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Original Article

Threshold-dependent effect of the neutrophil-to-albumin ratio (NAR) in early pregnancy: a novel insight for preeclampsia risk prediction

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Abstract: Objective: Preeclampsia (PE) is a major cause of adverse outcomes in pregnant, postpartum, and perinatal women; however, its early identification remains a clinical challenge, particularly in resource-scarce regions. The neutrophil-to-albumin ratio (NAR) reflects both systemic inflammatory response and nutritional status and has recently emerged as a promising early biomarker. This study aimed to investigate the association between NAR and subsequent PE risk and to compare its predictive efficacy with that of placental growth factor (PlGF) and mean arterial pressure (MAP). Methods: This retrospective cohort study enrolled 11,916 pregnant women with a gestational age of < 14 weeks. Logistic regression, restricted cubic spline (RCS), and two-stage regression analyses were applied to assess the association between NAR and PE. The diagnostic performance of NAR, PlGF, and MAP was compared using receiver operating characteristic (ROC) curve analysis. Results: After adjustment for maternal factors, elevated NAR was independently associated with an increased risk of PE (adjusted odds ratio [OR] = 2.04; 95% confidence interval [CI]: 1.42-2.92; P < 0.001). RCS analysis identified a nonlinear threshold at log-transformed NAR (LN[NAR]) = -1.92, beyond which PE risk increased sharply (OR = 4.26; 95% CI: 1.99-9.13). LN(NAR) and PlGF demonstrated comparable discriminative ability (area under the curve [AUC] = 0.591 vs. 0.605) but were inferior to MAP (AUC = 0.710). The correlation between NAR and PlGF was weak (r = 0.05). Conclusion: Elevated LN(NAR) is independently associated with PE in a threshold-dependent manner. In resource-limited settings, NAR may serve as a practical early PE biomarker for PE or as a component of multimodal prediction models.

Keywords: Inflammatory marker, preeclampsia, prediction model

Introduction

Preeclampsia (PE) - a complex disease involving multiple systems during pregnancy - is a leading cause of morbidity and mortality among pregnant and perinatal women worldwide [1-3]. PE affects 2% to 8% of pregnancies. It is defined as new-onset hypertension occurring after 20 weeks of gestation, accompanied by dysfunction of terminal organs. Associated adverse outcomes include preterm birth and intrauterine growth restriction of the fetus. In addition, PE is an independent risk factor for future cardiovascular diseases in both the mother and the offspring [4-6]. Although existing research has extensively explored the pathogenesis of this disease, its key pathophysiological mechanisms have not yet been fully elucidated. At present, although biomarkers such as mean arterial pressure (MAP), uterine artery Doppler

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blood flow, and placental growth factor (PlGF) have been used for early pregnancy screening, their widespread application in clinical practice - especially in areas with limited medical resources - is constrained by high cost, technical complexity, or limited predictive accuracy [7-9]. For this reason, it is particularly urgent in clinical practice to identify new, economical, and biologically meaningful biomarkers for early risk stratification.

Increasing evidence indicates that systemic inflammation is a core driving factor in the early development of PE. Long before clinical symptoms appear, maternal immune activation, neutrophil pre-activation, and factors derived from syncytiotrophoblast cells have already led to endothelial injury and placental perfusion disorders [10, 11]. Meanwhile, inflammatory stimulation can induce liver dysfunction and increased vascular permeability, thereby reducing serum albumin levels, which normally exert antioxidant and vascular stabilizing effects [12, 13]. The neutrophil-to-albumin ratio (NAR) can be easily obtained from routine blood tests and integrates the two pathophysiological components of inflammation and nutritional status into a single parameter. Although previous studies have demonstrated that NAR is associated with the prognosis of cardiovascular diseases and critical conditions, its predictive value for PE has been insufficiently investigated [14-16].

This study aims to explore the association between NAR in early pregnancy and the subsequent risk of PE through a large-scale retrospective cohort study. We further examined whether this relationship exhibits dose-response and nonlinear characteristics and evaluated the diagnostic performance of NAR in comparison with MAP and PlGF. We hypothesize that NAR, as an integrated biomarker of immune activation and hypoalbuminemia, may serve as an independent and easily accessible indicator for the early identification of women at high risk of PE.

Materials and methods

Study design and population

This study was a retrospective cohort study. A total of 11,916 pregnant women who completed early prenatal screening before 14 weeks of gestation from 2015 to 2024 were selected. Subjects with incomplete laboratory test data or obstetric clinical data, a history of chronic hypertension diagnosed before pregnancy, fetal death during pregnancy, artificial termination of pregnancy or spontaneous abortion, and intrauterine growth restriction or preterm birth unrelated to PE were excluded. Ultimately, only those with both NAR data and pregnancy outcome data were included for statistical analysis. The Reproductive Medicine Ethics Committee of Suzhou Municipal Hospital reviewed and approved this research (K-2025-200-K01). All patient information was anonymized in accordance with the Declaration of Helsinki. The research process is shown in **Figure 1**.

Sample size consideration

To assess the statistical power of our cohort, a post-hoc power analysis was conducted. The analysis considered the observed incidence of PE in the lowest NAR quartile (3%) and the highest NAR quartile (6%), with a PE-to-non-PE ratio of approximately 0.04. A two-sided α of 0.05 and 90% statistical power were applied, accounting for an anticipated 15% loss to follow-up. The analysis indicated that at least 7,146 participants (275 in the PE group) would be required. Our final cohort of 11,916 pregnant women (486 in the PE group and 11,430 in the non-PE group) exceeds this sample size requirement, confirming that the study has sufficient statistical power to analyze the reported associations.

