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# Can maternal inflammatory and nutritional status, evaluated by the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and the prognostic nutritional index (PNI) in the first trimester, predict late-onset fetal growth restriction?

Zeynep Seyhanli<sup>1\*</sup> , Burak Bayraktar<sup>1\*</sup> , Gulsan Karabay<sup>1</sup> , Ahmet Arif Filiz<sup>1</sup> , Mevlut Bucak<sup>1</sup> , Recep Taha Agaoglu<sup>1</sup> , Can Ozan Ulusoy<sup>1</sup> , Tugba Kolomuc<sup>2</sup> , Kadriye Yakut Yucel<sup>1</sup>  and Zehra Vural Yilmaz<sup>1</sup> 

## Abstract

**Objective** The aim of this study was to evaluate the potential of immunonutritional markers, specifically the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and the prognostic nutritional index (PNI), in predicting late-onset fetal growth restriction (LO-FGR) during the first trimester.

**Materials and methods** This retrospective study was conducted at a tertiary care center between October 2022 and August 2023. The study included a total of 213 singleton pregnancies, with 99 women in the LO-FGR group and 114 in the healthy control group, matched by maternal age and gestational age at delivery. All blood samples were collected between 11 and 14 weeks of gestation (during the first-trimester screening test). We analyzed first-trimester laboratory parameters, specifically focusing on hemoglobin levels, white blood cells (WBCs), lymphocytes, platelets, and albumin levels. Afterwards, we calculated the HALP score and PNI, and then compared the values of both groups.

**Results** Both HALP score ( $3.58 \pm 1.31$  vs.  $4.19 \pm 1.8$ ,  $p = 0.012$ ) and PNI ( $36.75 \pm 2.9$  vs.  $39.37 \pm 3.96$ ,  $p < 0.001$ ) were significantly lower in the FGR group than in the control group. The HALP score cut-off value of  $< 3.43$  in predicting FGR had a sensitivity of 62.3% and specificity of 54.5% (AUC = 0.600, 95% CI: 0.528–0.672,  $p = 0.012$ ). The PNI cut-off value of  $< 37.9$  in predicting FGR had a sensitivity of 65.8% and specificity of 62.9% (AUC = 0.707, 95% CI: 0.632–0.778,  $p < 0.001$ ). While the HALP score was not a significant predictor of composite adverse neonatal outcomes in the FGR group, PNI showed a cut-off value of  $< 37.7$  with a sensitivity of 60.9% and specificity of 59.7% (AUC = 0.657, 95% CI: 0.581–0.733,  $p < 0.001$ ).

\*Correspondence:

Zeynep Seyhanli  
drzeynepseyhanli@gmail.com  
Burak Bayraktar  
drburakbayraktar@gmail.com

Full list of author information is available at the end of the article



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**Conclusion** The HALP score and PNI are valuable prognostic tools for predicting the risk of FGR in the first trimester. Low PNI values are also associated with composite adverse neonatal outcomes in pregnancies complicated by FGR.

**Keywords** Fetal growth restriction, HALP score, Prognostic nutritional index, Albumin, Immunonutritional markers

## Introduction

Fetal growth restriction (FGR) is a multifactorial condition in which the fetus is unable to reach the estimated weight corresponding to the week of gestation [1]. Diagnosis of FGR is a critical aspect of prenatal care, because FGR significantly increases perinatal morbidity and mortality [2]. This condition, one of the most common causes of adverse perinatal outcomes, affects approximately 5–10% of all pregnancies [3]. Although the etio-pathogenesis of FGR is not fully understood, it is believed to involve multiple factors, which can be categorized as maternal, fetal, and placental. The primary cause of FGR is often placental insufficiency, which impairs the transport of essential nutrients and oxygen necessary for normal fetal development [4]. Several guidelines have been issued for the diagnosis of FGR, however, there is no consensus on universally accepted criteria. According to the Delphi consensus published in 2016 to define, classify and diagnose FGR, the 32nd week of gestation was determined as the cut-off point in the classification of early-onset FGR (EO-FGR) and late-onset FGR (LO-FGR) which exhibit different pathophysiological behaviors [5]. Although FGR is one of the most critical obstetric conditions, its prediction remains challenging, with current prediction rates still remarkably low [6].

