 2023 Accepted Jul 14, 2023 Published Dec 1, 2023</p> <p>*Corresponding author: Rendy Singgih rendyssinggih@gmail.com</p> <p>Keywords: Preeclampsia Neutrophil-to-lymphocyte ratio (NLR) Modified Obstetric Early Warning Systems (MEOWS) Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (https://creativecommons.org/licenses/by-nc-sa/4.0/)</p> 	<p>Objective: To describe modalities of detecting the severity of preeclampsia (PE) between neutrophil-to-lymphocyte ratio (NLR) levels and Modified Obstetric Early Warning Systems (MEOWS).</p> <p>Materials and Methods: We used a systematic search in PubMed, ScienceDirect, and Google Scholar for fully-accessed English articles, published between 2015 – 2023 that evaluated modalities between NLR levels and MEOWS for detecting the severity of preeclampsia, which resulted in 208 works of literature. Among the studies, we found 14 literature that met the PICO inclusion criteria and included in this study.</p> <p>Results: PE is still one of the high causes of morbidities and mortality in maternal patients. It is important to predict the possible risk of PE events. NLR is one of the markers that become a prognostic modality to determine the severity of PE. MEOWS is one of the tools to assess the level of care of patients who carry out the treatment. NLR and MEOWS can be modalities for predicting PE severity.</p> <p>Conclusion: NLR and MEOWS can be used even with limited resources. The combined use of NLR and MEOWS can be an alternative and potential modality in detecting PE severity.</p>

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Highlights:

1. Preeclampsia is still one of the contributors to morbidity and mortality which is quite high for pregnant women in Indonesia.
2. The use of NLR and MEOWS modalities as predictors of preeclampsia incidence shows significant potential and can be applied especially in facilities with limited resources.

INTRODUCTION

Maternal mortality rate (MMR) indicates a country's public health degree. Information regarding the level of MMR helps develop sustainable health improvement programs. Data from the World Health Organization states that every day in 2017, an estimated 810 women died due to the conditions of their pregnancy and childbirth. The most significant contributor to all maternal deaths of 94% occurs in developing countries, especially countries with low and middle incomes.¹ Based on 2017 World Bank data, the MMR in the world was 222.² In Indonesia, MMR ranges from 305 per 100,000 according to the 2015 *Survei Penduduk Antar Sensus* (Supas).³ The report describes that most maternal deaths occur mainly in hospitals.⁴ Several factors lead to poor pregnancy outcomes, such as socio-economic conditions and health conditions like antepartum and intrapartum events during pregnancy.⁵ The government is trying to reduce the still high MMR by targeting the number of MMR in 2024 to be 232 and targeting the Sustainable Development Goals (SDGs) in 2030 for MMR to be less than 70 per 100,000 live births.^{4,6}

The most considerable maternal morbidity and mortality to date include thrombosis, bleeding, sepsis, and hypertension.⁷ Hypertension in pregnancy affects 10% of all pregnancies and is currently defined as a new onset of hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) after 20 weeks gestation. This term includes chronic hypertension, gestational hypertension, and preeclampsia (de novo or superimposed).⁸ Preeclampsia (PE) is hypertension in pregnancy that often occurs for more than 20 weeks of gestation or close to the age of term.⁹ PE is a multisystem idiopathic disorder with no known exact cause and regarding 2-8% of all pregnancies.¹⁰ PE in pregnancy is divided into two categories, mild PE and severe PE, characterized by proteinuria and new onset of thrombocytopenia, renal insufficiency, renal function disorders, visual, brain, and pulmonary edema.¹¹ PE is the leading cause of fetomaternal morbidity and mortality.¹² Neonatal risks include intra-uterine growth restriction and low birth weight, perinatal death, and premature iatrogenic due to placental dysfunction and hypoxia.¹³ Normal pregnancy occurs because there is a semi-allograph reaction. Conditions of the balance of inflammatory response and systemic immune system are needed such as blastocyst implantation, trophoblast cell proliferation, differentiation, inflation, and placental growth and development so that pregnancy goes well.¹⁰

In PE, the excess inflammatory response is activated due to abnormal maternal immune tolerance. Changes occur in inflammatory cells in the blood, subsets of T

lymphocytes, acute protein reactive, plasma inflammatory cytokine factors, complement activity, and coagulation systems that can later cause PE.^{10,12} Neutrophil/Lymphocyte ratio (NLR) is one of the inflammatory markers and is being widely studied today. The combination of two essential mechanisms in PE pathogenesis, the abnormal immune and inflammatory responses is the basis for evaluating the value of NLR as a prognostic modality to determine the severity of PE.¹⁴ Good confectionery management including the duration of identification time can prevent the severity of obstetric complications so that the burden of maternal death and long-term complications can be prevented.

