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Original Article

Association and predictive performance of platelet-to-lymphocyte ratio and maternal serum ferritin level for preterm birth: A prospective cohort study

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Abstract

Although maternal inflammation is increasingly recognized in the pathogenesis of preterm birth, evidence regarding the combined predictive value of platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin levels remains scarce. The aim of this study was to evaluate the association and predictive performance of PLR and maternal serum ferritin levels, two readily available inflammatory biomarkers, with the incidence of preterm birth. A prospective cohort study was conducted. Pregnant women with singleton pregnancies between 28 and 36 weeks 6 days of gestation were consecutively recruited and followed until delivery. PLR was calculated from absolute platelet and lymphocyte counts obtained from complete blood count analysis, while maternal serum ferritin levels were measured using electrochemiluminescence immunoassay. The present study found that higher PLR (odds ratio (OR): 1.013; 95%CI: 1.002–1.025; p=0.025) and maternal serum ferritin levels (OR: 1.016; 95%CI: 1.002–1.031; p=0.029) were significantly associated with the incidence of preterm birth. In multivariable analysis, PLR ≥134.4 (adjusted OR: 3.701; 95%CI: 1.186–11.548; p=0.024) and maternal serum ferritin levels ≥29.3 ng/mL (adjusted OR: 4.513; 95%CI: 1.351–15.075; p=0.014) remained independently associated with preterm birth. Receiver operating characteristic analysis demonstrated very modest discriminatory performance for both PLR (area under the curve (AUC): 0.632, p=0.076) and maternal serum ferritin levels (AUC: 0.645, p=0.052), with optimal cut-off values of 134.4 and 29.3 ng/mL, respectively. These findings support the contribution of maternal inflammatory processes to the development of preterm birth and suggest that PLR and maternal serum ferritin levels may provide complementary information for risk assessment. However, the modest predictive performance observed indicates that these biomarkers are unlikely to be sufficient as standalone screening tools and should be interpreted alongside established clinical predictors.

Keywords: Preterm birth, ferritin, PLR, biomarker, inflammation

Introduction

Preterm birth remains a major cause of neonatal morbidity and mortality worldwide and is associated with substantial short- and long-term health consequences [1]. Despite advances in

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obstetric care, the underlying mechanisms leading to spontaneous preterm labor remain incompletely understood, limiting the development of effective prediction and prevention strategies. Preterm birth is a multifactorial condition influenced by cervical insufficiency, infection, hemorrhage, uterine overdistension, maternal stress, and immune dysregulation [2,3]. Among these factors, inflammatory processes have been extensively implicated in the pathogenesis of preterm labor [2-6].

Inflammatory activation plays a central role in the pathogenesis of both term and preterm labor. Activation of toll-like receptors (TLRs) triggers intracellular signaling pathways that promote inflammasome activation and the release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) [4]. These mediators activate nuclear factor-kappa B (NF-κB), which regulates the expression of genes involved in uterine contractility, cervical ripening, and membrane remodeling [6]. The resulting inflammatory cascade promotes myometrial contractions, cervical dilation, and fetal membrane rupture, ultimately leading to labor onset [2,4].

Platelet-to-lymphocyte ratio (PLR) has gained attention as a readily available biomarker of systemic inflammation [3,7-9]. Elevated PLR reflects increased platelet activation and relative lymphopenia, both of which are characteristic features of inflammatory states [10]. Activated platelets release cytokines, chemokines, and growth factors that contribute to prostaglandin synthesis, matrix metalloproteinase activation, and uterine contractility [7,8]. Furthermore, PLR has been shown to correlate with established inflammatory biomarkers, including IL-6, TNF-α, and C-reactive protein (CRP), suggesting its potential utility in identifying pregnancies at increased risk of adverse outcomes [7-9].

Maternal serum ferritin has also emerged as a potential biomarker linking inflammation and preterm birth [11-13]. Although ferritin is primarily recognized as an indicator of iron storage, it also functions as an acute-phase reactant [14]. Elevated maternal serum ferritin levels have been associated with increased production of pro-inflammatory cytokines and enhanced oxidative stress through iron-mediated free radical generation [15]. These processes may contribute to placental dysfunction, extracellular matrix degradation, and activation of pathways involved in premature labor [11-13,15-17].