FGR has increasingly been associated with maternal inflammatory processes, underscoring the critical role of inflammation in its pathogenesis. Extensive research has already explored the contribution of inflammation to FGR, examining various hematological parameters that reflect inflammatory status. Among these, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) have been particularly highlighted in previous studies [7–10]. The relationship between maternal nutrition status and FGR is also a critical area of research as adequate maternal nutrition is important for optimal fetal development. Maternal nutrition has previously been investigated in FGR cases with parameters such as body mass index (BMI) and mid-upper arm circumference [11, 12]. In recent years, new indicators reflecting both maternal inflammation and maternal nutritional status have emerged, but these indicators are relatively new and have not yet been investigated in FGR cases. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is one such indicator, increasingly used to assess systemic inflammation and nutritional status in various neoplasias [13–15].

However, the HALP score has been the subject of only a limited number of studies in obstetrics [16, 17]. Similarly, the prognostic nutritional index (PNI), which reflects immunonutritional status, has proven to be an important marker in cancer patients [18, 19]. However, its application in obstetrics has been explored in only a limited number of studies [20–22].

Research focused on using first-trimester laboratory exams to predict various obstetric complications is rapidly advancing and holds significant clinical implications. The HALP score and PNI are valuable markers that reflect both the inflammatory and nutritional status at the same time, but have not been investigated in FGR patients before. To our knowledge, this is the first study to investigate the predictive value of the HALP score and PNI in patients with FGR. Additionally, these markers have been examined in relation to predicting composite adverse neonatal outcomes. Our aim is to evaluate the HALP score and PNI during the first trimester as potential predictors of LO-FGR and composite adverse neonatal outcomes in these cases.

## Materials and methods

This retrospective study was conducted in the Department of Perinatology at Ankara Etlik City Hospital, a tertiary care center, between October 2022 and August 2023. The study adhered to the principles outlined in the Declaration of Helsinki, with ethical approval granted by the Ankara Etlik City Hospital Ethics Committee (approval number: AESH- EK1-2023-618). In this study, due to its retrospective nature, informed consent was waived with the approval of the Ethics Committee of Ankara Etlik City Hospital.

The study included a total of 213 singleton pregnancies, with 99 women in the LO-FGR group and 114 in the healthy control group, matched by maternal age and gestational age at delivery. Only pregnant women who had completed all their antenatal examinations and delivered at the hospital were included in the study. The diagnosis of FGR was based on the criteria established by the Delphi consensus, as recommended by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [5]. The assessment of FGR was conducted using the Delphi consensus criteria during ultrasonography performed  $\geq 32$  weeks of gestation. Late-onset FGR was diagnosed after 32 weeks of gestation if (1) the abdominal circumference (AC) or estimated fetal weight (EFW) was below the 3rd percentile, or if at least two of the following criteria were met: (2) AC or EFW below the

10th percentile, (3) AC or EFW crossing two quartiles, or (4) abnormal Doppler findings, such as a umbilical artery Doppler pulsatility index above the 95th percentile or a cerebro-placental ratio below the 5th percentile [5]. Patient data were extracted from medical records and the hospital information management system.

Exclusion criteria included fetal malformations or chromosomal anomalies, preterm premature rupture of membranes, acute or chronic inflammatory conditions, maternal comorbidities, and multiple pregnancies. Additionally, patients taking anti-inflammatory or cortisone-containing medications were also excluded.

All blood samples were collected between 11 and 14 weeks of gestation (during the first-trimester screening test). We analyzed first-trimester laboratory parameters, specifically focusing on hemoglobin levels, white blood cells (WBCs), lymphocytes, platelets, and albumin levels. Afterwards, we calculated the HALP score and PNI, and then compared the values of both groups. The HALP score was calculated using the following formula: Hemoglobin (g/l)  $\times$  albumin (g/l)  $\times$  lymphocyte count (/l) / platelet count (/l) [15]. The formula for calculating the PNI score was as follows:  $10 \times$  albumin (g/dl)  $+ 0.005 \times$  total lymphocyte count ( $\text{mm}^3$ ) [23, 24].

### Statistical analysis

The statistical analysis was conducted using IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess adherence to a normal distribution. Descriptive statistics of continuous variables are presented as “mean  $\pm$  standard deviation” for variables with normal distribution and “median (min-max value)” for variables

with non-normal distribution. The Chi-squared test or Fisher’s exact test was used to compare categorical variables. The Independent Sample t-test was used to compare continuous variables that were normally distributed, while the Mann-Whitney U test was used to compare continuous variables that were not normally distributed. The Receiver Operator Characteristic (ROC) curve was utilized to compute and compare the areas under the curve (AUC) in order to establish the optimal cut-off values. A *P*-value of less than 0.05 was used to establish statistical significance for all tests.

