

ORIGINAL ARTICLE

Predictive Value of Maternal Peripheral Blood PAF and sFlt-1 Levels for Preterm Birth Secondary to PPRM

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ABSTRACT

Background: Preterm premature rupture of membranes (PPROM) is a leading cause of preterm birth, which seriously endangers maternal and neonatal health. Platelet-activating factor (PAF) and soluble FMS-like tyrosine kinase-1 (sFlt-1) play important roles in pregnancy, but their predictive value for preterm birth following PPRM remains unclear. This study aimed to investigate the predictive value of maternal peripheral blood PAF and sFlt-1 levels for spontaneous preterm delivery (SPTD) secondary to PPRM.

Methods: A total of 85 singleton pregnant women with a gestational age of 23 + 0 to 30 + 6 weeks who were diagnosed with PPRM were enrolled. Based on the occurrence of SPTD within 14 days after sampling, the participants were divided into an imminent SPTD group (iSPTD, n = 45) and a non-imminent SPTD group (non-iSPTD, n = 40). Serum levels of PAF and sFlt-1 were measured by enzyme-linked immunosorbent assay. Multivariate logistic regression was used to analyze their independent association with SPTD within 14 days post-sampling, and receiver operating characteristic (ROC) curves were employed to evaluate their predictive value.

Results: Maternal peripheral blood levels of both PAF and sFlt-1 were significantly higher in the iSPTD group than in the non-iSPTD group (all $p < 0.05$). Multivariate logistic regression analysis revealed that PAF (odds ratio [OR] = 1.272, 95% confidence interval [CI]: 1.094 - 1.480) and sFlt-1 (OR = 1.179, 95% CI: 1.058 - 1.315) were independent risk factors for SPTD within 14 days after sampling. ROC curve analysis showed that the area under the curve (AUC) for predicting SPTD within 14 days was 0.762 for PAF and 0.738 for sFlt-1. The combined nomogram model achieved an AUC of 0.829, demonstrating good predictive performance.

Conclusions: Elevated maternal peripheral blood levels of PAF and sFlt-1 are independent risk factors for SPTD within 14 days after sampling in patients with PPRM. Both biomarkers exhibit predictive value for SPTD, and their combination in a nomogram model can further improve predictive performance, showing potential for clinical application.

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KEYWORDS

pregnant women, platelet-activating factor (PAF), soluble FMS-like tyrosine kinase-1 (sFlt-1), preterm premature rupture of membranes (PPROM), preterm birth, predictive value

INTRODUCTION

Preterm premature rupture of membranes (PPROM) continues to pose a major challenge in global obstetrics, occurring in almost 3% of pregnancies and responsible for about 30% - 40% of all preterm births [1-3]. As a

predominant cause of severe neonatal morbidity, mortality, and long-term disability, PPRM leads to adverse outcomes largely attributable to preterm delivery itself and complications arising from expectant management - including perinatal infection, cord prolapse, and placental abruption [4-6]. Recent studies further suggest that, in the context of PPRM or preterm birth, gestational age at delivery (or latency period) has a more substantial impact on short-term neonatal outcomes than either microbial invasion of the amniotic cavity (MIAC) or intra-amniotic inflammation (IAI) [7-9]. Therefore, the development of accurate biomarkers to predict spontaneous preterm delivery (SPTD) following PPRM, particularly in early gestations (≤ 30 weeks), has emerged as an urgent objective in maternal-fetal medicine.

Platelet-activating factor (PAF) participates in diverse physiological and pathological pathways [10]. As established in prior research, PAF operates as a pro-inflammatory mediator across multiple disease states - encompassing cardiovascular, renal, cerebrovascular, and neurological disorders, in addition to malignancies, infectious processes, and allergic/anaphylactic reactions [11, 12]. During pregnancy, PAF is present in gestational tissues, including amniotic fluid [13,14], myometrium [15], decidua [16], and uterine cervix [17]. Investigators have consistently reported increased PAF concentrations in amniotic fluid obtained from women with PPRM or preterm labor [18]. Furthermore, the stable carbamoyl-PAF (C-PAF) analog has been demonstrated to provoke inflammatory activation in gestational tissues, subsequently inducing preterm delivery in murine models [19,20]. Collectively, these findings support PAF's potential involvement in triggering preterm birth mechanisms across species.

The transmembrane tyrosine kinase FLT-1 functions as a crucial signaling receptor for vascular endothelial growth factor A (VEGFA), vascular endothelial growth factor B (VEGFB), and placental growth factor (PlGF), thereby playing an essential role in embryonic vasculogenesis and angiogenic regulation [21]. Its soluble isoform, soluble FMS-like tyrosine kinase-1 (sFlt-1), constitutes an anti-angiogenic factor produced by trophoblasts, endothelial cells, and monocytes, with established associations to anti-angiogenic conditions and systemic endothelial impairment [22,23]. Recent conceptual advances regarding "placental hypoperfusion" - a condition marked by pregnancy complications stemming from defective vascular remodeling - have revealed that sFlt-1 exhibits predictive capacity for these pathologies as early as the first trimester [24,25]. Existing literature documents elevated sFlt-1 concentrations among women delivering prematurely [26], suggesting its potential utility in predicting preterm birth onset [27]. However, the predictive value of peripheral blood sFlt-1 levels for SPTD following PPRM has not been investigated.

Therefore, this study aimed to evaluate the predictive value of maternal peripheral blood PAF and sFlt-1 lev-

els for SPTD following PPRM.

