



## RESEARCH ARTICLE

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### First-Trimester HALP and PNI Scores in Predicting Preterm Birth

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**Objective:** Preterm birth (PTB) is a major cause of neonatal morbidity and mortality. Reliable early biomarkers for predicting PB are limited. This study aimed to evaluate the effectiveness of first-trimester Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) scores and Prognostic Nutritional Index (PNI) scores in predicting PB.

**Materials and Methods:** This retrospective case-control study was conducted in a tertiary healthcare center from October 2023 to October 2024. Singleton pregnancies with preterm birth and term deliveries were included. Patients had complete blood count and serum albumin tests between 8–14 weeks of gestation, and groups were matched 1:1 for maternal age, gravidity, and parity. HALP and PNI scores were calculated and compared, and their predictive performance for PTB was analyzed.

**Results:** A total of 120 participants (60 PTB, 60 controls) were analyzed. Lymphocyte count and albumin levels were significantly lower, while platelet levels were higher in the PTB group ( $p<0.001$ ). HALP and PNI scores were also significantly lower in the PTB group, with AUC values of 0.786 and 0.761, respectively.

**Conclusion:** First-trimester HALP and PNI scores may be promising biomarkers for predicting preterm birth. The HALP score demonstrated the highest specificity for PB prediction. These findings suggest that non-invasive, cost-effective, and easily accessible biomarkers could aid in early risk assessment. However, prospective, large-scale studies are required to confirm these results.

**Key Words:** Preterm birth, HALP score, Prognostic Nutritional Index (PNI), Inflammation

#### İlk Trimester HALP ve PNI Skorlarının Preterm Doğum Öngörüsündeki Rolü

**Amaç:** Preterm doğum (PD), neonatal morbidite ve mortalitenin önde gelen nedenlerinden biridir. Günümüzde, PD'ü erken dönemde öngörebilecek güvenilir biyobelirteçler sınırlıdır. Bu çalışmada, ilk trimesterde değerlendirilen Hemoglobin, Albumin, Lenfosit ve Trombosit (HALP) skoru ile Prognostik Nutrisyonel İndeks (PNI) skorunun preterm doğum öngörüsündeki etkinliğini araştırmayı amaçladık.

**Gereç ve Yöntem:** Bu retrospektif vaka kontrol çalışması, Ekim 2023–Ekim 2024 tarihleri arasında üçüncü basamak bir sağlık kuruluşunda gerçekleştirildi. Çalışmaya, 8-14. gebelik haftaları arasında tam kan sayımı ve serum albümin testi sonuçları bulunan, tekil gebeliğe sahip preterm doğum yapan hasta ile sağlıklı kontroller dahil edildi. Gruplar anne yaşı, gebelik sayısı ve doğum sayısı açısından 1:1 oranında eşleştirildi. HALP ve PNI skorları hesaplandı ve gruplar arasında karşılaştırıldı. Ayrıca bu skorların preterm doğum öngörüsündeki etkinlikleri değerlendirildi.

**Bulgular:** Çalışmada 60 preterm doğum yapan, 60 sağlıklı gebe olmak üzere toplam 120 katılımcının verileri analiz edildi. Preterm doğum grubunda lenfosit sayısı ve albumin seviyeleri anlamlı şekilde daha düşük, trombosit seviyeleri ise daha yüksek bulundu ( $p<0.001$ ). HALP ve PNI skorları preterm doğum grubunda kontrol grubuna göre anlamlı şekilde daha düşük olup, eğri altında kalan alan (EAA) değerleri sırasıyla 0.786 ve 0.761 idi. Sonuç: Bu çalışma, ilk trimesterde değerlendirilen HALP ve PNI skorlarının preterm doğumu öngörmeye güçlü biyobelirteçler olabileceğini göstermektedir. Özellikle HALP skoru, preterm doğum öngörüsünde en yüksek özgüllüğe sahip parametre olarak dikkat çekmektedir.