Previous studies have reported associations between PLR, maternal serum ferritin levels, and preterm birth [3-5,7-9,11-13,15-17]; however, findings remain inconsistent, and data evaluating the predictive value of both biomarkers within the same population are limited. Furthermore, evidence from low- and middle-income countries remains scarce despite the disproportionate burden of preterm birth in these settings. Therefore, the aim of this study was to evaluate the association of PLR and maternal serum ferritin levels with the incidence of preterm birth and to assess its predictive performance among pregnant women in Indonesia.

Methods

Study design and setting

A prospective cohort study was conducted at Department of Obstetrics and Gynecology, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from December 2025 to March 2026. Pregnant women with singleton pregnancies between 28 and 36 weeks of gestation were recruited consecutively according to predefined inclusion and exclusion criteria. Peripheral venous blood samples were collected at enrollment for complete blood count and serum ferritin assessment. PLR was calculated from absolute platelet and lymphocyte counts obtained using an automated hematology analyzer, while maternal serum ferritin levels were measured using electrochemiluminescence immunoassay (ECLIA). The primary outcome was preterm birth, defined as delivery before 37 completed weeks of gestation. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values for PLR and maternal serum ferritin levels.

Sample size, sampling method, and eligibility criteria

The minimum sample size was calculated using a comparative formula for two independent groups based on maternal serum ferritin levels reported previously [12], yielded a minimum

requirement of 30 patients. After accounting for an anticipated 10% dropout rate, the minimum sample size was increased to 33 patients. Patients were recruited using consecutive sampling during the study period with the final 66 patients were recruited. Pregnant women with gestational ages between 28 weeks and 36 weeks were screened for eligibility. Inclusion criteria comprised singleton live pregnancy, primigravida or multigravida status, history of vaginal or cesarean delivery regardless of indication, history of previous preterm birth, and willingness to participate through written informed consent. Exclusion criteria included having hematologic disorders, autoimmune diseases, gestational diabetes mellitus, multiple gestation, cervical anatomical abnormalities, hypertensive disorders of pregnancy including preeclampsia, placental abnormalities, active malignancy, invasive prenatal procedures such as amniocentesis, and current use of tocolytic agents or progesterone therapy.

Data collection

Baseline demographic and obstetric characteristics were collected through structured interviews and review of medical records. Data collected included maternal age, gravidity, parity, previous history of preterm birth, gestational age at enrollment, mode of previous delivery, and relevant obstetric and medical histories. Parity was categorized according to the number of previous births into nulliparous (no previous delivery beyond the age of viability), primiparous (one previous delivery), multiparous (two to four previous deliveries), and grand multiparous (five or more previous deliveries). Previous obstetric history was classified according to the most recent pregnancy outcome as current pregnancy without prior delivery, previous vaginal delivery, previous cesarean delivery, or previous miscarriage. Gestational age at enrollment was determined based on the first day of the last menstrual period and/or first-trimester ultrasonography findings and expressed in completed weeks of gestation. Gestational age was categorized as very preterm (28–31 weeks) and moderate-to-late preterm (32–36 weeks). No participants were enrolled during the extremely preterm period (<28 weeks).

Peripheral venous blood samples were collected at enrollment when patients were between 28 weeks and less than 37 weeks of gestation. Approximately 3–5 mL of venous blood was drawn from the median cubital vein using a sterile vacuum collection system. For complete blood count analysis, blood samples were collected into ethylenediaminetetraacetic acid (EDTA) tubes and analyzed using an automated hematology analyzer at the Clinical Pathology Laboratory of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Absolute platelet and lymphocyte counts were recorded, and PLR was calculated using the following formula: PLR = absolute platelet count / absolute lymphocyte count.

For maternal serum ferritin level measurement, blood samples were collected in serum separator tubes and allowed to clot at room temperature for 15–30 minutes. Samples were subsequently centrifuged at 4,000 rpm for 10–15 minutes. The resulting serum was aliquoted into sterile labeled microtubes and stored at −20°C until analysis. Maternal serum ferritin levels were measured using an automated ECLIA platform according to the manufacturer's instructions. Patients were prospectively followed until delivery. Gestational age at delivery was determined based on first-trimester ultrasonography or reliable last menstrual period data. Pregnancy outcomes were recorded from hospital medical records and delivery reports.

