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Original Research

Naples Prognostic Score in Obstetrics: A Novel Tool for Preeclampsia Evaluation

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Abstract

Background: To investigate the predictive value of the mid-trimester Naples Prognostic Score (NPS) for the subsequent preeclampsia development. **Methods**: This retrospective nested case-control study included 249 women, comprising 120 who developed preeclampsia and 129 normotensive controls, who delivered between January 2019 and January 2024. Laboratory parameters, including complete blood count and biochemical markers, were obtained at 20–24 weeks of gestation. The NPS was calculated based on the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), serum albumin, and total cholesterol levels, using cutoff values adapted from oncology literature. Logistic regression and receiver operating characteristic (ROC) curve analyses were performed to evaluate the predictive performance of the NPS. **Results**: Women who developed preeclampsia had significantly higher mid-trimester NPS scores compared with controls (median [interquartile range] (IQR): 3.0 (3.0–3.0) vs. 2.0 (1.0–2.0), $p < 0.001$). ROC analysis demonstrated good diagnostic performance of the NPS (area under the curve (AUC) = 0.886; 95% confidence interval (CI): 0.846–0.926) with an optimal cutoff value of 2.5 yielding a sensitivity of 85.0% and a specificity of 82.9%. In the multivariate logistic regression analysis, the NLR (adjusted odds ratios (aOR) = 4.127), lymphocyte count (aOR = 0.266), serum albumin (aOR = 0.412), and total cholesterol (aOR = 0.993) were identified as independent predictors of preeclampsia, whereas the composite NPS was not retained in the final model. **Conclusions**: The NPS demonstrated excellent screening performance for predicting preeclampsia, primarily driven by its inflammatory components, particularly the NLR. Although NPS provides practical clinical utility as a composite screening tool, its underlying inflammatory parameters appear to be the true mechanistic predictors. Further validation using pregnancy-specific cutoff values is warranted before routine clinical implementation.

Keywords: preeclampsia; Naples Prognostic Score; neutrophil-to-lymphocyte ratio; inflammation; pregnancy complications; biomarkers

1. Introduction

Preeclampsia is a hypertensive disorder of pregnancy associated with severe maternal and fetal complications. Typically manifesting after the 20th week of gestation, it is characterized by new-onset hypertension and proteinuria and remains a leading cause of maternal and perinatal morbidity and mortality worldwide [1]. Although its pathophysiology has not been fully elucidated, placental dysfunction, systemic inflammation, and vascular dysregulation are considered central mechanisms [2]. These interconnected processes contribute to endothelial injury, oxidative stress, and the activation of inflammatory pathways, ultimately leading to the clinical manifestations of the disease.

Inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), have been extensively investigated in the context of preeclampsia, as they reflect underlying systemic inflammation and immune dysregulation [3,4]. Among these, NLR has emerged as a particularly promising indicator, with several studies demonstrating its predictive value for disease onset and adverse maternal-fetal outcomes [3–5]. Nevertheless, while NLR and related indices offer important pathophysiological insights, they do not capture the multifactorial nature of preeclampsia, which also involves metabolic and nutritional alterations.

The Naples Prognostic Score (NPS), originally developed in oncology, integrates inflammatory (NLR, LMR) and nutritional (serum albumin, total cholesterol) parameters to predict clinical prognosis [6–10]. Its ability to concurrently reflect systemic inflammation, immune competence, and nutritional status makes it theoretically well-suited for assessing pregnancy-related complications, in which these physiological domains play pivotal roles. A higher NPS indicates a less favorable prognostic profile. Despite its theoretical relevance, the clinical utility of NPS in obstetric populations remains underexplored, and pregnancy-specific reference values have yet to be established.

In this study, we examined the association between mid-trimester NPS and the subsequent development of preeclampsia. We hypothesized that NPS would demonstrate clinically meaningful predictive performance and

that its individual components—particularly the NLR—would independently correlate with the risk of developing preeclampsia.

2. Materials and Methods

2.1 Study Design and Population

This retrospective nested case-control study was conducted at a tertiary referral center. Medical records of women who delivered between January 2019 and January 2024 were retrospectively reviewed. The study aimed to determine whether inflammatory and nutritional biomarkers measured during a routine mid-trimester visit (20–24 weeks of gestation) could predict the subsequent development of preeclampsia.

2.2 Participant Selection

Patient data were extracted from the hospital's electronic medical record (EMR) system using International Classification of Diseases (ICD)-10 codes for preeclampsia (O14.0–O14.9) and normal pregnancy outcomes (Z34.0–Z34.9). All identified cases were subsequently verified through manual chart review to verify the diagnostic criteria. At the 20–24-week visit, all participants were normotensive (systolic blood pressure $<$140 mmHg and diastolic blood pressure $<$90 mmHg) and exhibited no proteinuria. Blood samples were collected during routine antenatal visits when patients were clinically stable, and all laboratory analyses were performed following standardized protocols.