Early warning systems (EWS) is one assessment for detecting high-risk conditions. EWS consists of a combination of clinical observations such as vital signs, physical examinations, and laboratory tests and has been used since 1997.¹⁵ At that time, EWS was designed for general population and was challenging to apply to obstetric patients, due to the physiological changes that occur during the gestation and puerperal phases.¹⁶ Based on the same principle as EWS, a modified prognostic modality has been developed to be applied to obstetric patients, i.e. modified obstetric early warning systems (MEOWS). Adaptation of MEOWS was recommended in 2007 from Confidential Enquiries into Maternal and Child Health (CEMACH) in the UK.¹⁷ MEOWS itself has been widely used in the UK and evaluated its use in the United States because it shows a reduction in maternal morbidity rates. However, this modality has not been widely used primarily in areas with less resources.¹⁸ Assessment and early detection is required for PE management. One of the predictors of PE is the value of NLR and the assessment of the level of care of PE patients with the modality of MEOWS although the research on these modalities is still limited. Therefore, in this systematic review, the authors described the combination of NLR values with MEOWS values as a predictor for detecting PE severity.

MATERIALS AND METHODS

Search strategy

We conducted a systematic literature review search on several databases such as ScienceDirect, PubMed, and Google Scholar for articles published from 2015 to June 2023 to evaluate the combination of the use of NLR and MEOWS modalities as predictors of preeclampsia severity. We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist rules and flow diagrams for searching, and selecting literature found to be in accordance with

PICO, inclusion, and exclusion criteria. Search terms were created using the term Medical Subject Headings (Mesh) with searches using the Boolean operator method: ("maternal early obstetric warning system" OR "modified early obstetric warning system") OR "neutrophil-to-lymphocyte ratio") AND preeclampsia. The article selection process was carried out by two reviewers (RS and MM). Details of literature search, screening, and selection can be found in Figure 1.

Eligibility criteria and quality assessment

Eligibility criteria were formulated using the Population, Intervention, Comparison, and Outcomes (PICO) framework as shown in Table 1. We included studies: (1) Investigation of the relationship between MEOVS scores and NLR scores as predictors of the incidence or severity of preeclampsia; (2) The subject of pregnant women undergoing treatment; and (3) The language used is English. The exclusion criteria included: (1) Articles in the form of abstracts, reviews, case reports, and case series; (2) Inaccessible articles; and (3) Articles not in accordance with the research topic. Then, we assessed the quality of the methodology using the Joanna Briggs Institute (JBI) critical appraisal checklist. Critical appraisal was performed by two reviewers (RS and MM), and only studies with a score of $\geq 50\%$ were included further. If there was a disagreement on the points in the critical appraisal, it was resolved through discussion by inviting a third reviewer (YT) to determine a solution.

Data extraction

Data extraction was carried out by two reviewers (RS and MM) with components including: (1) year of publication; (2) study design; (3) sample size; (4) NLR rate; (5) MEOVS score; and (6) study outcomes and results.

RESULT AND DISCUSSION

From literature searching, we obtained as many as 208 studies. Then, after passing through several selection processes, 14 studies were obtained that were in accordance with PICO and inclusion criteria. Of the fourteen studies, two were cross-sectional studies, five were cohort studies, and seven were case-control

studies.^{13,14,19-30} The studies included samples of women with median age of 17.4 to 35.5 years and a range of 101 to 1481. This systematic review revealed that NLR and MEOVS had the ability to detect the incidence and severity of preeclampsia. Some studies were described in the form of tables related to the level of meaning and its ability to detect preeclampsia. We present the data extraction and methodological assessment scores in Table 2.