**Sonuç:** erken gebelik döneminde preterm doğum riski taşıyan hastaların belirlenmesine yönelik non-invaziv, düşük maliyetli ve kolay erişilebilir biyobelirteçlerin klinik kullanıma kazandırılmasına katkı sağlayabilir. Ancak, bu sonuçların doğrulanması için prospektif ve geniş ölçekli çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Preterm doğum, HALP skoru, Prognostik Nutrisyonel İndeks (PNI), inflamasyon

#### Introduction

Preterm birth (PTB), defined as delivery occurring between 20 and 36+6 weeks of gestation, is a major global health problem and remains a leading cause of neonatal and infant morbidity and mortality (1, 2). PTB can be classified as either iatrogenic or spontaneous, the latter accounts for approximately 5% of all pregnancies worldwide (3).

Preterm birth is associated with a variety of short- and long-term health problems for the newborn (e.g., respiratory distress syndrome, sepsis, necrotizing enterocolitis) and long-term adverse outcomes such as neurodevelopmental disorders and adult metabolic diseases (4, 5). Despite significant advances in neonatal care that have

significantly improved survival rates and neonatal outcomes, prevention and prediction of PTB remain challenging, as many cases occur without identifiable risk factors.

The etiopathogenesis of PTB is multifactorial and not yet fully understood. However, some key factors, such as maternal hormonal disorders, placental insufficiency and abnormalities, cervical insufficiency, and intrauterine inflammation, have been implicated in the pathogenesis (6, 7). However, the fact that a large proportion of preterm births occur without apparent risk factors, making early prediction challenging. In daily practice, various methods are used to predict preterm birth, such as measuring cervical length and determining fetal fibronectin levels in vaginal fluid (8). However, current practice is generally used for high-risk pregnant women or patients with preterm birth symptoms (e.g., painful uterine contractions), with limited utility in low-risk populations.

There is increasing evidence of the role of systemic inflammation in the development of preterm and term births (6, 7, 9). Several inflammatory indices derived from routine blood tests, such as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, have shown potential in predicting PTB, particularly in the second and third trimesters (10, 11). Recently, composite hematological scores combining inflammatory and nutritional markers, such as the HALP score (hemoglobin, albumin, lymphocytes, platelets) and Prognostic Nutritional Index (PNI), have drawn attention. These scores incorporate albumin, a marker associated with both inflammation and nutritional status, and have been linked to adverse obstetric outcomes including fetal growth restriction, preeclampsia, and intrahepatic cholestasis (12–15). Furthermore, Hrubaru et al. indicated that HALP scores during the third trimester may be potential biomarkers for predicting preterm birth (13).

Identifying individuals at risk for PTB during early pregnancy and implementing suitable precautions is essential. Nonetheless, techniques for assessing the risk of PTB throughout this timeframe remain limited in clinical practice. Noninvasive, cost-effective, and easy-to-use methods to predict PTB during the first trimester of pregnancy are necessary. We hypothesize that HALP and PNI levels assessed in the first trimester may be significant indicators for predicting preterm birth. In this context, we aimed to evaluate these two scores in relation to preterm birth.

## Materials and Methods

**Research and Publication Ethics:** This retrospective case-control study was performed at Ankara Etlik City Hospital from October 2023 to October 2024. The Ethics Committee of our Center accepted the study protocol (Protocol No: AEŞH-EK1-2023-615), and the study was conducted in compliance with the universal ethical principles outlined in the Declaration of Helsinki. As this was a retrospective study, informed consent was not necessary. All requisite data were acquired from the hospital's electronic database and

patient records. Patient confidentiality was preserved, and all data were anonymized before analysis.

The preterm birth group consisted of pregnant women aged 18 to 40 years with singleton pregnancies who experienced spontaneous preterm birth before 37 weeks of gestation and delivered at our hospital between October 2023 and October 2024. The control group consisted of women who delivered at term ( $\geq 37$  weeks) during the same period and had no history of preterm birth. To minimize potential confounding effects, the control group was matched with the preterm birth group at a 1:1 ratio using a matched-pairs methodology based on maternal age and gravidity. Only women who had undergone a complete blood count and albumin test during the first trimester (8–14 weeks of gestation) were included in the study. The exclusion criteria were women with a history of previous preterm birth, multiple pregnancies, or pregnancies complicated by congenital fetal anomalies. Pregnancies identified as high risk based on first- or second-trimester serum screening tests, those with structural anomalies detected during second-trimester ultrasound screening, and those diagnosed with fetal or neonatal chromosomal or structural anomalies during prenatal follow-up or after birth were excluded. Additionally, women with preterm premature rupture of membranes (PPROM), maternal systemic diseases (e.g., pregestational diabetes mellitus, chronic hypertension), or obstetric complications (e.g., gestational diabetes, gestational hypertension, preeclampsia) were not included in the study. Pregnant women with a history of smoking, alcohol, or illicit drug use were excluded. Furthermore, those who did not give birth at our hospital, and pregnancies that resulted in iatrogenic preterm birth due to obstetric indications, were also excluded from the analysis.