Women who were normotensive at 20–24 weeks but subsequently developed preeclampsia were classified as cases, whereas those who remained normotensive and experienced uncomplicated deliveries served as controls. The final study population comprised 120 cases and 129 controls.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria at 20–24 weeks of gestation were as follows: maternal age between 18 and 45 years, singleton pregnancy, and availability of complete blood count and biochemical test results obtained during the 20–24 weeks visit.

Exclusion criteria included pre-existing chronic hypertension, diabetes mellitus, or chronic kidney disease; presence of active infectious or systemic inflammatory conditions at the time of blood sampling; multiple gestation; and incomplete medical records.

2.4 Case and Control Definitions

Preeclampsia was defined as new-onset hypertension occurring after 20 weeks of gestation, characterized by a systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg on at least two occasions measured $\geq$4 hours apart, accompanied by proteinuria ($\geq$300 mg/24 h or a protein-to-creatinine ratio $\geq$0.3) [11]. Control participants remained normotensive and exhibited no evidence of proteinuria throughout pregnancy and at delivery.

2.5 Data Collection and Variables

Predictor variables (measured at the 20–24 weeks visit) included absolute neutrophil, lymphocyte, and monocyte counts, as well as serum albumin and total cholesterol levels. All blood samples were collected after a minimum fasting period of 8 hours. Outcome and demographic variables included maternal age, body mass index (BMI), gestational age at delivery, mode of delivery, infant birth weight, and final diagnosis of preeclampsia.

2.6 Calculation of Markers and NPS

The NLR was calculated as the neutrophil count divided by the lymphocyte count, and the LMR as the lymphocyte count divided by the monocyte count. The components and cutoff values of the NPS were adopted from oncology literature due to the absence of pregnancy-specific reference thresholds: serum albumin $<$3.5 g/dL = 1 point; total cholesterol $<$180 mg/dL = 1 point; NLR $\geq$2.96 = 1 point; and LMR $<$4.44 = 1 point. The total NPS ranged from 0 to 4, with higher scores indicating a poorer prognostic profile. These cutoffs may not be optimal for pregnant populations and are considered a key limitation, underscoring the need to establish obstetric-specific thresholds in future studies.

2.7 Units

Absolute leukocyte counts are reported in $10^3/\mu L$, serum albumin in g/dL, and total cholesterol in mg/dL. NLR and LMR are unitless.

2.8 Statistical Analysis

Normality of continuous variables was evaluated using the Kolmogorov-Smirnov test. As most continuous data were non-normally distributed, values are presented as median (interquartile range [IQR]), and between-group comparisons were performed using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Forward stepwise (likelihood ratio) logistic regression analysis was used to identify independent predictors while minimizing overfitting and accounting for potential multicollinearity among correlated hematologic parameters. Candidate variables included maternal age, BMI, serum albumin, lymphocyte count, neutrophil count, total cholesterol, monocyte count, NLR, and LMR. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, explained variance was quantified using the Nagelkerke R^2 statistic, and overall model accuracy was reported.

Spearman's rank correlation analysis was used to examine associations between continuous variables. Receiver

Table 1. Demographic and clinical characteristics.

Parameter	Control (n = 129)	Preeclampsia (n = 120)	*p*-value
Age (years)	29.0 (24.0–34.0)	31.5 (23.3–36.0)	0.271
BMI (kg/m^2)	25.8 (22.0–29.5)	25.0 (22.3–29.3)	0.857
Gestational age (weeks)	38.0 (37.0–38.0)	37.0 (36.0–37.0)	<0.001
Birth weight (g)	3060 (2890–3375)	2896 (2660–3273)	<0.001

Footnote: Data are presented as median (interquartile range (IQR)). Continuous variables were compared using the Mann-Whitney U test. BMI, body mass index.

Table 2. Laboratory parameters and NPS at 20–24 weeks.