The study of Sitotaw et al. (2018) showed that NLR values significantly increased in women with PE compared to healthy women. NLR is shown to increase significantly along with the severity of PE with $p < 0.05$.¹⁹ Gogoi et al. (2018) in their study found similar results that the average NLR value was higher in women with PE (6.8 ± 7.6) compared to the control group (3.0 ± 0.98) with a value ($p=0.001$). This suggests that inflammatory markers such as NLR are higher in women with PE.²⁰ Mannaerts et al. (2017) divided the NLR value between gestational age before 20 weeks and shortly before delivery. However, significant results were found at the end of pregnancy ($p < 0.00$) just before delivery, NLR values tended to be higher (6.79 ± 2.84) than the control group (3.60 ± 1.17).¹³

In a study by Sachan et al. (2017), where the group was divided between severe PE, mild PE, and control or healthy groups, the mean values of each group in the healthy mild, and severe PE groups were respectively as follows 3.14 ± 0.16 , 3.38 ± 0.16 , and 4.26 ± 0.31 .²³ Faraji et al. (2022) stated that NLR was higher in the mild and severe PE groups than in the gestational hypertension group in the first and early third trimesters ($p < 0.05$).²⁴ A case-control study conducted by Cakmak et al. (2017) found that NLR increased significantly in PE group compared to control group and in comparison between mild and severe PE groups, NLR values were also higher in severe PE group ($p=0.001$).²⁵ Oglak et al. (2021) divided three groups into control groups, mild PE, and severe PE. Significant results were obtained in the comparison between the control group with mild PE and the control group with severe PE ($p < 0.001$), while the comparison between the mild and severe PE groups was less ($p=0.441$).²⁶ Gezer et al. (2016) performed a complete blood count in the early trimester to predict the incidence of PE. From the study, NLR was found to be a predictor of PE in their analysis ($p=0.005$).²⁷