Exposure assessment: neutrophil-to-albumin ratio

Both demographic and laboratory data were collected during the routine early pregnancy (< 14 weeks) screening. The median gestational age at blood sampling for the entire cohort was 12.43 weeks (interquartile range [IQR]: 11.81-13.00 weeks). In the non-PE group, the median was 12.43 weeks (IQR: 11.81-13.00 weeks), while in the PE group it was 12.29 weeks (IQR:11.71-13.00 weeks); the difference between groups was not statistically significant (P >0.05) (Table S1). The calculation method of NAR is to calculate the ratio of the absolute neutrophil count measured in fasting peripheral blood samples to the serum albumin concentration. Participants were categorized into quartiles according to the population distribution of NAR values.

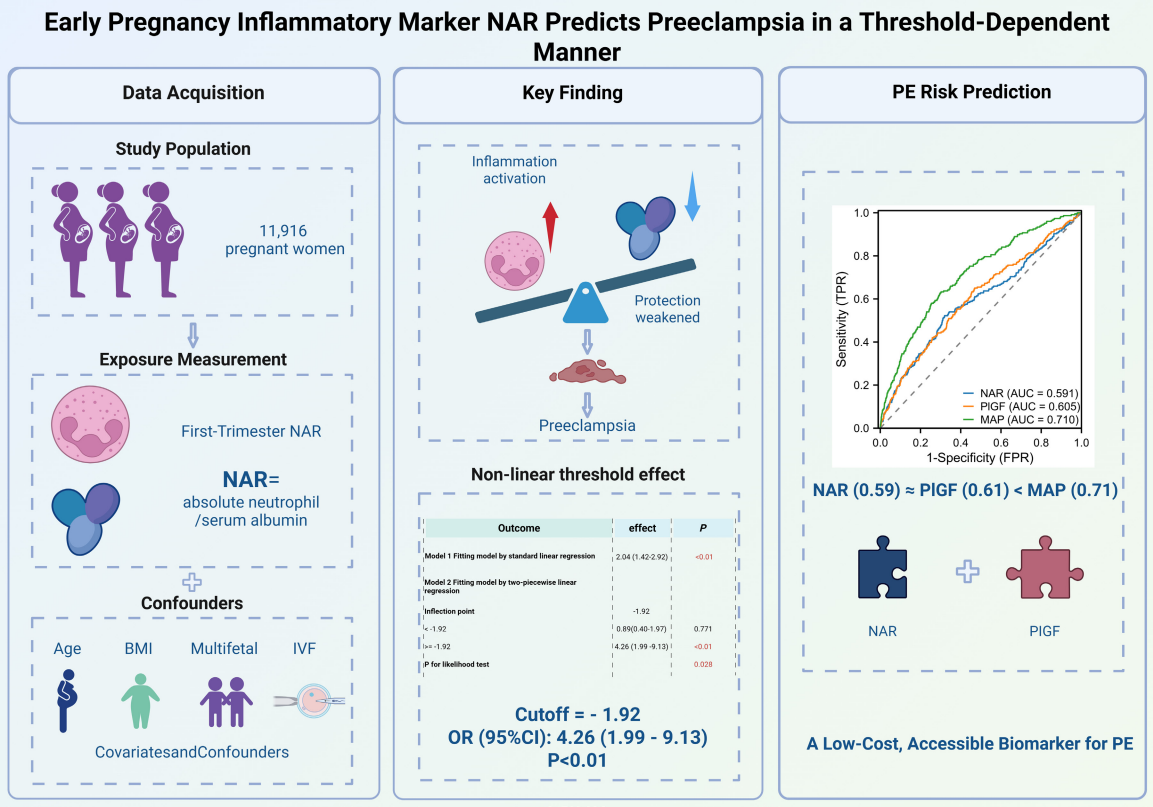

Figure 1. Association between first-trimester NAR and the risk of preeclampsia. This retrospective cohort study of 11,916 pregnant women evaluated the relationship between early-pregnancy neutrophil-to-albumin ratio (NAR) and subsequent preeclampsia (PE) risk. After adjustment for maternal and pregnancy-related confounders, elevated log-transformed NAR (LN[NAR]) was independently associated with increased PE risk, exhibiting a nonlinear, threshold-dependent pattern. When the LN(NAR) exceeded -1.92, the risk of PE rose sharply (OR = 4.26). In predictive performance, LN(NAR) (AUC = 0.591) was comparable to PIGF (AUC = 0.605) but lower than MAP (AUC = 0.710). These findings suggest that NAR, as an accessible inflammatory marker derived from routine testing, may serve as a complementary biomarker for PE risk stratification. NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, PE: preeclampsia, PIGF: placental growth factor, MAP: mean arterial pressure.

Outcome assessment

The primary outcome of this study was PE, and the diagnosis followed the criteria set by the American College of Obstetricians and Gynecologists (ACOG): New-onset hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) occurred after 20 weeks of pregnancy, accompanied by proteinuria (test strip detection ≥ 1 + with positive results in both cases, 24-hour urine protein quantification ≥ 300 mg or urine protein/creatinine ratio ≥ 30 mg/millimole); If proteinuria does not occur, PE can also be diagnosed when hypertension is combined with thrombocytopenia, elevated liver enzymes, renal insufficiency, pulmonary edema, new neurological symptoms or any other maternal organ dysfunction. All data related to pregnancy outcomes were derived from electronic medical records and were independently verified by two obstetricians and gynecologists who were not familiar with the NAR results.

Covariates

The potential confounding factors involved in the study were all extracted from medical records, mainly including: maternal age, body mass index (BMI), parity (primiparas/multiparas), conception method (natural conception/in vitro fertilization [IVF] conception), and number of fetuses (singleton/multifetal pregnancies). All these variables have been incorporated into the multivariate model for analysis.