Maternal age, gravidity, parity, body mass index (BMI), neonatal outcomes such as birth weight, gestational age at birth, first and fifth-minute Apgar scores, and neonatal intensive care unit (NICU) admission were extracted from the electronic medical records. First-trimester laboratory parameters included hemoglobin (g/dL), neutrophil count ( $10^9/L$ ), lymphocyte count ( $10^9/L$ ), platelet count ( $10^9/L$ ), and albumin (g/L). HALP and PNI scores were calculated as follows:

HALP score:  $\text{hemoglobin (g/dL)} \times \text{lymphocyte count (} 10^9/L \text{)} \times \text{albumin (g/L)} / \text{Platelet (} 10^9/L \text{)}$

Prognostic Nutritional Index (PNI):  $10 \times \text{serum albumin [g/dL]} + (0.005 \times \text{lymphocytes}/\mu\text{L})$ .

Cases with missing first-trimester laboratory values were not included in the final cohort.

The primary outcome was the ability of first-trimester HALP and PNI scores to predict preterm birth. The dependent variable was preterm birth ( $< 37$  weeks). Independent variables included first-trimester HALP and PNI scores.

A priori power analysis was conducted to determine the required sample size for this study. Since

no prior studies have examined first-trimester HALP scores in relation to preterm birth, the sample size calculation was based on an effect size of 0.52. Using GPower 3.1.9.7 software, with an alpha error probability of 0.05 and a power of 0.80, it was calculated that 120 participants (60 preterm birth cases and 60 control cases) would be needed to achieve sufficient statistical power.

Statistical analyses were performed using the IBM SPSS Statistics 27.0 package program. Descriptive statistics and frequency tables were used for data analysis. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the continuous variables follow a normal distribution. To compare measured values between two independent groups, the Student t-test was applied if the data conformed to a normal distribution, with the results expressed as mean $\pm$ SD. The Mann-Whitney U test (Z-table value) was used for non-normally distributed data, and results were expressed as median (25th-75th percentile). The relationships between the qualitative variables were analyzed using Pearson's  $\chi^2$  test. Spearman correlation coefficients were calculated to assess relationships between binary categorical and continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive power of lymphocyte, platelet, albumin, HALP and PNI scores for preterm birth (PB). The optimal cut-off values for each parameter were determined based on the highest Youden index (calculated as sensitivity plus specificity minus one) to maximize the discriminatory power of the test. Statistical significance was defined as a  $p$ -value $<$ 0.05.

## Results

A comparison of demographic, clinical, laboratory, and neonatal parameters was presented in Table 1.

There were no significant differences between groups regarding maternal age, gravidity, parity, hemoglobin levels, and neutrophil count ( $p>0.05$ ). The lymphocyte count and albumin levels were significantly lower in the preterm birth group than in the control group. The mean HALP Score in the Preterm Birth group was  $3.577\pm1.580$ , which was lower than in the control ( $5.467\pm2.012$ ) ( $p<0.001$ ). Similarly, the PNI scores of the preterm birth group were also lower than those in the control group ( $p<0.001$ ). The gestational age at birth, birth weight, and Apgar scores at the first and fifth minutes were significantly lower in the preterm birth group than in the control group ( $p<0.001$  for all of them). NICU admission rate was higher in the preterm birth group than in the control group ( $p<0.001$ ).

The correlation analysis between hematological parameters and preterm birth was shown in Table 2. Lymphocyte count ( $r=0.324$ ,  $p<0.001$ ), albumin levels ( $r=-0.379$ ,  $p<0.001$ ), HALP score ( $r=-0.496$ ,  $p<0.001$ ), and PNI ( $r=-0.452$ ,  $p<0.001$ ) were moderately negatively correlated with preterm birth. In contrast, platelet count showed a moderate positive correlation ( $r=0.456$ ,  $p<0.001$ ).