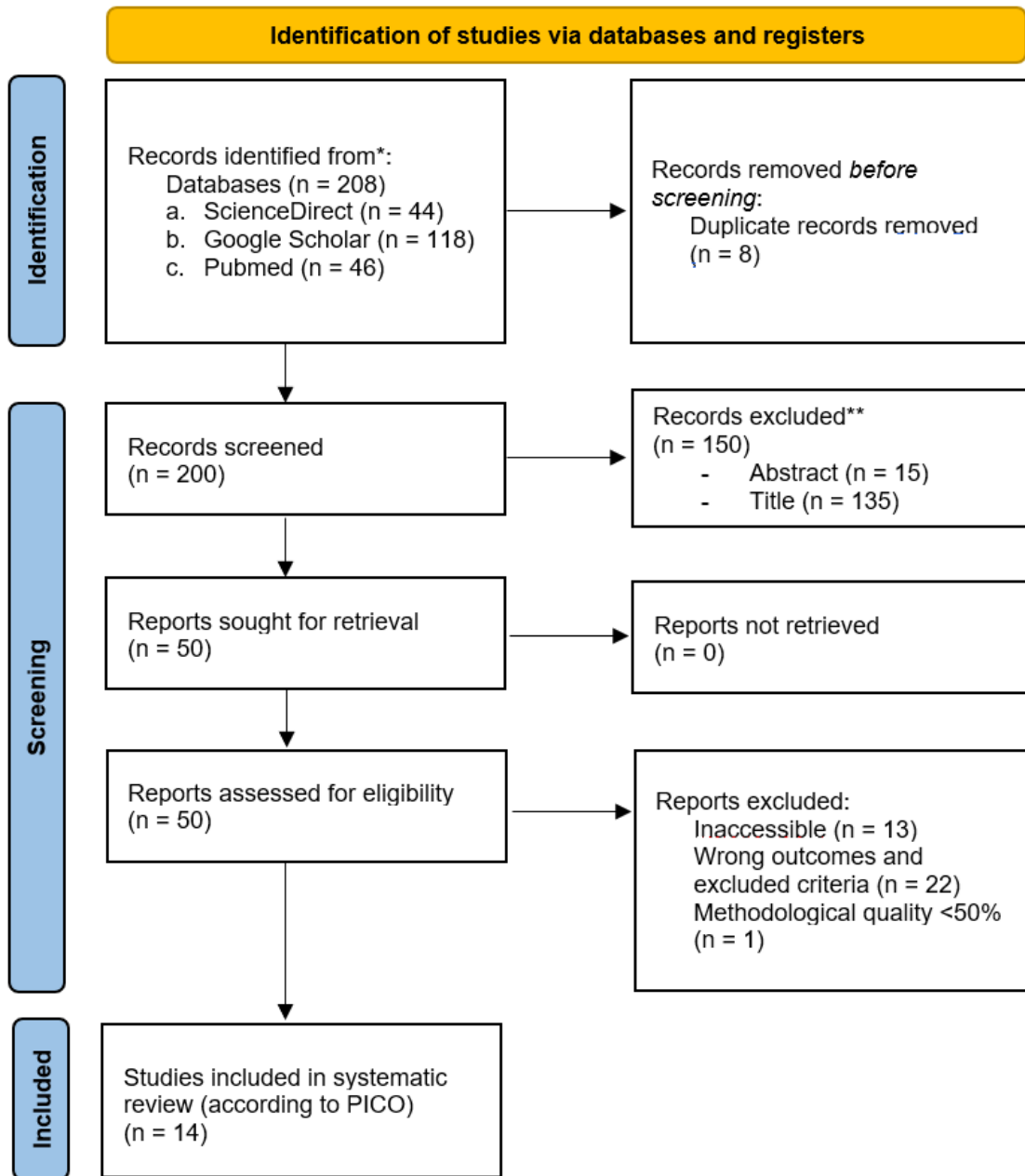


Figure 1. PRISMA flowchart diagram of the screening process and the included final articles

Table 1. PICO Table

Population (P)	Pregnant women
Intervention (I)	NLR (neutrophil-lymphocyte ratio) rate and MEOWS (modified early obstetric warning system) score
Comparison (C)	No intervention
Outcome (O)	Determine the severity of preeclampsia

Table 2. Summary of included studies showing the combination of NLR and MEOVS in a review

First Author (Year)	Study design	Age (median in years)	Sample size	Outcomes	NLR/MEOVS Parameter	Results	JB1 score
Sitotaw et al., (2018) ¹⁹	Cross-sectional study	25 - 26	126	NLR parameter and preeclampsia women	NLR (control 2.92 ± 0.50 , PE 4.67 ± 1.50)	<ul style="list-style-type: none"> NLR showed significant elevation in women with PE. NLR significantly increased with the severity of PE ($p < 0.05$). NLR correlation analysis ($\rho = 0.31$) in PE group. 	100%
Gogoi et al., (2018) ²⁰	Cross-sectional study	27 - 28	134	NLR between women with pre-eclampsia and normotensive	NLR (control 6.8 ± 7.6 , PE 3.0 ± 0.98)	<ul style="list-style-type: none"> NLR was higher in women with pre-eclampsia. Mean NLR was higher in women with preeclampsia ($p=0.001$). 	100%
Singh et al., (2016) ²¹	Cohort study	-	1065	MEOVS chart evaluation: <ul style="list-style-type: none"> Single markedly abnormal observation (red trigger) Combination of two simultaneously mildly abnormal observations (two yellow triggers) 	Trigger (284) 26.6% vs Non-Trigger (781) 73.4%	<ul style="list-style-type: none"> Two hundred and eighty-four (26.60%) women were triggered to abnormal zones after admission. One hundred and seventy-seven (16.61%) fitted our criteria for morbidity. Most common morbidity was hypertensive disorders (69.4%) 	63%
Kaur et al., (2023) ²²	Cohort study	33.4	267	Trigger definition: <ul style="list-style-type: none"> Single severely abnormal parameter (red zone) Two mildly abnormal parameters (yellow zone) 	Criteria for a trigger: <ul style="list-style-type: none"> 88 patients (33.0%) during triage 44 patients (17.6%) during the first treating nurse assessment 	<ul style="list-style-type: none"> Twenty-one (7.9%) patients met the criteria for severe maternal morbidity. There were no maternal deaths. Sensitivity of MEOVS tools 85.7% (95% CI 63.7-97%) Specificity 67.9% (95% CI 61.7-73.7%) PPV 18.6% (95% CI 15.1-22.7%) NPV 98.2% (95% CI 95.1-99.4%) Severe preeclampsia and eclampsia were the most common outcome category of severe maternal morbidity in 16 (76.2%) cases. 	100%
Mannaerts et al., (2017) ¹³	Cohort study	28.9 – 30.2	1613	Usability of NLR between women who develop PE and those that will not	NLR (preeclampsia group 2.81 ± 0.95 , control group 3.08 ± 1.07)	<ul style="list-style-type: none"> NLR before 20th pregnancy week ($p = 0.173$) NLR before primary cesarean section ($p < 0.00$) NLR (AUC 0.863), (95% CI 0.783 – 0.944), (Optimal cut-off point 3.92), (Sensitivity 84.4%), (Specificity 69.4%) 	100%