Parameter	Control (n = 129)	Preeclampsia (n = 120)	*p*-value
Serum albumin (g/dL)	3.70 (3.25–4.20)	3.43 (3.20–3.80)	0.001
Total cholesterol (mg/dL)	240.0 (217.0–271.5)	233.5 (183.5–259.0)	0.009
Monocyte (10^3/μL)	0.60 (0.47–0.73)	0.66 (0.47–0.85)	0.039
Lymphocyte (10^3/μL)	2.05 (1.83–2.91)	1.69 (1.36–1.87)	<0.001
Neutrophil (10^3/μL)	5.87 (4.95–6.85)	6.14 (5.53–8.25)	<0.001
NLR	2.85 (2.59–3.11)	3.56 (3.24–3.87)	<0.001
LMR	4.03 (2.69–5.30)	2.69 (2.07–3.51)	<0.001
NPS	2.0 (1.0–2.0)	3.0 (3.0–3.0)	<0.001

Footnote: Data arepresented as median (interquartile range [IQR]). *p*-values were calculated using the Mann-Whitney U test. NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NPS, Naples Prognostic Score.

operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance, with the area under the curve (AUC) and corresponding 95% CIs reported. Optimal cutoff values were determined by maximizing the Youden index. A two-tailed p value < 0.05 was considered statistically significant.

3. Results

3.1 Participant Characteristics

A total of 249 participants (129 controls, 120 with preeclampsia) were included in the study. Age and BMI did not differ significantly between groups. Women with preeclampsia delivered earlier and had infants with lower birth weights ($p < 0.001$ and $p < 0.001$, respectively) (Table 1).

3.2 Comparison of Laboratory Parameters and NPS

Compared with controls, women who developed preeclampsia exhibited lower serum albumin levels, lymphocyte counts, LMRs, and total cholesterol concentrations, along with higher neutrophil and monocyte counts and elevated NLR. In multivariate logistic regression analysis, NLR emerged as the strongest independent predictor of preeclampsia (aOR = 4.127), followed by lymphocyte count, serum albumin, and total cholesterol. The composite NPS was not retained in the final stepwise model, indicating that its predictive capacity is primarily driven by individual components, particularly NLR and lymphocyte count (Tables 2,3).

3.3 Correlation Analysis

NPS correlated positively with NLR (r = 0.626, $p <$ 0.001) and negatively with LMR (r = –0.589, $p < 0.001$), lymphocyte count (r = –0.572, $p < 0.001$), and serum albumin (r = –0.459, $p < 0.001$).

3.4 ROC Analysis

NPS showed good diagnostic performance (AUC = 0.886; 95% CI: 0.846–0.926; $p < 0.001$) with a cutoff 2.5 (sensitivity: 85.0%; specificity: 82.9%). NLR also demonstrated good accuracy (AUC = 0.809; 95% CI: 0.756–0.862) (Table 4).

4. Discussion

The primary finding of this study is that mid-trimester NPS demonstrated a strong association with the subsequent development of preeclampsia and exhibited strong discriminative ability (AUC = 0.886). However, in multivariate modeling, the composite NPS was not retained as an independent predictor. Instead, its key inflammatory and nutritional components—elevated NLR, reduced lymphocyte count, decreased serum albumin, and lower total cholesterol—were independently associated with preeclampsia, indicating that the underlying mechanistic drivers lie within these specific pathophysiological pathways.

The central role of the NLR observed in this study is consistent with the well-established inflammatory pathophysiology of preeclampsia. Our findings identify NLR as a robust early predictor, representing the strongest independent determinant of preeclampsia (aOR = 4.127) and ex-

Table 3. Univariate and multivariate logistic regression for independent predictors of preeclampsia.

Variable	Univariate Analysis			Multivariate Analysis		
	Unadjusted (uOR)	95% CI	*p*-value	Adjusted (aOR)	95% CI	*p*-value
NLR	7.156	3.992–12.826	<0.001	4.127	2.201–7.737	<0.001
Lymphocyte	0.158	0.086–0.290	<0.001	0.266	0.142–0.499	<0.001
Serum albumin	0.488	0.305–0.778	0.003	0.412	0.232–0.734	0.003
Total cholesterol	0.992	0.986–0.997	0.002	0.993	0.987–0.999	0.032

Footnote: uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval. Unadjusted OR values and their 95% CIs were derived from individual logistic regression models. Adjusted OR values were taken from the original manuscript's multivariate model.

Table 4. ROC analysis for the prediction of preeclampsia.

Parameter	AUC	95% CI	Cutoff value	Sensitivity	Specificity	*p*-value
NPS	0.886	0.846–0.926	2.5	85.0%	82.9%	<0.001
NLR	0.809	0.756–0.862	3.32	71.7%	82.2%	<0.001
Lymphocyte	0.770	0.712–0.828	-	-	-	<0.001
LMR	0.732	0.672–0.792	-	-	-	<0.001

Footnote: Units as specified; NLR/LMR are unitless. AUC, area under the curve; ROC, receiver operating characteristic.

hibiting good standalone diagnostic performance (AUC = 0.809). These results are consistent with previous literature. For instance, a meta-analysis by Kang *et al*. [3] reported that elevated NLR values are significantly associated with an increased risk of preeclampsia. Furthermore, studies evaluating second-trimester NLR for preeclampsia prediction have reported AUC values ranging from 0.75 to 0.82, which are directly comparable to our findings [4,5]. Collectively, these data reinforce the reliability and reproducibility of NLR as a key inflammatory biomarker for early screening of preeclampsia.