Study variables

The primary outcome variable was the incidence of preterm birth, defined as delivery occurring between 28 weeks and less than 37 completed weeks of gestation. The primary independent variables were PLR and maternal serum ferritin levels measured during pregnancy. PLR was defined as the ratio of absolute platelet count to absolute lymphocyte count obtained from peripheral blood analysis. PLR was analyzed both as a continuous variable and as a categorized variable based on the optimal cut-off value determined through ROC curve analysis. Maternal serum ferritin concentration was defined as the ferritin level measured in peripheral venous blood using ECLIA. Maternal serum ferritin levels were analyzed as a continuous variable and subsequently categorized according to the optimal cut-off value identified through ROC analysis. Potential confounding variables evaluated included maternal age, gravidity, parity, previous history of preterm birth, and gestational age at enrollment.

Statistical analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test. Logistic regression was used to evaluate the association between PLR and maternal serum ferritin levels with the incidence of preterm birth. Crude odds ratio (OR) with 95% confidence intervals (95%CIs) were reported. Multivariable logistic regression analysis was performed using the enter method to identify independent predictors of preterm birth while controlling for potential confounders. The final model was reported as adjusted odds ratio (aOR) with 95%CI. ROC curve analysis was performed to determine the optimal cut-off values of PLR and maternal serum ferritin levels for predicting preterm birth. The area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. All statistical tests were two-tailed, and a p-value<0.05 was considered statistically significant. Data were analyzed using SPSS Statistics version 23 (IBM, New York, US).

Results

Baseline characteristics of the included patients

A total of 66 pregnant women were included in the present study (**Table 1**). Maternal age ranged from 19 to 44 years. Multiparous women represented the largest parity group (43.9%), followed by primiparous (30.3%), nulliparous (24.2%), and grand multiparous women (1.5%). Most patients were housewives (77.3%), while teachers and nurses each accounted for 6.1% of the study population, and other occupations accounted for 10.5%. For pregnancy outcomes, 36.4% of participants experienced preterm birth, whereas 63.6% delivered at term. Based on obstetric history, previous vaginal delivery was reported in 36.4% of patients, followed by previous cesarean delivery in 33.3%; 27.3% were in their first pregnancy, and 3.0% had a history of miscarriage. At enrollment, most patients were classified as moderate-to-late preterm gestation (32–36 weeks; 65.2%), while the remaining 34.8% were classified as very preterm gestation (28–31 weeks) (**Table 1**).

Table 1. Baseline demographic and obstetric characteristics of the included patients (n=66)

Variable	Frequency (%)
Age (years), median (min–max)	31 (19–44)
Parity	
Nulliparous	16 (24.2)
Primiparous	20 (30.3)
Multiparous	29 (43.9)
Grand multiparous	1 (1.5)
Occupation	
Housewife	51 (77.3)
Teacher	4 (6.1)
Nurse	4 (6.1)
Other	7 (10.5)
Pregnancy outcome	
Preterm birth	24 (36.4)
Aterm birth	42 (63.6)
Previous obstetric history	
Current pregnancy	18 (27.3)
Vaginal delivery	24 (36.4)
Cesarean delivery	22 (33.3)
Miscarriage	2 (3.0)
Gestational age at enrollment	
Extremely preterm (<28 weeks)	0 (0.0)
Very preterm (28–31 weeks)	23 (34.8)
Moderate-to-late preterm (32–36 weeks)	43 (65.2)

Association between platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin with preterm birth

PLR was significantly associated with the occurrence of preterm birth with OR of 1.013 (95%CI: 1.002–1.025), indicating that each one-unit increase in PLR was associated with a 1.3% increase in the odds of preterm birth (**Table 2**). Maternal serum ferritin level was also significantly associated with the incidence of preterm birth with OR was 1.016 (95%CI: 1.002–1.031). This

indicates that higher ferritin levels were associated with increased odds of preterm birth (**Table 2**).