Sachan et al., (2017) ²³	Cohort study	25.1 – 25.9	101	Accuracy of NLR in the prediction of nonsevere PE and severe PE	NLR (mean±standard error) of three groups (13-20 weeks of gestation). Mild PE (Group 1), severe PE (Group 2), normotensive (Group 3) : <ul style="list-style-type: none"> • Group 1 NSPE (n=34) (3.38±0.16) • Group 2 SPE (n=16) (4.26±0.31) • Group 3 Controls (n=51) (3.14±0.16) 	Comparison of mean NLR between groups at 13-20 weeks : <ul style="list-style-type: none"> • Group 3 vs Group 1 (p < 0.006) • Group 3 vs Group 2 (p < 0.001) • Group 1 vs Group 2 (p < 0.001) NLR comparison before and after the development of preeclampsia: <ul style="list-style-type: none"> • Before (13-20 weeks) <ul style="list-style-type: none"> - Group 1 (NSPE) 3.38±0.16 - Group 2 (SPE) 4.26±0.31 • After (development of hypertensive disorders) <ul style="list-style-type: none"> - Group 1 (NSPE) 4.26±0.31 - Group 2 (SPE) 4.79±0.53 	100%
Faraji et al., (2022) ²⁴	Cohort study	17.4 – 22.7	449	Accuracy of NLR for predicting PE in the first and early-third trimester of pregnancy in a normal population	NLR First trimester: <ul style="list-style-type: none"> • Normotensive (2.21±0.62) • Gestational HTN (2.3±0.91) • Mild PE (2.96±0.4) • Severe PE (3.13±0.25) NLR Early-third trimester: <ul style="list-style-type: none"> • Normotensive (2.77±0.69) • Gestational HTN (70±0.4) • Mild PE (3.8±1.14) • Severe PE (4.1±1) 	NLR comparison between first trimester and early-third trimester : <ul style="list-style-type: none"> • First trimester <ul style="list-style-type: none"> - Mild PE (AUR 0.92), (Sensitivity 85%), (Specificity 90.9%), (PPV 96.5%), (NPV 38.8%). - Severe PE (AUR 0.95), (Sensitivity 85.7%), (Specificity 90.0%), (PPV 96.5%), (NPV 67.9%). • Early-third trimester <ul style="list-style-type: none"> - Mild PE (AUR 0.92), (Sensitivity 90.51%), (Specificity 79.4%), (PPV 92.9%), (NPV 38.1%). - Severe PE (AUR 0.91), (Sensitivity 90.5%), (Specificity 79.4%), (PPV 92.9%), (NPV 73.5%). 	73%
Cakmak et al., (2017) ²⁵	Case-control study	27.5 – 28.5	140	Evaluation of the relations between NLR with the presence and severity of preeclampsia	NLR baseline between PE and control : <ul style="list-style-type: none"> • Preeclampsia (5.3±1.4) • Control (3±0.8) • p=0.001 NLR baseline between Mild PE and Severe PE: <ul style="list-style-type: none"> • Mild PE (4.5±1) • Severe PE (6.3±1.1) • p=0.001 	Result of univariate and multivariate regression NLR analysis : <ul style="list-style-type: none"> • Univariate <ul style="list-style-type: none"> - (p=0.001), (OR 9.154), (95% CI) 4.139 - 20.247 • Multivariate <ul style="list-style-type: none"> - (p=0.001), (OR 8.161), (95% CI) 3.091 – 21.548 	70%