Statistical analyses

All analyses were conducted using R software (version 4.3.3), and the statistical significance

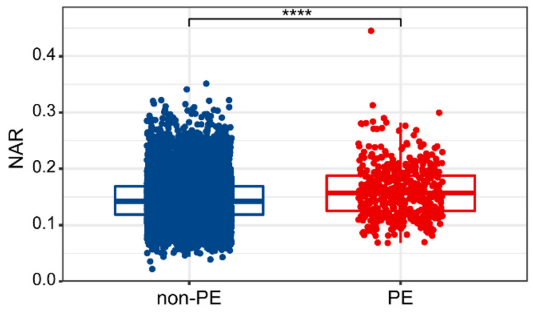

Figure 2. Comparison of NAR Levels between pregnancies with and without subsequent preeclampsia. NAR levels were significantly elevated in pregnancies that subsequently developed PE compared to those without PE. ****, $P < 0.0001$. NAR: Neutrophil-to-albumin ratio, PE: preeclampsia.

level was set at two-sided P < 0.05. For continuous variables, the mean ± standard deviation or median (IQR) is used for description. For comparisons between groups, the Mann-Whitney U test is selected depending on the data distribution. For categorical variables, frequency (percentage) is used for description, and chi-square test is used for comparison between groups.

To explore the association between NAR in the early stage of pregnancy and PE, this study conducted multivariate logistic regression analysis and reported the adjusted odds ratio (OR) and its 95% confidence interval (CI). We successively constructed three models: Model 1 was not corrected. Model 2 corrected for age, BMI, and parity. Model 3 further corrected IVF conception and multifetal pregnancy on the basis of Model 2.

To analyze the dose-response relationship and its possible nonlinear characteristics, this study adopted restricted cubic spline (RCS) regression for modeling and further explored the potential threshold effects through a piecewise model. In addition, the study also conducted subgroup analyses based on the mother's age, BMI, parity, the method of IVF conception, and the status of multifetal pregnancy. Interactions were tested by introducing product terms.

In the subset containing 5,427 valid individual's data, Pearson's correlation coefficient was used to evaluate the correlation between NAR and PIGF. The predictive efficacy of NAR, PIGF and MAP for PE was compared through ROC analysis and DeLong test, and the differences in the area under the curve (AUC) were analyzed.

Results

Elevated first-trimester NAR and risk of preeclampsia

Pregnant women who were diagnosed with PE in the third trimester of pregnancy had significantly higher NAR levels in the early trimester than those without the disease (P < 0.001; **Figure 2**; Table S1). After adjusting for factors such as maternal age, BMI, parity, IVF conception, and multifetal pregnancy, elevated log-transformed NAR (LN[NAR]) levels were still independently associated with an increased risk of PE (adjusted OR = 2.04, 95% CI: 1.42-2.92, $P < 0.001$; **Table 1**). In addition, in the multivariable model, maternal age, BMI, IVF conception and multifetal pregnancy are also independent risk factors for PE, while vaginal delivery is shown as a protective factor.

Dose-dependent increase in preeclampsia risk with rising NAR levels in early pregnancy

To evaluate the potential dose-response relationship between early-pregnancy inflammation and the risk of PE, the LN(NAR) was divided into quartiles. This stratification allowed for the assessment of whether progressively higher levels of LN(NAR) were associated with differential maternal characteristics and PE risk. Participants were evenly distributed across four quartiles: Q1 (n = 2,979; 25.00%), Q2 (n = 2,979; 25.00%), Q3 (n = 2,979; 25.00%), and Q4 (n = 2,979; 25.00%). Significant differences in baseline characteristics were observed across the quartiles (**Table 2**). Maternal BMI demonstrated a stepwise increase from Q1 (median 21.48 [IQR, 19.85-23.31]) to Q4 (22.48 [IQR, 20.57-24.61]; $P < 0.001$). The proportion of multifetal pregnancy rose in parallel with LN(NAR), from 0.77% in Q1 to 2.32% in Q4 ($P < 0.001$). Similarly, the prevalence of IVF conception increased from 8.26% in Q3 to 10.91% in Q4 ($P = 0.001$). Most importantly, the incidence of PE increased progressively across quartiles, from 2.99% in Q1 to 6.31% in Q4 ($P < 0.001$), supporting a possible dose-dependent association between elevated early-pregnancy LN(NAR) and PE risk. By contrast, maternal age

Table 1. Association of LN(NAR) and maternal characteristics with preeclampsia

Variables	β	S.E.	Z	*P*	OR (95% CI)
Age (years)	0.05	0.01	3.63	< 0.001	1.05 (1.02-1.08)
BMI (kg/m^2)	0.20	0.01	14.65	< 0.001	1.22 (1.19-1.25)
Parity	-0.42	0.11	-3.70	< 0.001	0.66 (0.53-0.82)
IVF conception					
No					1.00 (Reference)
Yes	0.79	0.13	6.18	< 0.001	2.19 (1.71-2.82)
Multifetal pregnancy					
No					1.00 (Reference)
Yes	1.94	0.19	10.09	< 0.001	6.94 (4.77-10.12)
LN(NAR)	0.71	0.18	3.88	< 0.001	2.04 (1.42-2.92)

NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, IVF: in vitro fertilization.

and parity did not vary significantly across quartiles (*P* = 0.654 and *P* = 0.180, respectively).

To further investigate the relationship between early-pregnancy inflammatory status and the risk of PE, logistic regression analyses were performed using LN(NAR) quartiles as categorical predictors. In the unadjusted model (Model 1), women in the highest LN(NAR) quartile (Q4) had a significantly increased risk of developing PE compared to those in the lowest quartile (Q1) (OR: 2.19; 95% CI: 1.69-2.83; *P* < 0.001), whereas no significant associations were observed for Q2 or Q3. This finding suggests a potential threshold effect rather than a linear dose-response across all quartiles.