### Results

Among the 213 participants in the study, 114 (53.5%) were part of the control group, while 99 (46.5%) were in the FGR group. The descriptive and comparative analysis of demographic and laboratory data are shown in Table 1. No significant difference was found between the control group and the FGR group in terms of maternal age, BMI, gravidity, and parity ( $p > 0.05$ , for all). However, hemoglobin level, WBC count, neutrophil count, monocyte count, platelet count, and albumin level were significantly different between the groups. Hemoglobin level, platelet count, and albumin level were significantly lower in the FGR group ( $p < 0.05$ , for all). WBC count, neutrophil count, and monocyte count were significantly higher in the FGR group ( $p > 0.05$ , for all). No significant difference was detected in lymphocyte count. Both HALP score ( $3.58 \pm 1.31$  vs.  $4.19 \pm 1.8$ ,  $p = 0.012$ ) and PNI ( $36.75 \pm 2.9$  vs.  $39.37 \pm 3.96$ ,  $p < 0.001$ ) were significantly lower in the FGR group than in the control group. (Table 1).

The comparison of birth and newborn characteristics are shown in Table 2. There was no significant differences

**Table 1** Descriptive and comparative analysis of demographic and laboratory data

|                                                   | Control Group<br><i>n</i> = 114 (53.5%) | FGR<br><i>n</i> = 99 (46.5%) | <i>P</i> -value |
|---------------------------------------------------|-----------------------------------------|------------------------------|-----------------|
| Age (year)                                        | 27.6 $\pm$ 5                            | 26.4 $\pm$ 5.4               | 0.184           |
| BMI at first trimester ( $\text{kg}/\text{m}^2$ ) | 29.2 $\pm$ 4.8                          | 27.8 $\pm$ 6.6               | 0.088           |
| Gravidity                                         | 2 (1–6)                                 | 1 (1–6)                      | 0.066           |
| Parity                                            | 1 (0–4)                                 | 0 (0–4)                      | 0.002           |
| In vitro fertilization                            | 4 (3.5%)                                | 1 (1%)                       | 0.375           |
| Smoking                                           | 6 (5.3%)                                | 10 (10.1%)                   | 0.182           |
| Diagnosis week (week)                             | -                                       | 35 (32–39)                   | N/A             |
| Hemoglobin (g/dl)                                 | 12.7 $\pm$ 0.9                          | 11.8 $\pm$ 1.3               | < 0.001         |
| WBC count ( $10^9/\text{l}$ )                     | 9 $\pm$ 2.2                             | 10.6 $\pm$ 3.1               | < 0.001         |
| Neutrophil count ( $10^9/\text{l}$ )              | 6.3 $\pm$ 2                             | 8 $\pm$ 2.8                  | < 0.001         |
| Lymphocyte count ( $10^9/\text{l}$ )              | 2 $\pm$ 0.7                             | 1.8 $\pm$ 0.6                | 0.069           |
| Monocyte count ( $10^9/\text{l}$ )                | 0.5 $\pm$ 0.1                           | 0.6 $\pm$ 0.2                | < 0.001         |
| Platelet count ( $10^9/\text{l}$ )                | 258.8 $\pm$ 63.5                        | 237 $\pm$ 63.5               | 0.022           |
| Albumin (g/dl)                                    | 39.3 $\pm$ 3.9                          | 36.6 $\pm$ 2.9               | < 0.001         |
| HALP score                                        | 4.19 $\pm$ 1.8                          | 3.58 $\pm$ 1.31              | 0.012           |
| PNI                                               | 39.37 $\pm$ 3.96                        | 36.75 $\pm$ 2.9              | < 0.001         |

FGR: Fetal growth restriction, BMI: Body mass index, WBC: White blood cell, HALP score: Hemoglobin, albumin, lymphocyte, and platelet score, PNI: Prognostic nutritional index