Oglak et al., (2021) ²⁶	Case-control study	27.4 – 28.7	301	Examination of the diagnostic value of the SIR marker (NLR) during the first trimester of pregnancy to predict PE development.	First trimester NLR marker (mean±SD): <ul style="list-style-type: none"> • Control Group (3.1±1.1) • Mild PE Group (4.3±1.4) • Severe PE Group (4.6±1.8) 	Area Under the Receiver Operating Characteristic (ROC) of NLR : <ul style="list-style-type: none"> • ROC (0.767), Standard Error (0.030), (95% CI) 0.709 – 0.826, (<i>p-value</i> <0.001) 	90%
Gezer et al., (2016) ²⁷	Case-control study	25.8 – 26.6	430	Determine whether first-trimester NLR would be useful as new predictors of subsequent preeclampsia.	Clinical characteristic of the study group (mean±SD) : <ul style="list-style-type: none"> • PE group (3.8±1.5) • Normotensive group (3.1±1.3) • <i>P-value</i> <0.001 	Prognostic value of optimum cut-off for first trimester NLR in predicting preeclampsia: <ul style="list-style-type: none"> • (AUC 0.716), (Sensitivity 74.6), (Specificity 70.1), (PPV 70.3%), (NPV 74.5%), (LR⁺ 2.5), (LR⁻ 0.4), (cut-off value 3.08) 	70%
Panwar et al., (2019) ²⁸	Case-control study	-	440	Conducted to evaluate the role of NLR in predicting the development and severity of PE.	Distribution of the mean value of NLR between 16-18 weeks in normal women and who developed PE: <ul style="list-style-type: none"> • Normal women (4.55±0.66) • PE (5.55±0.81) • <i>p</i> <0.001 Distribution of the mean value of NLR between 16-18 weeks in who developed mild PE and severe PE: <ul style="list-style-type: none"> • Mild PE (5.39±0.84) • Severe PE (6.08±0.43) • <i>p</i>=0.001 	Distribution of the sensitivity (SN) and specificity (SF) of NLR between 16-18 weeks in predicting the development of PE: <ul style="list-style-type: none"> • (AUC 0.84), (95% CI) 0.77 – 0.90, (cut off ≥ 5.6), (SN 73.4%), (SF 88.6%) Distribution of the sensitivity (SN) and specificity (SF) of NLR between 16-18 weeks in predicting the development of severe PE: <ul style="list-style-type: none"> • (AUC 0.95), (95% CI) 0.90 – 1.00, (cut off ≥ 5.61), (SN 93.3%), (SF 86.6%) 	70%
Kirbas et al., (2015) ²⁹	Case-control study	27 – 29.3	934	To investigate hematological changes in early pregnancy using simple complete blood count such as NLR.	Comparison NLR results of severe PE (group 1), mild PE (group 2), and the control group (Group 3): <ul style="list-style-type: none"> • Group 1 (4.54±2.98) • Group 2 (3.97±1.34) • Group 3 (3.23±1.33) <i>P-values</i> : <ul style="list-style-type: none"> • <i>P</i>^{1vs2} 0.86 • <i>P</i>^{1vs3} <0.001 • <i>P</i>^{2vs3} 0.005 	NLR accurately predicted PE: <ul style="list-style-type: none"> • {AUC=0.568 (95% CI 0.524-0.612), <i>p</i>=0.002}, (Sensitivity 79.1%), (Specificity 38.7%), (PPV 73.6%), (NPV 72.3%) 	80%