After adjusting for maternal age, BMI, and parity (Model 2), the association between Q4 and PE remained robust (OR: 1.70; 95% CI: 1.30-2.21; *P* < 0.001), with risk estimates for Q2 and Q3 remaining non-significant. In the fully adjusted model (Model 3), which additionally accounted for IVF conception and multifetal pregnancy, women in Q4 continued to exhibit a significantly elevated risk of PE (OR: 1.56; 95% CI: 1.19-2.03; *P* = 0.001), confirming that a high LN(NAR) in early pregnancy is independently associated with an increased risk of PE, even after adjusting for key maternal and pregnancy-related factors (**Table 3**).

Elevated LN(NAR) exhibits nonlinear risk elevation for preeclampsia in early gestation

In order to further explore the potential nonlinear relationship between the LN(NAR) and the risk of PE in early pregnancy, this study constructed a RCS regression model. The number of knots was chosen based on the Akaike Information Criterion (AIC), with 5 knots selected for the model. The positions of these knots were spaced equally along the range of LN(NAR) values, which allows for a comprehensive and flexible representation of the nonlinear association between LN(NAR) and PE risk. This approach ensured that the model captured the nonlinear relationship effectively without overfitting or underfitting the data. In the unadjusted model, the correlation between LN(NAR) and PE risk is generally statistically significant (total *P* value < 0.001), and there is an obvious nonlinear relationship (nonlinear *P* value = 0.001) (**Figure 3A**). PE risk increases with the increase of LN(NAR) level, especially when LN(NAR) exceeds the -1.95 threshold, this upward trend is more obvious, suggesting a nonlinear dose response effect. After further adjusting the mixed factors such as maternal age, BMI, parity, multifetal pregnancy and IVF conception, this correlation is still strong (*P* for overall < 0.001), and nonlinear characteristics still exist (*P* for nonlinear = 0.020) (**Figure 3B**). The above results show that the increase in LN(NAR) levels in early pregnancy independently increases the risk of PE in a nonlinear mode. This finding further confirms the potential application value of NAR as a PE predictive biomarker.

Nonlinear threshold detected in the inflammatory marker LN(NAR) for predicting preeclampsia

In view of the fact that a nonlinear relationship between LN(NAR) and the risk of PE has been observed in the RCS analysis, this study further

Table 2. Baseline maternal characteristics and preeclampsia incidence across quartiles of LN(NAR)

Variables	Total (n = 11916)	Q1 (n = 2979)	Q2 (n = 2979)	Q3 (n = 2979)	Q4 (n = 2979)	Statistic	*P*
Gestational week at testing, M (Q_1, Q_3)	12.43 (11.81, 13.00)	12.29 (11.71, 12.98)	12.38 (11.81, 13.00)	12.43 (11.81, 13.10)	12.43 (11.86, 13.14)	χ^2 = 40.97#	< 0.001
Age, years, M (Q_1, Q_3)	31.00 (28.00, 34.00)	31.00 (28.00, 34.00)	31.00 (28.00, 34.00)	31.00 (28.00, 34.00)	31.00 (28.00, 34.00)	χ^2 = 1.62#	0.654
BMI, kg/m^2, M (Q_1, Q_3)	21.86 (20.20, 23.86)	21.48 (19.85, 23.31)	21.76 (20.27, 23.61)	21.89 (20.28, 24.02)	22.48 (20.57, 24.61)	χ^2 = 181.42#	< 0.001
Parity, M (Q_1, Q_3)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	χ^2 = 4.89#	0.180
Multifetal pregnancy, n (%)						χ^2 = 28.24	< 0.001
No	11737 (98.50)	2956 (99.23)	2945 (98.86)	2926 (98.22)	2910 (97.68)		
Yes	179 (1.50)	23 (0.77)	34 (1.14)	53 (1.78)	69 (2.32)		
IVF conception, n (%)						χ^2 = 15.79	0.001
No	10826 (90.85)	2712 (91.04)	2727 (91.54)	2733 (91.74)	2654 (89.09)		
Yes	1090 (9.15)	267 (8.96)	252 (8.46)	246 (8.26)	325 (10.91)		
PE (%)						χ^2 = 52.69	< 0.001
Non-PE	11430 (95.92)	2890 (97.01)	2881 (96.71)	2868 (96.27)	2791 (93.69)		
PE	486 (4.08)	89 (2.99)	98 (3.29)	111 (3.73)	188 (6.31)		

#: Kruskal-wailis test, χ^2: Chi-square test. M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile. NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, PE: preeclampsia, IVF: in vitro fertilization.

Table 3. The multiple logistic regression analysis of the relationship between LN(NAR) with preeclampsia

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
LN(NAR)	3.62 (2.55-5.14)	< 0.001	2.43 (1.70-3.47)	< 0.001	2.04 (1.42-2.92)	< 0.001
LN(NAR) (Quartile)						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.10 (0.83-1.48)	0.504	1.03 (0.76-1.38)	0.862	1.01 (0.75-1.36)	0.938
3	1.26 (0.95-1.67)	0.114	1.11 (0.83-1.48)	0.481	1.06 (0.79-1.42)	0.702
4	2.19 (1.69-2.83)	< 0.001	1.70 (1.30-2.21)	< 0.001	1.56 (1.19-2.03)	0.001
P for trend		< 0.001		< 0.001		< 0.001

Model 1: unadjusted; Model 2: adjusted for maternal age, BMI, and parity; Model 3: additionally adjusted for multifetal pregnancy and IVF conception. NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, IVF: in vitro fertilization.