**Table 2** Comparison of birth and newborn characteristics

|                                        | Control Group<br>n = 114 (53.5%) | FGR<br>n = 99 (46.5%) | P-value |
|----------------------------------------|----------------------------------|-----------------------|---------|
| Gestational age at delivery (week)     | 37 (34–39)                       | 37 (33–39)            | 0.415   |
| Preterm birth (<37 week)               | 8 (7%)                           | 11 (11.1%)            | 0.340   |
| Birth type                             |                                  |                       | 0.628   |
| Vaginal delivery                       | 66 (57.9%)                       | 54 (54.5%)            |         |
| Cesarean section                       | 48 (42.1%)                       | 45 (45.5%)            |         |
| Neonatal gender                        |                                  |                       | 0.137   |
| Female                                 | 54 (47.4%)                       | 57 (57.6%)            |         |
| Male                                   | 60 (52.6%)                       | 42 (42.4%)            |         |
| Birth weight (gram)                    | 3236.5 ± 433.9                   | 2366.6 ± 347.3        | < 0.001 |
| APGAR score at 1st minute              | 9 (6–9)                          | 9 (4–9)               | < 0.001 |
| APGAR score at 5th minute              | 10 (8–10)                        | 10 (6–10)             | < 0.001 |
| APGAR score at 5th minute < 7          | 0 (0%)                           | 3 (3%)                | < 0.001 |
| RDS                                    | 2 (1.8%)                         | 7 (7.1%)              | 0.084   |
| NICU admission                         | 1 (0.9%)                         | 23 (23.2%)            | < 0.001 |
| Composite adverse neonatal outcomes ** | 8 (7%)                           | 33 (33%)              | < 0.001 |
| Perinatal mortality                    | 0                                | 1 (1%)                | N/A     |

FGR: Fetal growth restriction, RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit

\*\* The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: Preterm birth, APGAR score at 5th minute < 7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU)

**Table 3** Evaluation of HALP score and PNI in predicting fetal growth restriction using ROC analysis

|            | LR+  | LR-  | Cut-off* | Sensitivity | Specificity | AUC   | 95% CI      | P-value |
|------------|------|------|----------|-------------|-------------|-------|-------------|---------|
| HALP score | 1.37 | 0.27 | < 3.43   | 62.3%       | 54.5%       | 0.600 | 0.528–0.672 | 0.012   |
| PNI        | 1.76 | 0.19 | < 37.9   | 65.8%       | 62.9%       | 0.707 | 0.632–0.778 | < 0.001 |

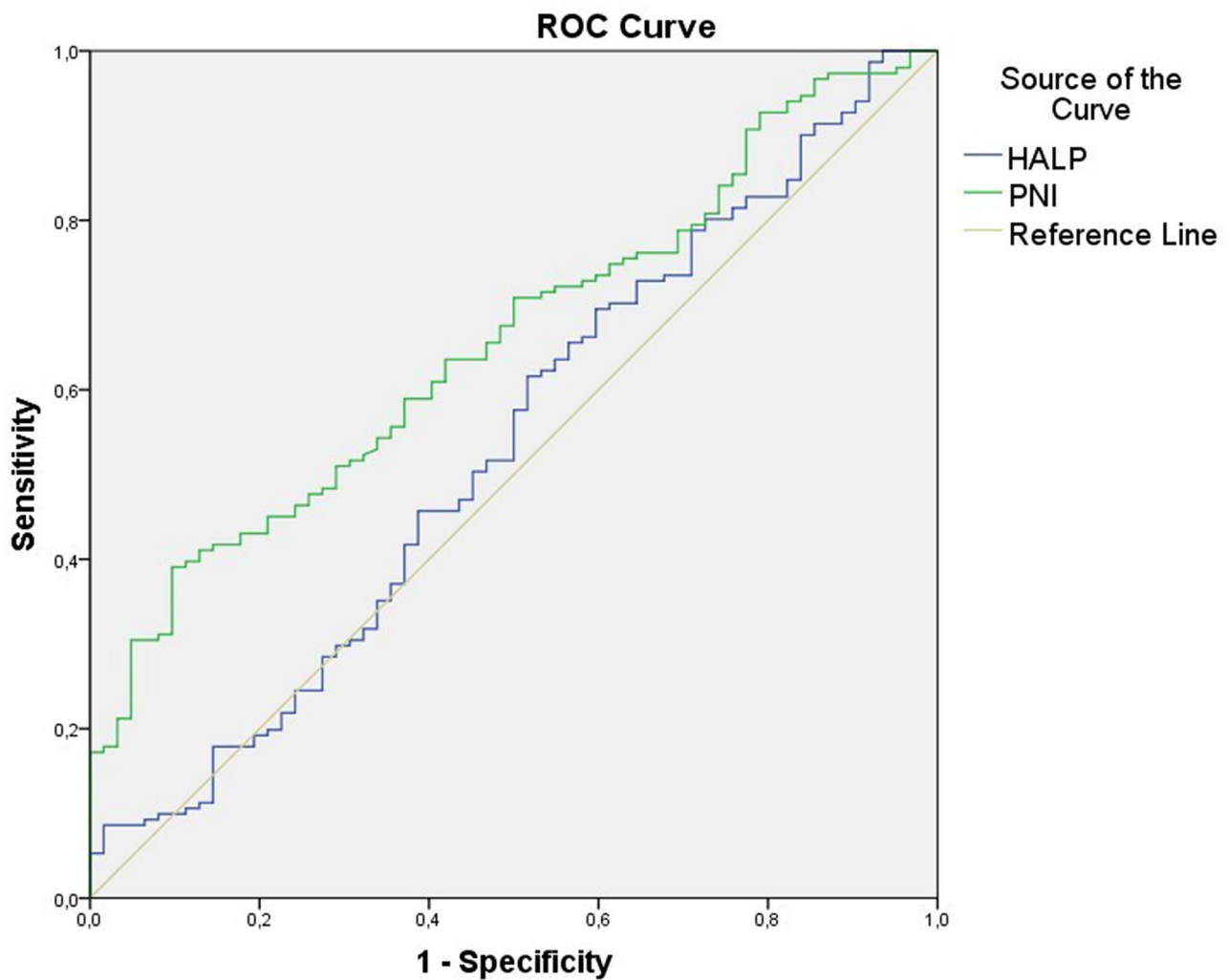
\*Cut-off values were found according to Youden index. LR: Likelihood ratio, AUC: Area under the curve, CI: Confidence interval, HALP score: Hemoglobin, albumin, lymphocyte, and platelet score, PNI: Prognostic nutritional index