Table 2. Association between platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin level with the incidence of preterm birth

Variable	Odds ratio (OR)	95% confidence interval (95%CI)	*p*-value[a]
Platelet-to-lymphocyte ratio (PLR)	1.013	1.002–1.025	0.025*
Maternal serum ferritin level	1.016	1.002–1.031	0.029*

[a] Analyzed using binary logistic regression
* Statistically significant at $p<0.05$

Multivariable logistic regression analysis showing association between platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin levels with preterm birth incidence

The optimal cut-off values of PLR and maternal serum ferritin level to determine preterm birth incidence using the Youden index were 134.4 and 29.3 ng/mL, respectively. These values were used as cut-off values for multivariable logistic regression model. The final model of multivariable logistic regression showed that only PLR and maternal serum ferritin level remained significantly associated with preterm birth after (**Table 3**). Patients with PLR values ≥134.4 had increased odds of preterm birth compared with those with PLR values <134.4 (aOR: 3.701; 95%CI: 1.186–11.548; $p=0.024$). Similarly, patients with maternal serum ferritin level ≥29.3 ng/mL had significantly higher odds of preterm birth than those with maternal serum ferritin level <29.3 ng/mL (aOR: 4.513; 95%CI: 1.351–15.075; $p=0.014$) (**Table 3**).

Table 3. Final multivariable logistic regression analysis showing the association between platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin levels with preterm birth incidence

Variable	Adjusted odds ratio (aOR)	95% confidence interval (95%CI)	*p*-value[a]
Platelet-to-lymphocyte ratio (PLR) ≥134.4	3.701	1.186–11.548	0.024*
Maternal serum ferritin level ≥29.3 ng/mL	4.513	1.351–15.075	0.014*

[a] Analyzed using multivariable logistic regression with adjustment for potential confounders
* Statistically significant at $p<0.05$

Diagnostic performance of platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin levels for predicting preterm birth incidence

ROC curve analysis was performed to evaluate the ability of PLR to predict preterm birth (**Figure 1A**). The AUC was 0.632 (95%CI: 0.482–0.782), with $p=0.076$, indicating very modest discriminatory performance. The optimal PLR cut-off value determined using the Youden index was 134.4 (**Table 4**). At this threshold, the sensitivity and specificity were 54.2% and 76.2%, respectively, with PPV and NPV of 56.5% and 74.4%, respectively. Overall diagnostic accuracy was 68.2% (**Table 4**).

Table 4. Optimal cut-off value and diagnostic performance of platelet-to-lymphocyte ratio (PLR) and maternal serum ferritin levels for predicting preterm birth incidence

Variable	Criterion	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PLR	Youden index	134.4	54.2	76.2	56.5	74.4	68.2
Maternal serum ferritin level	Youden index	29.3 ng/mL	79.2	54.8	50.0	82.1	63.6

NPV: negative predictive value; PPV: positive predictive value; PLR: platelet-to-lymphocyte ratio

ROC curve analysis was also performed to assess the discriminatory ability of maternal serum ferritin levels for predicting preterm birth (**Figure 1B**). The AUC was 0.645 (95%CI: 0.496–0.794) with $p=0.052$, indicating very modest discriminatory performance. The optimal maternal serum ferritin level cut-off value determined using the Youden index was 29.3 ng/mL (**Table 4**). At this threshold, the sensitivity and specificity were 79.2% and 54.8%, respectively.

The PPV was 50.0%, whereas the NPV was 82.1% with the overall diagnostic accuracy was 63.6% (**Table 4**).