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of hematological parameters for preterm birth (Table 3). Among the evaluated markers, the HALP score demonstrated the highest discriminatory ability, with an AUC of 0.786 (95% CI: 0.702–0.856), a sensitivity of 63.3%, and a specificity of 83.3% at a cut-off value of  $\leq 3.745$  ( $p<0.001$ ). PNI also showed significant predictive performance (AUC=0.761, 95% CI: 0.674–0.834), with a sensitivity of 68.3% and a specificity of 81.7% at a cut-off value of  $\leq 52.15$  ( $p<0.001$ ). Similarly, platelet count (AUC=0.763, 95% CI: 0.677–0.836) and albumin levels (AUC=0.719, 95% CI: 0.629–0.797) exhibited moderate predictive accuracy (Figure 1).

**Table 1.** Comparison of Maternal, Hematological, and Neonatal Parameters Between Preterm Birth and Control Groups

| Variables                               | Preterm Birth Group<br>n=60 | Control Group<br>n=60  | p-Value                         |
|-----------------------------------------|-----------------------------|------------------------|---------------------------------|
| Maternal age (years)                    | 26 (23-29)                  | 26 (24-28)             | 0.611 <sup>a</sup>              |
| Gravidity (n)                           | 2 (1-2)                     | 2 (2-3)                | 0.188 <sup>a</sup>              |
| Parity (n)                              | 1 (0-1)                     | 1 (1-2)                | 0.188 <sup>a</sup>              |
| Hemoglobin (g/dL)                       | 12.6 (11.3-13.4)            | 12.6 (11.7-13.4)       | 0.767 <sup>a</sup>              |
| Neutrophil count ( $10^3/\mu\text{L}$ ) | $6.45\pm1.95$               | $5.87\pm1.64$          | 0.082 <sup>a</sup>              |
| Lymphocyte count ( $10^3/\mu\text{L}$ ) | $1.89\pm0.70$               | $2.30\pm0.62$          | <b><math>&lt;0.001^b</math></b> |
| Platelet ( $10^3/\mu\text{L}$ )         | $278\pm33$                  | $239\pm40$             | <b><math>&lt;0.001^b</math></b> |
| Albumin (g/L)                           | $42.1\pm2.6$                | $44.2\pm2.8$           | <b><math>&lt;0.001^b</math></b> |
| HALP score                              | $3.577\pm1.580$             | $5.467\pm2.012$        | <b><math>&lt;0.001^b</math></b> |
| PNI                                     | 51.050 (48.675-53.675)      | 55.375 (53.025-58.425) | <b><math>&lt;0.001^a</math></b> |
| GA at Birth (weeks)                     | 35 (34-36)                  | 39 (38-39)             | <b><math>&lt;0.001^a</math></b> |
| Birth weight (g)                        | 2500 (2145-2755)            | 3175 (2965-3450)       | <b><math>&lt;0.001^a</math></b> |
| Apgar score at 1 <sup>st</sup> minute   | 9 (8-9)                     | 9 (9-9)                | <b><math>&lt;0.001^a</math></b> |
| Apgar score at 5 <sup>th</sup> minute   | 10 (9-10)                   | 10 (10-10)             | <b><math>&lt;0.001^a</math></b> |
| NICU admission (n, %)                   | 15 (25.0%)                  | -                      | <b><math>&lt;0.001^c</math></b> |

<sup>a</sup> The differences between groups were analyzed using the Student's t-test

<sup>b</sup> The differences between groups were analyzed using the Mann-Whitney U test

<sup>c</sup> The association between the two categorical variables was analyzed using the Pearson chi-square test

Abbreviations: HALP Score, Hemoglobin, Albumin, Lymphocyte, and Platelet Score; PNI, Prognostic Nutritional Index; GA, Gestational age; NICU, Neonatal intensive care unit