in gestational age at delivery or the incidence of preterm birth (<37 week) between the two groups ( $p > 0.05$  for both). Similarly, mode of delivery and neonatal gender distribution did not differ significantly between the groups ( $p > 0.05$ , for both). The FGR group had a significantly lower mean birth weight compared to the control group ( $2366.6 \pm 347.3$  g vs.  $3236.5 \pm 433.9$  g,  $p < 0.001$ ). APGAR scores at both the 1st and 5th minutes were significantly lower in the FGR group ( $p < 0.05$ , for both). Specifically, 3% of neonates in the FGR group had an APGAR score below 7 at the 5th minute, while none in the control group had a score below 7 ( $p < 0.001$ ). Although rates of RDS were similar between the groups, NICU admission was markedly more frequent in the FGR group (23.2%) compared to the control group (0.9%) ( $p < 0.001$ ). The composite adverse neonatal outcome, defined as the presence of at least one adverse event such as preterm birth, APGAR score at 5th minute < 7, RDS, and NICU admission, was significantly higher in the FGR group (33%) compared to the control group (7%) ( $p < 0.001$ ). There was one reported case of perinatal mortality in the FGR group, with no cases in the control group. (Table 2).

Table 3 presents the evaluation of the HALP score and PNI in predicting fetal growth restriction FGR using ROC analysis. The HALP score, with a cut-off value

of < 3.43 as determined by the Youden index, showed a sensitivity of 62.3% and a specificity of 54.5%. The likelihood ratios (LRs) for positive and negative results were 1.37 and 0.27, respectively. The AUC for the HALP score was 0.600, with a 95% confidence interval (CI) of 0.528 to 0.672, and the  $P$ -value was 0.012, indicating statistical significance. For the PNI, a cut-off value of < 37.9 was identified, with a sensitivity of 65.8% and a specificity of 62.9%. The positive and negative LR were 1.76 and 0.19, respectively. The AUC for PNI was higher at 0.707, with a 95% CI of 0.632 to 0.778, and the  $P$ -value was < 0.001, indicating a strong predictive value. (Table 3; Fig. 1).

Table 4 presents the evaluation of the HALP score and PNI in predicting composite adverse neonatal outcomes using ROC analysis in fetal growth restriction group. The HALP score was not a statistically significant predictor of composite adverse neonatal outcomes in the FGR group. In contrast, the PNI showed a cut-off value of < 37.7, with a sensitivity of 60.9% and a specificity of 59.7%. The positive and negative LR were 1.51 and 0.65, respectively. The AUC for PNI was 0.657, with a 95% CI of 0.581 to 0.733, and the  $P$ -value was < 0.001, suggesting that the PNI has a statistically significant ability to predict composite adverse neonatal outcomes in the FGR group. (Table 4; Fig. 2).