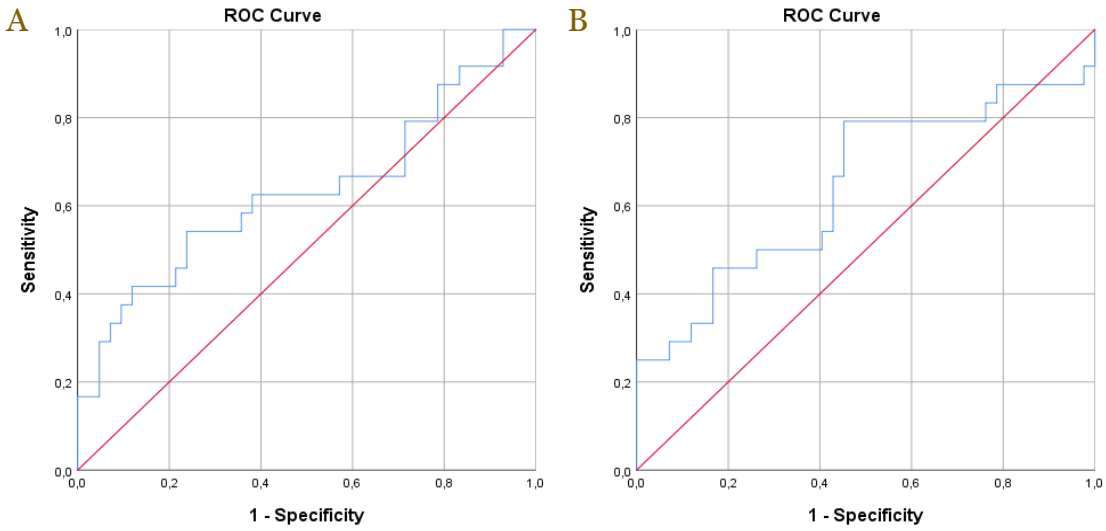

Figure 1. Receiver operating characteristic (ROC) curve analysis of the platelet-to-lymphocyte ratio (PLR) (A) and maternal serum ferritin levels (B) for predicting preterm birth.

Discussion

The present study demonstrated that both PLR and maternal serum ferritin level were independently associated with preterm birth. Furthermore, maternal serum ferritin level and PLR remained significant predictors in multivariable analysis, suggesting that maternal systemic inflammation might play an important role in the pathophysiology of preterm birth. The association between elevated PLR and preterm birth supports the growing studies linking maternal inflammatory status to adverse pregnancy outcomes [2,3]. Activation of TLRs represents a critical early event in the inflammatory cascade leading to both term and preterm labor [4,6]. In infection-related preterm labor, activation of the TLR4/MyD88/NF-κB signaling pathway increases the production of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, and CRP, which promote uterine contractions and cervical ripening [6]. Experimental studies have demonstrated that inhibition of TLR4 or NF-κB signaling reduces inflammatory cytokine expression and delays preterm birth [4,6,18].

Similarly, upregulation of the NLRP3 inflammasome further amplifies inflammatory responses through enhanced cytokine release [18,19]. These molecular events are accompanied by recruitment of leukocytes, including macrophages, neutrophils, T cells, and natural killer T cells, into the myometrium, cervix, decidua, placenta, and fetal membranes [20]. Infiltrating monocytes differentiate into macrophages that secrete IL-1β and other pro-labor mediators, while shifts in decidual immune-cell populations, particularly increased M1 macrophage polarization and altered T-cell balance, have been consistently associated with spontaneous preterm birth [19,20].

The present findings are consistent with previous studies demonstrating higher PLR values among women who subsequently experienced preterm birth [3,7-9]. A study reported significantly elevated PLR levels in preterm deliveries compared with term pregnancies and suggested that PLR may be useful for identifying women at increased risk of spontaneous preterm labor [9]. Similarly, another study identified PLR as a significant maternal inflammatory biomarker associated with preterm birth [3], whereas other studies reported that elevated PLR was associated with increased preterm birth risk and may represent a simple and readily available screening marker [7,8]. Collectively, these findings support the hypothesis that systemic inflammation contributes to the initiation of premature labor pathways.

Despite the significant association observed in this study, the discriminatory performance of PLR was modest. This finding suggests that although PLR reflects inflammatory activity associated with preterm birth, it is unlikely to be sufficiently accurate when used as a standalone

screening tool. The relatively limited predictive performance may be attributable to the multifactorial nature of preterm birth, which involves not only inflammatory mechanisms but also genetic, endocrine, mechanical, infectious, and environmental factors [5,21]. In addition, PLR is a non-specific inflammatory marker that may be influenced by various maternal conditions, including subclinical infection, nutritional status, stress, and other inflammatory disorders.

Interpretation of PLR during pregnancy should account for normal hematological adaptations. Platelet counts normally decline throughout pregnancy as part of physiological maternal adaptation due to hemodilution, increased platelet consumption, and placental sequestration [22,23]. A large multicenter study involving 35,045 pregnancies demonstrated a progressive reduction in platelet counts across gestation, reaching the lowest levels around delivery and the early postpartum period [24]. However, compared with non-pregnant women, most lymphocyte populations did not change markedly across pregnancy stages [25,26]. These physiological changes may influence PLR values and should be considered when assessing its clinical significance during pregnancy.