**Table 2.** Correlation analysis between Hematological Parameters and Preterm Birth

| Variables                              | Preterm Birth |                      |
|----------------------------------------|---------------|----------------------|
|                                        | r             | p-Value <sup>a</sup> |
| Lymphocyte count (10 <sup>3</sup> /μL) | -0.324        | <0.001 <sup>a</sup>  |
| Platelet (10 <sup>3</sup> /μL)         | 0.456         | <0.001 <sup>a</sup>  |
| Albumin (g/L)                          | -0.379        | <0.001 <sup>a</sup>  |
| HALP Score                             | -0.496        | <0.001 <sup>a</sup>  |
| PNI                                    | -0.452        | <0.001 <sup>a</sup>  |

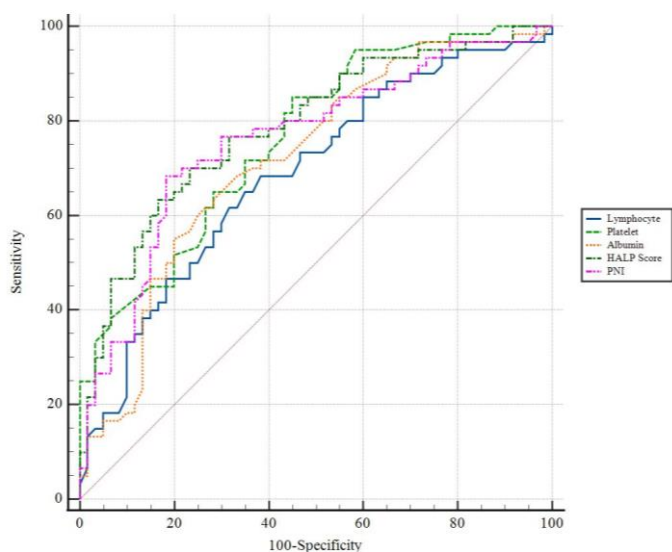
<sup>a</sup>Correlation analysis was performed using Spearman's rank correlation test

Abbreviations: HALP Score, Hemoglobin, Albumin, Lymphocyte, and Platelet Score; PNI, Prognostic Nutritional Index

**Table 3.** Diagnostic Performance of Hematological Parameters in Predicting Preterm Birth (ROC Analysis)

| Variables                              | Cut-off | AUC   | 95% CI      | Sensitivity (%) | Specificity (%) | +LR  | -LR  | p-value |
|----------------------------------------|---------|-------|-------------|-----------------|-----------------|------|------|---------|
| Lymphocyte count (10 <sup>3</sup> /μl) | ≤2.03   | 0.687 | 0.596-0.768 | 61.7            | 68.3            | 1.95 | 0.56 | <0.001  |
| Platelet (10 <sup>3</sup> /μl)         | >247    | 0.763 | 0.677-0.836 | 85.0            | 55.0            | 1.89 | 0.7  | <0.001  |
| Albumin (g/L)                          | ≤41.9   | 0.719 | 0.629-0.797 | 55.0            | 80.0            | 2.75 | 0.56 | <0.001  |
| HALP score                             | ≤3.745  | 0.786 | 0.702-0.856 | 63.3            | 83.3            | 3.80 | 0.44 | <0.001  |
| PNI                                    | ≤52.15  | 0.761 | 0.674-0.834 | 68.3            | 81.7            | 3.73 | 0.39 | <0.001  |

Abbreviations: ROC, Receiver operative characteristics; AUC, Area Under the Curve; CI, Confidence interval; LR, Likelihood Ratio; HALP Score, Hemoglobin, Albumin, Lymphocyte, and Platelet Score; PNI, Prognostic Nutritional Index.

**Figure 1** Receiver Operating Characteristic (ROC) curve analysis of lymphocyte, platelet, albumin, HALP Score, and PNI in predicting preterm birth

## Discussion

PTB is the predominant cause of newborn mortality, responsible for roughly 35-40% of neonatal fatalities (4). Despite medical advancements, PTB remains inadequately predictable and preventable. Early prediction of preterm birth facilitates the identification of high-risk pregnancies and the prompt management of suitable follow-up and interventions. Nonetheless, despite the development of many methodologies to

predict PTB, reliable predictive models have not been established for low-risk individuals. Consequently, discovering easily accessible, economical, and highly diagnostic biomarkers is crucial for therapeutic care. Our results indicate that the first-trimester HALP and PNI scores of patients who experienced preterm birth were considerably lower than those of patients who delivered at term. Furthermore, HALP and PNI scores were identified as effective predictors of preterm birth, with AUCs of 0.786 and 0.761 in ROC analysis.