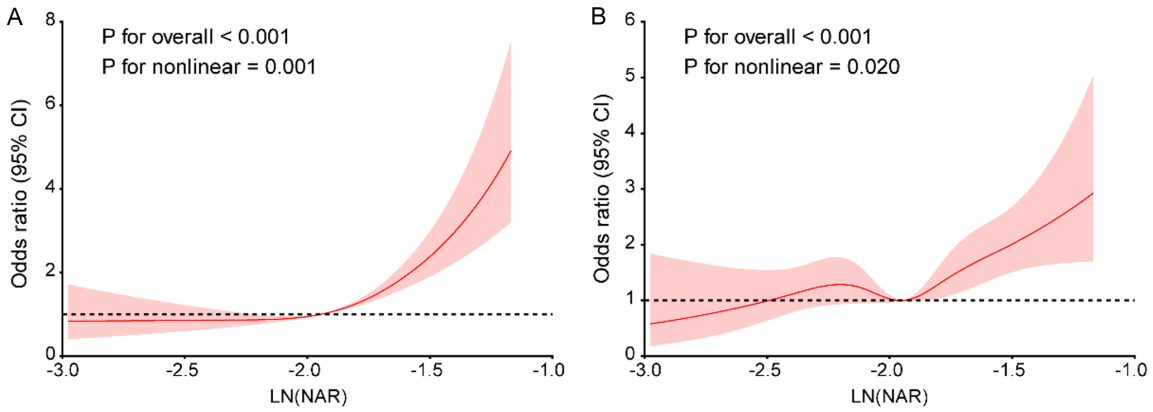

Figure 3. Nonlinear relationship between LN(NAR) and the risk of preeclampsia. A. Restricted cubic spline analyses revealed a significant nonlinear relationship in the unadjusted model (*P* for overall < 0.001; *P* for nonlinearity = 0.001). B. After adjusting for maternal age, BMI, parity, IVF conception, and multifetal pregnancy, the nonlinear association remained statistically significant (*P* for overall < 0.001, *P* for nonlinearity = 0.020). NAR: Neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, IVF: in vitro fertilization.

adopts segmented linear regression analysis (with the help of segmented software packages) to explore the threshold effect, the purpose is to find If a potential inflection point - LN(NAR) exceeds this inflection point, its correlation with PE risk may increase significantly.

Judging from the overall results, in the standard linear regression model, the association between LN(NAR) and PE is still statistically significant (OR: 2.04; 95% CI: 1.42-2.92; *P* < 0.001). Segmented linear regression analysis further determines that LN(NAR) = -1.92 is a related turning point, below this threshold, and there is no significant correlation between LN(NAR) and PE risk (OR: 0.89; 95% CI: 0.40-1.97; *P* = 0.771). When LN(NAR) exceeds -1.92, the two are strongly positively correlated (OR: 4.26; 95% CI: 1.99-9.13; *P* < 0.001). The likelihood ratio test confirms the existence of this threshold effect (*P* = 0.028), suggesting that the risk of PE occurrence will only increase significantly when the level of LN(NAR) in early pregnancy exceeds the above critical value (**Table 4**).

Robust association between early-pregnancy LN(NAR) and preeclampsia across subgroups

Data is stratified according to maternal age, BMI, parity, multifetal pregnancy status and IVF conception method. Interactions were also examined to evaluate the robustness of the association between the risk of early pregnancy LN(NAR) and PE in different maternal subgroups. Among all the subjects, there is a strong correlation between the two (OR: 3.62; 95% CI: 2.55-5.14; *P* < 0.001). Further analysis

Table 4. Threshold effect of LN(NAR) on risk of preeclampsia: comparison of linear and two-piecewise regression models

Outcome	effect	*P*
Model 1 Fitting model by standard linear regression	2.04 (1.42-2.92)	< 0.001
Model 2 Fitting model by two-piecewise linear regression		
Inflection point	-1.92	
< -1.92	0.89 (0.40-1.97)	0.771
≥ -1.92	4.26 (1.99-9.13)	< 0.001
P for likelihood test		0.028

NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR.

Table 5. Subgroup analyses and interaction effects

Variables	n (%)	OR (95% CI)	*P*	*P* for interaction
All patients	11916 (100.00)	3.62 (2.55-5.14)	< 0.001	
Age (years)				0.863
< 35	9427 (79.11)	3.54 (2.35-5.34)	< 0.001	
≥ 35	2489 (20.89)	3.79 (1.94-7.41)	< 0.001	
BMI (kg/m^2)				0.779
< 30	11695 (98.15)	3.22 (2.23-4.67)	< 0.001	
≥ 30	221 (1.85)	2.68 (0.77-9.26)	0.120	
Parity				0.420
Primipara (0)	7873 (66.07)	3.28 (2.17-4.96)	< 0.001	
Multipara (> 0)	4043 (33.93)	4.54 (2.31-8.92)	< 0.001	
Multifetal pregnancy				0.022
No	11737 (98.50)	3.53 (2.43-5.11)	< 0.001	
Yes	179 (1.50)	0.82 (0.25-2.69)	0.746	
IVF conception				0.242
No	10826 (90.85)	2.99 (2.00-4.48)	< 0.001	
Yes	1090 (9.15)	4.84 (2.40-9.75)	< 0.001	

IVF: in vitro fertilization.