Ali et al., (2021) ¹⁴	Case-control study	26.6 – 28.5	132	To evaluate NLR in the diagnosis of preeclampsia and its severity and to determine the correlation between them.	Comparison of NLR among the study groups: <ul style="list-style-type: none"> • Controls (3.90±1.8) • Non-severe PE (4.10±3.41) • Severe PE (5.81±5.25) • p= 0.025 	ROC curve showed non-significant criterion for severe and non-severe cases: <ul style="list-style-type: none"> • p >0.05, (AUC 0.56), (95% CI) 0.4-0.7, (p=0.46) • Spearman’s correlation coefficient of 0.107 and p=0.39 	50%
Ryan et al., (2017) ³⁰	Case-control study	34 – 35.5	1841	To evaluate the performance of the Modified Early Obstetric Warning System (MEOVS) to predict maternal ICU admission in an obstetric population.	Comparison of demographic variables, patient characteristics and MEOVS variables: <ul style="list-style-type: none"> • ICU admitted women (n=46) • Non-ICU admitted women (n=138) MEOVS activation was defined as the occurrence ≥ 1 “red” or ≥ 2 “yellow” MEOVS triggers.	MEOVS chart triggers: <ul style="list-style-type: none"> • ≥ 1 red or ≥ 2 amber <ul style="list-style-type: none"> - (p <0.0001), RR (95% CI) 15.83 (3.96-63.36), (Sensitivity 0.96%), (Specificity 0.54%), (PPV 41%), (NPV 97%), (LR⁺ 2.10), (LR⁻ 0.08) • ≥ 1 red <ul style="list-style-type: none"> - (p <0.0001), RR (95% CI) 13.35 (4.99-35.71), (Sensitivity 0.91%), (Specificity 0.72%), (PPV 52%), (NPV 96%), (LR⁺ 3.23), (LR⁻ 0.12) • ≥ 2 red <ul style="list-style-type: none"> - (p <0.0001), RR (95% CI) 5.79 (3.49-9.60), (Sensitivity 0.65%), (Specificity 0.89%), (PPV 67%), (NPV 89%), (LR⁺ 6.00), (LR⁻ 0.39) 	70%

Panwar et al. (2019) conducted blood sampling at the beginning of the second trimester to compare groups of healthy women with PE and the between mild and severe PE. Both comparisons obtained significant results ($p < 0.001$).²⁸ Kirbas et al. (2015) divided three groups between the control, mild, and severe PE group. However, the results were found only between the comparison of the control group with severe PE ($p < 0.001$) and the control with mild PE ($p = 0.005$).²⁹ Ali et al. (2021) compared the three groups directly, the control group, mild, and severe PE. From these three comparisons, significant differences in NLR between the groups studied were obtained ($p = 0.027$).¹⁴

Furthermore, starting with a discussion of MEOWS parameters a study conducted by Singh et al. (2016) found that as many as two eighty-four patients (26.60%) met the abnormal criteria after admission and the greatest morbidity due to hypertension (69.4%).²¹ Kaur et al. (2023) conducted a similar study on MEOWS parameters. Of 267 patients, 21 (7.9%) patients met maternal morbidity criteria with MEOWS modality sensitivity of 85.7% (95% CI 63.7 – 97%) and specificity of 67.9% (95% CI 61.7 – 73.7%). Severe PE and eclampsia were the most common outcomes in 16 maternal patients (76.2%) of all patients who met the maternal morbidity criteria.²² Ryan et al. (2017) obtained data from several maternal and ICU units. From their study of MEOWS parameters, 46 patients were admitted to the ICU and 138 were not. With MEOWS chart triggers between all triggers ≥ 1 red and or ≥ 2 yellow, and ≥ 2 red obtained significant results ($p < 0.0001$).³⁰

In this systematic review, we discussed in detail the benefits of NLR and MEOWS modalities for predicting PE events. From the results of the systemic search and review, several articles were obtained that discussed the two modalities. The entire article explains that NLR and MEOWS can be used as predictors of PE, especially when applied to facilities with limited resources. However, it must be admitted that there are limitations of this study. This systematic review was carried out on a small scale and it is expected that in the future systematic reviews and meta-analyses will be carried out to a larger number of articles so that the results obtained will better clearly illustrate the benefits of NLR and MEOWS.

CONCLUSION

The results of the overall research presented in this systematic review suggest that the combination of NLR and MEOWS can be used as a potential modality to detect and predict PE events. Another benefit is that the

modality can be used simply and applied to facilities with limited resource conditions.

DISCLOSURES

Acknowledgment

None.

Conflict of interest

There was no conflict of interest among all authors in this study.

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Author contribution

RS, MM, dan YT have contributed to the overall process of this study starting from data collection, processing, analysis, and completion process to publication of the study.

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