Another biomarker that undergoes substantial physiological alterations during pregnancy is ferritin. Some population-based studies have shown that ferritin concentrations are highest during the first trimester and progressively decline during the second and third trimesters [27-29]. During early pregnancy, cessation of menstruation may contribute to a modest increase in iron stores, resulting in ferritin levels comparable to those observed before conception [28]. As pregnancy advances, rapid fetal and placental growth, expansion of maternal red blood cell mass, and marked plasma volume expansion increase iron requirements, leading to mobilization of maternal iron stores and a decline in ferritin levels [28]. This reduction becomes more pronounced during the third trimester, when fetal growth and maternal erythropoiesis reach their peak and hepcidin levels remain suppressed to facilitate iron transfer to the fetus, further depleting maternal iron stores [27,28].

Several biological mechanisms have been proposed to explain the association between elevated maternal serum ferritin levels and preterm birth. In third-trimester pregnancies, serum ferritin has been shown to correlate with IL-6 and leukocyte counts, and elevated ferritin levels are associated with an increased risk of preterm birth, suggesting a link between iron metabolism and inflammation-related adverse pregnancy outcomes [15]. Experimental studies further demonstrate that ferritin heavy chain can activate macrophages and stimulate the production of pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, and TNF-α [15,19,20]. These cytokines contribute to the inflammatory cascade within gestational tissues by promoting the expression of matrix metalloproteinases, prostaglandins, and uterine activation proteins such as cyclooxygenase-2, connexin-43, and oxytocin receptors, ultimately leading to cervical ripening, membrane rupture, and uterine contractions [20]. Among these mediators, IL-1β appears to play a pivotal role, as inhibition of IL-1 signaling or inflammasome activation has been shown to suppress inflammation-induced uterine contractions and delay preterm birth [19].

The present findings are consistent with previous reports demonstrating higher maternal serum ferritin levels among women who experienced preterm birth. A study observed an increased risk of preterm delivery among women with elevated second-trimester ferritin concentrations [29], while another study reported significantly higher maternal serum ferritin levels in preterm compared with term deliveries [11]. More recently, a study highlighted the role of maternal serum ferritin as a biomarker reflecting both inflammation and oxidative stress in high-risk pregnancies [30]. Together, these observations suggest that maternal serum ferritin may capture several biological pathways involved in preterm birth, extending beyond iron metabolism alone.

In the multivariable model, maternal serum ferritin level demonstrated a stronger association with preterm birth than PLR. This finding may reflect the broader biological role of ferritin as both an inflammatory and oxidative stress marker. While PLR primarily reflects systemic inflammatory activity, maternal serum ferritin level may additionally represent iron dysregulation, placental dysfunction, and oxidative injury, all of which have been implicated in the pathogenesis of preterm birth [7-9,11,17,29]. Nevertheless, the predictive performance of both

biomarkers remained modest, indicating that neither marker should be considered sufficient for risk prediction in isolation.

Both PLR and maternal serum ferritin level can be obtained from routine laboratory investigations that are widely available, relatively inexpensive, and easily implemented in routine antenatal care. Consequently, these biomarkers may provide a practical approach for early risk stratification, particularly in resource-limited settings where access to more advanced predictive tools may be restricted. However, given the modest discriminatory performance observed, PLR and maternal serum ferritin level should be integrated with established clinical risk factors, cervical assessment, and other biochemical markers to improve predictive accuracy.

Some limitations should be acknowledged. Only PLR and ferritin were evaluated, whereas other inflammatory biomarkers implicated in the pathogenesis of preterm birth, such as IL-6, TNF-α, and CRP, were not assessed. Residual confounding from unmeasured maternal, environmental, and obstetric factors also cannot be excluded. Future studies involving larger multicenter cohorts are warranted to validate the predictive value of PLR and maternal serum ferritin levels, establish population-specific cut-off values, and develop comprehensive prediction models incorporating clinical characteristics, cervical assessment, and additional inflammatory biomarkers to improve risk stratification for preterm birth.

Conclusion

Higher PLR and maternal serum ferritin levels were independently associated with preterm birth, with ferritin demonstrated a stronger association than PLR. Although PLR and maternal serum ferritin levels showed potential utility as readily available inflammatory biomarkers for risk stratification, its predictive performance was very modest. Therefore, these markers should be interpreted alongside clinical assessment and other established predictors of preterm birth.

Ethics approval

Protocol of the present study was reviewed and approved by Ethical Committee for Health Research, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (approval number: 379/ETIK-RSUDZA/2025).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

Artificial intelligence (AI) tool, ChatGPT, was employed in improving grammar, sentence structure, and readability of the manuscript. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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