found that young (< 35 years old, OR: 3.54; 95% CI: 2.35-5.34), elderly (≥ 35 years old, OR: 3.79; 95% CI: 1.94-7.41) pregnant women, non-obese (BMI < 30 kg/m^2, OR: 3.22; 95% CI: 2.23-4.67) and obese (BMI ≥ 30 kg/m^2, OR: 2.68; 95% CI: 0.77-9.26) pregnant, primipara (parity = 0, OR: 3.28; 95% CI: 2.17-4.96) and multipara (parity > 0, OR: 4.54; 95% CI: 2.31-8.92) , the correlation pattern between women and between mothers and mothers is consistent, and there is no significant interaction (P > 0.05) (**Table 5**). It is worth noting that there is a significant interaction between multifetal pregnancy and LN(NAR) (P = 0.022): the relationship between the two is still significant in singleton pregnancy (OR: 3.53; 95% CI: 2.43-5.11; P < 0.001), but there is no such relationship in multifetal pregnancy. Link (OR: 0.82; 95% CI: 0.25-2.69; P = 0.746). In the IVF population, the intensity of the association between the two seems to be higher than that of natural conception (OR: 4.84; 95% CI: 2.40-9.75; P < 0.001), but this difference does not reach the statistically significant interaction level (P = 0.242) (**Table 5**). In general, the association between LN(NAR) and PE was consistent in most maternal subgroups, and only multifetal pregnancy may have a potential regulatory effect on this association.

Comparative diagnostic performance of LN(NAR), PlGF, and MAP for early prediction of preeclampsia

In order to evaluate the diagnostic value of LN(NAR) as an early biomarker of PE, this study analyzed its correlation with PlGF and compared it with the differential effect of the tradi-

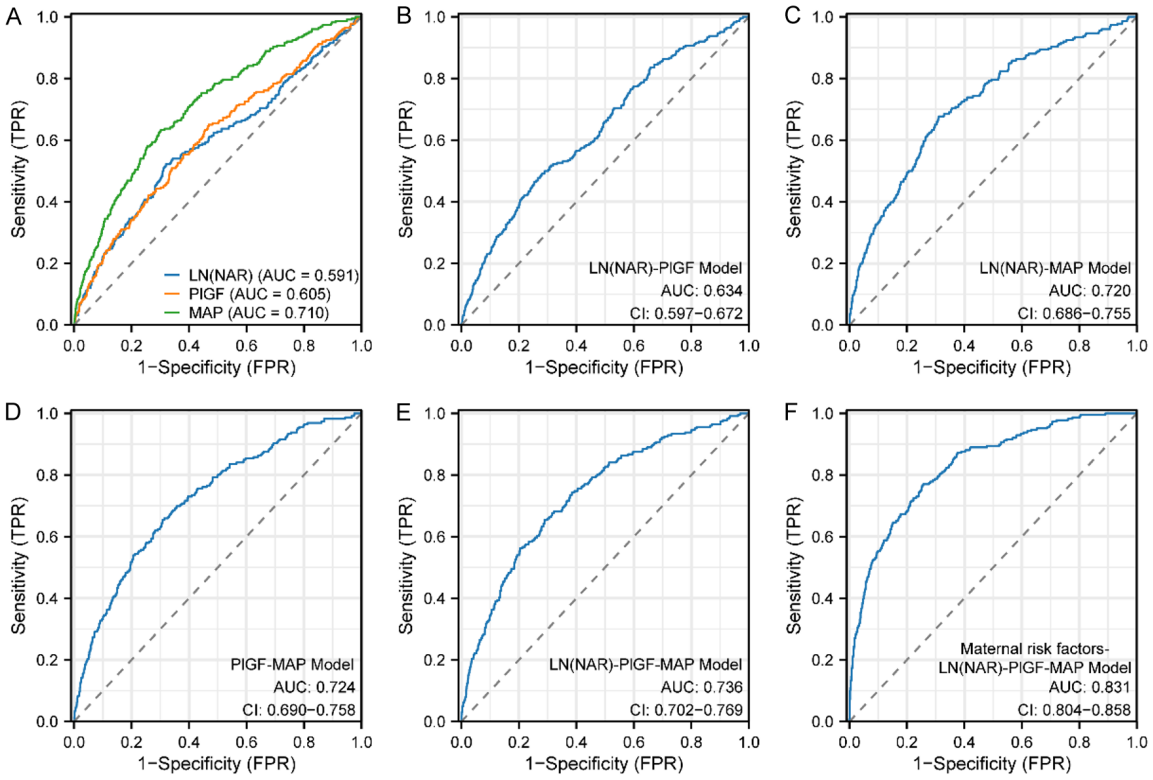

Figure 4. Diagnostic performance of LN(NAR) for early prediction of preeclampsia. (A) ROC analysis revealed that the AUC for LN(NAR) was 0.591, which was similar to that of PIGF (AUC = 0.605; $P = 0.6639$, as per the DeLong test). However, both markers performed less effectively compared to MAP (AUC = 0.710; $P = 4.2\times10^{-6}$ vs NAR, $P = 8.07\times10^{-5}$ vs PIGF). Predictive performance of models (B) combined LN(NAR) and PIGF (AUC: 0.634); (C) Combined LN(NAR) and MAP (AUC: 0.720); (D) Combined PIGF and MAP (AUC: 0.724); (E) Combined LN(NAR), PIGF and MAP (AUC: 0.736); (F) Combined maternal risk factors (age, BMI, parity, IVF conception, and multifetal pregnancy), LN(NAR), PIGF and MAP (AUC: 0.831). NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, PIGF: placental growth factor, MAP: mean arterial pressure, IVF: in vitro fertilization.

tional indicator MAP. This helped clarify whether this simple inflammation indicator can be used as a separate and easily accessible alternative or supplement to existing forecasting tools. Correlation analysis shows that LN(NAR) and PIGF are only weakly correlated (r = 0.04971; 95% CI: 0.02314-0.07622; P = 0.0002), suggesting that the two reflect two different biological processes, systemic inflammation and placental angiogenesis disorder, and can provide non-redundant information for the PE prediction model.