Diagonal segments are produced by ties.

**Fig. 1** Evaluation of HALP score and PNI in predicting fetal growth restriction using ROC analysis

**Table 4** Evaluation of HALP score and PNI in predicting composite adverse neonatal outcomes\*\* using ROC analysis in fetal growth restriction group

|            | LR+  | LR-  | Cut-off* | Sensitivity | Specificity | AUC   | 95% CI      | P-value |
|------------|------|------|----------|-------------|-------------|-------|-------------|---------|
| HALP score | 1.13 | 0.84 | < 3.39   | 57.6%       | 50%         | 0.534 | 0.442–0.622 | 0.439   |
| PNI        | 1.51 | 0.65 | < 37.7   | 60.9%       | 59.7%       | 0.657 | 0.581–0.733 | < 0.001 |

\*Cut-off values were found according to Youden index. LR: Likelihood ratio, AUC: Area under the curve, CI: Confidence interval, HALP Score: Hemoglobin, albumin, lymphocyte, and platelet score, PNI: Prognostic nutritional index

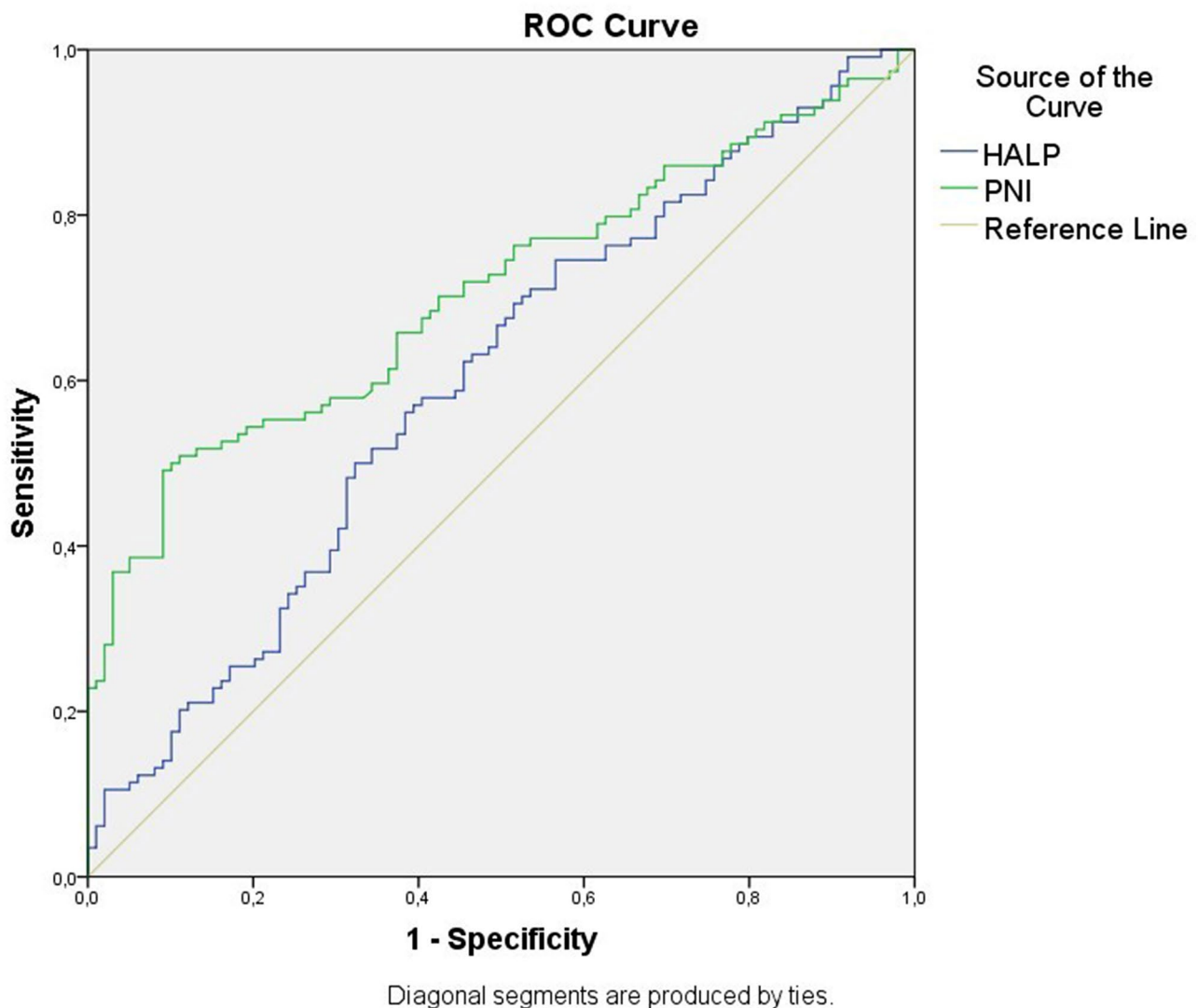
\*\* The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: Preterm birth, APGAR score at 5th minute < 7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU)