Inflammation serves as a trigger in preterm birth, both in the onset of preterm labor and concerning complications such as placental malfunction and early rupture of membranes (7, 9). The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is a composite biomarker indicative of systemic inflammation and nutritional status. It has been examined in numerous obstetric conditions recently (12–15). Sert et al. demonstrated a substantial association between the HALP score and severe preeclampsia (15). They indicated that this marker could be beneficial in forecasting the severity of preeclampsia. Bayram et al. proposed that HALP scores may function as significant and objective biomarkers for predicting the occurrence and severity of hyperemesis gravidarum (12). In a different study, Seyhanlı et al. highlighted that patients with late-onset FGR (LO-FGR) had a considerably lower HALP score in the first trimester and that this parameter can be used to predict the risk of FGR (14).

Given the role of inflammation and infectious processes in the development of preterm birth, the relationship between the HALP score and preterm birth is a clinically important area to investigate. The first study on this topic was conducted by Hrubaru et al., who

found lower HALP scores in PTB patients in the third trimester (13). In addition, regression analyses showed that this marker has the greatest predictive power for PTB, with an odds ratio (OR) of 6.09. These data are promising in that the HALP score could serve as a strong biomarker for predicting the risk of preterm birth. In our study, we extended these findings, examined the HALP scores of PTB patients in the first trimester, and found that this score was even lower in the first trimester. Inadequate placentation in early pregnancy, imbalances in immunological adaptation, and activation of inflammatory processes may lower HALP scores. Therefore, evaluating the HALP score in the first trimester can help to identify patients at risk of preterm birth and provide the necessary therapeutic care without delay.

The Prognostic Nutritional Index (PNI) is a biomarker for nutritional state and immune system functionality, calculated from the lymphocyte count and serum albumin concentration. PNI was initially employed to evaluate the prognosis of malignant conditions (16,17). It was later investigated as a prognostic marker for cardiovascular diseases, chronic inflammation, and post-operative recovery (18,19). Since inflammation and nutritional status are crucial factors affecting maternal and fetal health during pregnancy, this value has potential for obstetrics. Wei et al. (20) pointed out that increased PNI levels in pre-eclampsia patients correlate with a lower risk of adverse events. At the same time, Seyhanlı et al. (14) found that PNI levels in the first trimester were significantly lower in patients with LO-FGR, where inflammation and nutritional status were important factors, compared to the control group. They emphasized that the determination of PNI in the first trimester could serve as a valuable biomarker for the identification of high-risk pregnancies with fetal growth restriction. Since PNI is closely related to inflammation

and nutritional status, poor PNI values in the first trimester could be a significant predictor of the risk of preterm birth later in pregnancy. Our study found that preterm birth, similar to fetal growth restriction (FGR), is closely related to inflammation and nutritional status, as shown by significantly lower PNI scores in the first trimester in patients with preterm birth. The results of our study suggest that HALP and PNI scores may predict preterm birth.

One of the strengths of this study is that it is the first to examine HALP and PNI scores during the first trimester as predictors of preterm birth. In addition, the influence of potential confounders was mitigated by adjusting the patient cohorts for significant variables such as maternal age and parity. In addition, patients with a history of preterm birth and those who smoked or used drugs were excluded from the study, ensuring that the survey reflected a population at low risk of preterm birth. However, our study has some limitations. The retrospective methodology and the fact that the study was conducted at a single center may limit the generalizability of the results. Another drawback is that the HALP and PNI measurements were performed at a single time point in the first trimester; tracking the changes in these parameters during pregnancy could improve the understanding of the mechanisms underlying preterm birth.

In summary, the HALP and PNI scores in the first trimester are strong biomarkers for predicting preterm birth. In particular, the HALP score is the parameter with the highest specificity in predicting preterm birth. Our results may contribute to the use of easily accessible, inexpensive, and non-invasive biomarkers in the clinic to identify patients at risk of preterm birth already in early pregnancy and to take the necessary precautions. However, prospective studies with a larger patient population are needed to confirm these results.

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