ROC curve analysis shows that the AUC of LN(NAR) is 0.591 (95% CI: 0.550-0.633), which matches the 0.605 (95% CI: 0.565-0.644; DeLong test, P = 0.664) of PIGF (**Figure 4A**). Both predictions are significantly lower than MAP (AUC: 0.710; 95% CI: 0.675-0.745), and there are significant differences between MAP and LN(NAR) ($P = 4.2\times10^{-6}$) and MAP and PIGF ($P = 8.07\times10^{-5}$). At its optimal cut-off value (-1.837), the LN(NAR) model yielded a sensitivity of 52.2%, a specificity of 68.0%, a positive predictive value of 6.6%, and a negative predictive value of 97.0% (Table S2).

To assess whether NAR adds complementary value to existing markers, we developed combined prediction models. The combination of LN(NAR) and PIGF yielded an AUC of 0.634 (95% CI: 0.597-0.672), while combining LN(NAR) and MAP resulted in an AUC of 0.720 (95% CI: 0.686-0.755), and the combination of PIGF and MAP also yielded an AUC of 0.724 (95% CI: 0.690-0.758) (Table S2; **Figure 4B-D**). The triple-marker model integrating LN(NAR), PIGF, and MAP achieved an AUC of 0.736 (95% CI: 0.702-0.769), surpassing the performance of any individual marker (Table S2; **Figure 4E**). Notably, the comprehensive model incorporating maternal risk factors (age, BMI, parity, IVF

conception, and multiple pregnancies) along with LN(NAR), PlGF, and MAP demonstrated the highest discriminative ability, with an AUC of 0.831 (95% CI: 0.804-0.858) (Table S2; **Figure 4F**).

Although MAP is still the strongest independent prediction factor, LN(NAR) performs as well as PlGE, and it can add complementary value to other biomarkers. Overall, the identification effect of LN(NAR) and PlGF is equivalent, but the correlation is low, which supports the hypothesis that LN(NAR) can capture complementary inflammatory axes in PE pathophysiology.

Discussion

This study confirmed, through a large retrospective cohort analysis, that an elevated NAR in early pregnancy can independently predict the occurrence of PE. Notably, even when multiple established clinical risk factors, such as age, BMI, IVF conception, and multifetal pregnancy, were simultaneously taken into account, the independent predictive value of NAR remained significant [17]. Quartile analysis of LN(NAR) revealed a progressively increasing risk of PE, with women in the highest quartile exhibiting a 56% higher adjusted risk compared with those in the lowest quartile. Further analysis using the restricted cubic spline (RCS) model demonstrated a nonlinear association between LN(NAR) and PE risk, with a clear threshold effect. When LN(NAR) exceeded -1.92, the risk of PE increased sharply, with the odds ratio reaching approximately 4.3. These findings suggest that mildly elevated inflammatory activity in early pregnancy may fall within a physiological compensatory range. However, once the inflammatory response surpasses a specific threshold, it may trigger pathological processes, leading to a disproportionate increase in PE risk.

The predictive value of NAR is further reflected in its combination with two categories of indicators. Its predictive performance is comparable to that of placental growth factor (PlGF), an established marker of angiogenesis, while also complementing mean arterial pressure (MAP), the strongest current clinical predictor. Collectively, these findings indicate that NAR in early pregnancy - as a highly accessible and integrative biomarker - can reflect early systemic immune dysregulation involved in the pathogenesis of PE.

Our findings are consistent with and expand previous studies investigating inflammation-related indicators and PE. For instance, Caglayan Bicer et al. reported that elevated NAR in early pregnancy is associated with the subsequent development of PE [18]. The novelty of the present study lies in the identification of a nonlinear, threshold-dependent relationship between LN(NAR) and PE risk in early pregnancy. While most earlier studies assumed a linear association between systemic inflammation and PE, our RCS and piecewise regression analyses revealed a distinct inflection point at LN(NAR) = -1.92, beyond which PE risk increased sharply. These results suggest that, in early pregnancy, the body may maintain homeostasis through physiological compensation in response to low-to-moderate inflammatory activity. However, once the inflammation exceeds a critical threshold, endothelial dysfunction and immune imbalance may be triggered, ultimately leading to PE. Importantly, this study is the first large-scale cohort analysis to clearly quantify the strength of the association between elevated LN(NAR) and PE risk after rigorous adjustment for confounding factors such as BMI, conception mode, and multifetal pregnancy. It is well established that both neutrophil activation and hypoalbuminemia are involved in the pathogenesis of PE. Based on these findings, we propose that NAR represents a “double hit” model: on the one hand, it reflects neutrophil-mediated excessive inflammatory reactions; on the other hand, it captures the reduction in antioxidant capacity and impaired endothelial stability resulting from decrease albumin levels. Therefore, compared with single biomarkers, this composite index may more accurately reflect the vulnerable vascular state in early pregnancy.

By directly comparing LN(NAR) with established early pregnancy biomarkers, including PlGF and MAP, we found that the correlation between LN(NAR) and PlGF was weak ($r = 0.05$), despite comparable AUC values. This finding suggests that these markers represent two complementary pathophysiological mechanisms: systemic inflammation and placental dysfunction, respectively. Although MAP remains the single indicator with the highest predictive perfor-

mance, the integration of LN(NAR) can further enhance multimodal prediction models by incorporating inflammatory dimensions not fully captured by current screening approaches. These results highlight the advantages of NAR as a cost-effective and easily obtainable biomarker, particularly suitable for resource-limited settings where advanced angiogenesis testing is not routinely available. From a translational perspective, this study not only identifies a clinically relevant inflammatory threshold but also provides a rationale for incorporating NAR into PE risk stratification strategy, thereby deepening our understanding of disease mechanisms.