## Discussion

Early prediction of FGR is crucial for ensuring appropriate follow-up, timely interventions, and delivery at tertiary centers equipped to manage high-risk pregnancies. Also, early detection of pregnancies at risk may offer the potential to identify patients for targeted follow-up and to implement prophylactic strategies with daily low doses of acetylsalicylic acid, which could potentially reduce the

incidence of this condition by half [25]. Currently, there is no universally applicable approach to predict FGR or adverse neonatal outcomes. Consequently, it is crucial to identify practical and cost-effective predictors. The main findings of this study indicate that pregnant women with LO-FGR had significantly lower levels of HALP score and PNI—markers of inflammation and nutritional status—as observed in first-trimester laboratory results. This study





**Fig. 2** Evaluation of HALP score and PNI in predicting composite adverse neonatal outcomes using ROC analysis in fetal growth restriction group

revealed that a HALP score lower than 3.43 and a PNI lower than 37.9 were significant predictors of LO-FGR during the first trimester. Furthermore, a HALP score lower than 3.39 and a PNI lower than 37.7 were significant predictors of composite adverse neonatal outcomes in pregnancies complicated by LO-FGR. To our knowledge, this is the first study to investigate the predictive value of the HALP score and PNI in patients with FGR.

Several early ultrasound and biochemical markers have been studied for their potential in predicting FGR. Among these, uterine artery Doppler has been a key ultrasound tool for assessing placental blood flow, with increased resistance typically indicating a higher risk of FGR. Early biochemical markers, including soluble endoglin (sEng), soluble fms-like tyrosine kinase-1 (sFlt-1), pregnancy-associated plasma protein A (PAPP-A), and free beta-human chorionic gonadotropin ( $\beta$ -hCG), have

also been evaluated for their predictive value in FGR. All of these markers are closely linked to placental function and maternal-fetal health, offering insights into the mechanisms that may contribute to FGR development [26–28]. Despite their utility, the predictive accuracy of these markers remains limited and can be costly. An ideal predictive tool for FGR should be standardized, cost-effective, and easy to implement in clinical practice. The HALP score and PNI are both inflammatory and immune indices recently used in various pathologies, and this feature may make them markers in line with the pathogenesis of FGR. Additionally, they are simple to use and inexpensive, which enhances their practicality for routine clinical use. Therefore, in our study, we investigated the predictive value of the HALP score and PNI in identifying cases of LO-FGR. Our findings suggest that both markers show promise as practical tools for predicting LO-FGR.

However, it is important to note that while the PNI demonstrated predictive value for adverse neonatal outcomes in FGR cases, the HALP score did not. This distinction highlights the potential of PNI as a more reliable indicator for adverse outcomes in FGR-affected pregnancies.

Maternal nutritional status is a critical factor in understanding fetal development and provides valuable insights into the overall health of a pregnancy. Malnutrition, a complex condition marked by reduced protein reserves, insufficient caloric intake, and a weakened immune system, is a common comorbidity among pregnant women and is strongly associated with adverse outcomes [29, 30]. Moreover, maternal nutrient deficiencies may result in placental insufficiency, which is a major factor in the development of LO-FGR. On the other hand, the etiology of LO-FGR has been progressively attributed to inflammation, which is now widely acknowledged as a crucial role. The placenta, which plays a vital role in fetal growth and development, can have its function impaired by inflammatory processes, resulting in inadequate delivery of nutrients and oxygen to the fetus [31]. The HALP score and PNI are utilized to assess the nutritional and immunological status of patients, particularly in predicting prognosis and long-term survival in cancer and severe illnesses [13, 15, 19]. Research focusing on the use of first-trimester laboratory exams to predict various obstetric complications is advancing rapidly and holds significant clinical implications. The HALP score, a composite marker that includes hemoglobin, albumin, lymphocytes, and platelets, reflects both systemic inflammation and nutritional status and has recently emerged as a potential predictive tool in obstetrics. In the study conducted by Sert et al., a significant correlation was found between lower HALP scores and severity of preeclampsia, suggesting that the lower HALP score could be useful in predicting the severity of preeclampsia [32]. Another study conducted by Hrubaru et al. demonstrated that the lower HALP score had substantial predictive value for preterm birth [17]. Additionally, Bayram et al. found a negative correlation between increasing severity of hyperemesis gravidarum and the HALP score [16]. In our study, we explored the relationship between first-trimester HALP scores and the prediction of LO-FGR, finding that the HALP score was significantly lower in pregnant women who developed LO-FGR. However, it is important to note that while the HALP score was a significant predictor of LO-FGR, it was not effective in predicting composite adverse outcomes in the fetal growth restriction group. These findings highlight the potential role of the HALP score in early pregnancy assessments but also underscore its limitations in predicting broader adverse neonatal outcomes in the context of FGR.