Similarly, a lower LMR, another marker of systemic inflammation, was significant in our initial analyses, consistent with previous studies emphasizing the role of lymphocyte-monocyte interactions in the inflammatory cascade of preeclampsia [12]. However, its predictive power was ultimately superseded by stronger variables in the final multivariate model. More importantly, a reduced lymphocyte count (lymphopenia) was retained as an independent predictor (aOR = 0.266), highlighting the immune dysregulation central to the pathogenesis of preeclampsia. This relative decline in lymphocytes, together with systemic neutrophil activation, shifts the immune balance toward the pro-inflammatory state characteristic of the disease.

The observed association between low serum albumin levels and increased preeclampsia risk (aOR = 0.412) may reflect not only potential nutritional insufficiency but also increased vascular permeability and subclinical protein loss that precede the clinical onset of proteinuria. Conversely, the finding of lower total cholesterol contrasts with some reports in established preeclampsia. Possible explanations include sampling during the mid-trimester—prior to the full metabolic adaptations of late pregnancy—differences in cohort characteristics, and the use of non-pregnancy-specific NPS cutoffs. We acknowledge this limitation as important and emphasize the need to establish and validate pregnancy-specific thresholds in future research.

From a clinical perspective, the NPS is appealing as a well-established prognostic tool originally developed and extensively validated in oncology to capture systemic inflammation and nutritional status [7–10]. Its potential utility in obstetrics stems from the same principle—it integrates routine, low-cost laboratory parameters obtainable during the 20–24-week visit, thereby offering an accessible approach for risk stratification. NPS may also serve as a complementary screening method in settings where assays such as the soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio are unavailable or cost-prohibitive. We emphasize that NPS should be considered a screening rather than a diagnostic tool until further external validation and pregnancy-specific cutoff values are established.

The clinical applicability of NPS should be considered within the broader context of existing first- and second-trimester screening modalities for preeclampsia. The search for reliable blood-based biomarkers to predict preeclampsia remains a major focus of ongoing research, and our findings contribute to this growing body of evidence [13–16]. Biomarkers such as the sFlt-1/PlGF ratio and uterine artery Doppler velocimetry have demonstrated strong predictive performance, particularly for early-onset preeclampsia [17]. However, their widespread implementation is often limited by cost, the need for specialized equipment, and operator expertise—constraints that are especially relevant in resource-limited settings.

In contrast, the NPS is derived from parameters routinely measured in standard antenatal care, including the

complete blood count and basic biochemical profile. Thus, NPS should not be considered a replacement for established biomarkers such as the sFlt-1/PlGF ratio, but rather a potentially valuable, universally accessible, and cost-effective first-line tool for risk stratification. Its simplicity and accessibility could facilitate broader population-level screening to identify women at increased risk who may benefit from closer monitoring or advanced testing. Future prospective studies are warranted to directly compare the predictive performance of NPS with that of established obstetric biomarkers.

Limitations

The retrospective, single-center design constitutes a major limitation of this study. Furthermore, given the inherent constraints associated with retrospective data collection, several important potential confounders—such as parity, smoking status, socioeconomic factors, previous history of preeclampsia, and family history of hypertensive disorders—could not be included in the analysis. The absence of these variables may have introduced residual bias and could limit the external validity and generalizability of the findings. Future prospective, multicenter studies designed to establish and validate obstetric-specific thresholds are warranted to confirm these results.

5. Conclusions

Mid-trimester NPS is significantly associated with the subsequent development of preeclampsia and demonstrates good screening performance. Its independent predictive value appears to derive primarily from its inflammatory and nutritional components—particularly the NLR—highlighting their mechanistic relevance in disease pathogenesis. Following validation with pregnancy-specific thresholds and in external cohorts, NPS may serve as a practical, noninvasive, and cost-effective screening tool for early identification of women at increased risk of preeclampsia.

Availability of Data and Materials

Datasets are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: TKK, YK; Data curation: YK; Formal analysis/Statistics: TKK; Methodology: TKK; Writing—original draft: TKK; Writing—review & editing: TKK, YK; Supervision: YK. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Approved by the Giresun University Ethics Committee for Human Research (Approval number: 30/10/2024-147). The study complied with the Declaration of Helsinki; informed consent was waived due to the retrospective design.

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Conflict of Interest

The authors declare no conflict of interest.

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