The association between elevated NAR and PE is likely mediated by multiple interacting mechanisms [19, 20]. Placental ischemia and syncytiotrophoblast stress in early pregnancy can induce systemic inflammation. Increased levels of cytokines (such as IL-8) and placental microparticles activate maternal neutrophils, promoting oxidative damage and endothelial dysfunction [11, 15]. Neutrophils in patients with PE are prone to activation, releasing elastase and forming neutrophil extracellular traps (NETs), which are abundant in PE placentas and may further impair placental perfusion [10, 21]. Meanwhile, serum albumin, the principal antioxidant protein and a negative acute phase reactant, exhibits reduced synthesis and increased vascular leakage during inflammation, leading to hypoalbuminemia - a phenomenon repeatedly observed in PE. Reduced albumin levels can exacerbate oxidative stress and endothelial injury [13]. Consequently, NAR captures the combined effects of intensified neutrophil-driven inflammation and diminished albumin-mediated vascular protection, enabling identification of high-risk populations characterized by inflammation-nutritional imbalance and heightened susceptibility to endothelial dysfunction in PE [9].

This study has several limitations. First, as a retrospective analysis, data on certain important confounders, including pre-pregnancy diabetes, chronic kidney disease, smoking status, family history of PE, and preventive interventions (such as low-dose aspirin or calcium supplementation), were unavailable, potentially resulting in residual confounding. Second, although women with chronic hypertension were excluded, detailed subgroup analyses of hypertension disorders during pregnancy were not feasible due to incomplete electronic medical records regarding antihypertensive regimens, medication adherence, and longitudinal blood pressure monitoring. Third, the identified threshold requires external validation in independent cohorts, particularly those involving different ethnic backgrounds, healthcare systems, or gestational age windows. Finally, although NAR is inherently cost-effective due to its derivation from routine laboratory tests, a formal health economic evaluation was not performed. Future prospective, multicenter studies incorporating more comprehensive clinical data are warranted to validate the generalizability and clinical applicability of these findings across diverse populations.

In conclusion, this study demonstrates that elevated LN(NAR) in early pregnancy is independently associated with an increased risk of PE, and it exhibits a nonlinear dose-response relationship with a clear threshold effect. The predictive performance of LN(NAR) is comparable to that of PlGF and provides complementary value to MAP, the current strongest clinical predictor. Accordingly, NAR represents a promising, cost-effective complementary biomarker for early PE risk assessment, particularly in resource-limited settings. It may be incorporated into multimodal prediction strategies, especially where widespread PlGF testing is impractical or where enhancement of MAP-based screening is a needed.

Disclosure of conflict of interest

None.

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Table S1. Baseline maternal and pregnancy characteristics in women with and without preeclampsia

Variables	Total (n = 11916)	Non-PE (n = 11430)	PE (n = 486)	Statistic	*P*
Gestational week at testing, M (Q_1, Q_3)	12.43 (11.81, 13.00)	12.43 (11.81, 13.00)	12.29 (11.71, 13.00)	Z = -1.85	0.064
Age (years), M (Q_1, Q_3)	31.00 (28.00, 34.00)	31.00 (28.00, 34.00)	32.00 (29.00, 35.00)	Z = -4.14	< 0.001
BMI (kg/m^2), M (Q_1, Q_3)	21.86 (20.20, 23.86)	21.79 (20.20, 23.73)	24.03 (21.48, 26.56)	Z = -12.83	< 0.001
Gravidity, M (Q_1, Q_3)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	Z = -0.76	0.450
Parity, M (Q_1, Q_3)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	Z = -3.56	< 0.001
IVF conception, n(%)				χ^2 = 155.21	< 0.001
No	10826 (90.85)	10462 (91.53)	364 (74.90)		
Yes	1090 (9.15)	968 (8.47)	122 (25.10)		
Multifetal pregnancy, n(%)				χ^2 = 289.67	< 0.001
No	11737 (98.50)	11303 (98.89)	434 (89.30)		
Yes	179 (1.50)	127 (1.11)	52 (10.70)		
NAR, M (Q_1, Q_3)	0.14 (0.12, 0.17)	0.14 (0.12, 0.17)	0.16 (0.13, 0.19)	Z = -6.74	< 0.001

Z: Mann-Whitney test, χ^2: Chi-square test. M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile. NAR: neutrophil-to-albumin ratio, IVF: in vitro fertilization.

Table S2. Performance of models for predicting preeclampsia

Model	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value	Youden's Index
LN(NAR)	0.591 (0.550-0.633)	-1.837	0.522	0.680	0.674	0.066	0.970	0.203
PlGF	0.605 (0.565-0.644)	0.846	0.650	0.531	0.536	0.057	0.972	0.181
MAP	0.710 (0.675-0.745)	1.063	0.633	0.698	0.695	0.083	0.978	0.331
LN(NAR)-PlGF	0.634 (0.597-0.672)	-2.930	0.478	0.734	0.723	0.072	0.970	0.212
LN(NAR)-MAP	0.720 (0.686-0.755)	-3.081	0.677	0.689	0.689	0.086	0.980	0.366
PlGF-MAP	0.724 (0.690-0.758)	-3.070	0.655	0.691	0.690	0.084	0.979	0.346
LN(NAR)-PlGF-MAP	0.736 (0.702-0.769)	-3.033	0.655	0.709	0.707	0.089	0.979	0.364
Maternal risk factors-LN(NAR)-PlGF-MAP	0.831 (0.804-0.858)	-3.199	0.770	0.744	0.745	0.115	0.987	0.514

NAR: neutrophil-to-albumin ratio, LN[NAR]: log-transformed NAR, PlGF: placental growth factor, MAP: mean arterial pressure, IVF: in vitro fertilization.