The PNI, calculated based on serum albumin concentration and total lymphocyte count, provides a direct and

objective assessment of a patient's immunonutritional status. The PNI was initially described by Buzby et al. in 1980 [23]. Subsequently, Onodera et al. revealed the correlation between low PNI and surgical risk in patients with cancer [24]. Following that, numerous prognostic studies have been carried out on various forms of cancer with regards to PNI [18, 19]. Research has also been carried out in the field of obstetrics to investigate the correlation between PNI and different disorders that occur during pregnancy. In the study conducted by Wei et al., a high PNI score at admission was found to be associated with a reduced risk of adverse events during hospitalization in preeclamptic patients [20]. The study conducted by Tak et al. found that the nutritional status, as assessed by PNI, emerged as a novel predictor of adverse cardiovascular outcomes among people diagnosed with peripartum cardiomyopathy [21]. Çintesun et al. examined the PNI score 3 days before delivery in LO-FGR and control group patients and found no significant difference between the groups [22]. Our study demonstrates that assessing PNI during the first trimester is a valuable indicator for predicting LO-FGR. Furthermore, we found that low PNI values are associated with composite adverse neonatal outcomes in pregnancies complicated by FGR. When compared to other time-consuming prognostic tests, PNI has the advantage of being easily obtained from routine blood and biochemical tests, making it more accessible and cost-effective.

Limitations of our study include its retrospective design, reflecting only single-center experience, and relatively limited number of cases. While we aimed to control for as many variables as possible, the retrospective nature of the study and the data available for analysis may have limited our ability to account for all potential confounding factors. Future research should include a more comprehensive approach to identifying and adjusting for these confounders, ideally through prospective study designs or advanced statistical methods, to strengthen the validity of the findings. Nevertheless the study's strength lies in several factors: The cases were obtained from a tertiary maternal-fetal medicine center and ensuring homogeneity, standardized protocols were followed for all cases, the investigation of HALP score and PNI in LO-FGR is a novel contribution to the literature.

## Conclusion

Early identification of pregnancies at risk for LO-FGR is crucial for enabling healthcare providers to implement prompt interventions and initiate appropriate fetal surveillance. This study highlights the potential utility of the HALP score and PNI as valuable prognostic tools for predicting the risk of FGR as early as the first trimester. Furthermore, low PNI values are associated with composite adverse neonatal outcomes in pregnancies complicated

by FGR. However, further research is necessary to refine these indices and to identify the immunonutritional markers most specific to pregnancies complicated by FGR.

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#### Author contributions

ZS: Conceptualization, Methodology, Writing – Review & Editing. BB: Methodology, Formal Analysis, Resources, Writing – Review & Editing. GK: Resources, Writing – Review & Editing. AAF: Formal Analysis, Resources. MB and RTA: Resources, Writing – Review & Editing. COU and TK: Resources. KY and ZVY: Supervision.

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#### Data availability

The data supporting this study are available from the corresponding authors upon reasonable request.

#### Declarations

##### Ethics approval and consent to participate

The study adhered to the principles outlined in the Declaration of Helsinki, with ethical approval granted by the Ankara Etik City Hospital Ethics Committee (approval number: AESH- EK1-2023-618). In this study, due to its retrospective nature, informed consent was waived with the approval of the Ethics Committee of Ankara Etik City Hospital.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

##### Author details

<sup>1</sup>Department of Perinatology, Ankara Etik City Hospital, Ankara, Turkey

<sup>2</sup>Department of Obstetrics and Gynecology, Ankara Etik City Hospital, Ankara, Turkey

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