MATERIALS AND METHODS

Study population

This study included women with singleton pregnancies diagnosed with PPRM at a gestational age of $23 + 0$ to $30 + 6$ weeks who presented to Ganzhou Hospital-Nanfeng Hospital, Southern Medical University (Ganzhou People's Hospital). The inclusion criteria were: 1) Patients who delivered a live fetus; 2) patients who had a peripheral blood sample available for analysis. The exclusion criteria were: 1) Patients with medically indicated preterm birth within 14 days after sampling (for fetal or maternal indications); 2) patients with multiple pregnancies; 3) patients in active labor (cervical dilation > 3 cm on sterile speculum examination); 4) patients with evidence of clinical chorioamnionitis at presentation; 5) patients with a fetus exhibiting major congenital anomalies. PPRM was defined as the spontaneous rupture of membranes occurring before the onset of labor and confirmed clinically at a gestational age of < 37 weeks. Based on previous reports, early PPRM was defined as rupture of membranes occurring at a gestational age of $\geq 23 + 0$ and $\leq 30 + 6$ weeks [28]. Diagnosis was confirmed by visualizing amniotic fluid pooling in the vagina or leakage from the cervical os, supported by a positive nitrazine test. Gestational age was determined from the last menstrual period and verified by first- or second-trimester (≤ 20 weeks) ultrasound.

The study was approved by the institutional ethics committee of Ganzhou Hospital-Nanfeng Hospital, Southern Medical University (Ganzhou People's Hospital), and written informed consent was obtained from all participants. The primary study outcome was defined as the incidence of SPTD within the 14-day period following blood sample collection.

Measurement of peripheral blood PAF and sFlt-1 levels

Blood samples (5 mL) were collected from all study participants via the antecubital vein in the morning after an overnight fast. Following centrifugation, the serum was stored at -80°C . The serum concentrations of PAF and sFlt-1 were quantified employing commercial enzyme-linked immunosorbent assay (ELISA) kits in strict compliance with the manufacturer's protocols (Shanghai Jingkang Bioengineering Co., Ltd., China).

Clinical management of PPRM

The standardized obstetric care for PPRM cases followed established guidelines detailed in a previous publication [29]. According to the treatment protocol, patients diagnosed with PPRM were administered preventive treatment with extended-spectrum antibacterial agents, specifically a regimen of ampicillin or amoxicillin in conjunction with macrolide antibiotics (clarith-

romycin, azithromycin, or erythromycin). For those presenting with PPROM between 23.0 and 33.6 weeks of gestation, therapeutic interventions included corticosteroid administration and tocolytic therapy utilizing magnesium sulfate, ritodrine, or atosiban, according to the clinical evaluation of the treating physician.

Statistical analysis

Data analysis was performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Continuous data were compared using the Mann-Whitney U test or Student's *t*-test based on normality distribution (evaluated by the Shapiro-Wilk test), while categorical data were compared using the chi-squared test or Fisher's exact test. Independent factors associated with SPTD within 14 days after sampling were evaluated by multivariable logistic regression analysis. The predictive value of peripheral blood PAF and sFlt-1 levels for SPTD within 14 days after sampling was assessed by receiver operating characteristic (ROC) curve analysis. A *p*-value < 0.05 was considered statistically significant. A nomogram was generated using R software. No artificial intelligence-assisted technologies were used in the production of this manuscript.

RESULTS

Demographic and clinical characteristics of the study population

A total of 85 women with PPROM who met all inclusion and exclusion criteria were enrolled in this study. Based on the occurrence of SPTD within 14 days after sampling, participants were divided into an imminent SPTD (iSPTD) group (*n* = 45) and a non-imminent SPTD (non-iSPTD) group (*n* = 40). Comparative analysis revealed that the iSPTD group exhibited more advanced gestational age at the time of blood sampling, along with significantly greater utilization of tocolytic medications relative to the non-iSPTD group (Table 1).

Peripheral blood PAF and sFlt-1 levels were higher in the iSPTD group

Serum levels of PAF and sFlt-1 were measured using ELISA kits. Significantly higher peripheral blood levels of both PAF and sFlt-1 were observed in the iSPTD group compared to the non-iSPTD group (Figure 1A, B).

Elevated peripheral blood PAF and sFlt-1 levels are independent risk factors for SPTD within 14 days after sampling

A multivariable logistic regression model was constructed to assess factors associated with SPTD occurrence within 14 days following blood collection, with SPTD status (occurred = 1, not occurred = 0) serving as the outcome variable. The model incorporated gestational age at sampling, administration of tocolytic agents (used = 1, not used = 0), and circulating concen-

trations of PAF and sFlt-1 as predictor variables. The regression analysis identified elevated peripheral blood concentrations of both PAF and sFlt-1 as significant independent determinants for SPTD development during the 14-day observation period following specimen collection (Table 2).

Peripheral blood PAF and sFlt-1 levels have predictive value for SPTD within 14 days after sampling

The predictive value of peripheral blood PAF and sFlt-1 levels for SPTD within 14 days was assessed by ROC curve analysis. The analysis showed that the area under the curve (AUC) for peripheral blood PAF level in predicting SPTD was 0.762 (95% confidence interval [CI]: 0.660 - 0.863), with an optimal cutoff value of 3.04 ng/mL, a sensitivity of 87.50%, and a specificity of 57.80%. The AUC for peripheral blood sFlt-1 level was 0.738 (95% CI: 0.631 - 0.844), with an optimal cutoff value of 5.52 pg/mL, a sensitivity of 67.50%, and a specificity of 80.00% (Figure 2A, B). These results indicate that peripheral blood PAF and sFlt-1 levels have predictive value for SPTD within 14 days after sampling.

Development of a nomogram prediction model

A nomogram prediction model was developed based on multivariate logistic regression analysis (Figure 3A). The model calibration curve analysis demonstrated good agreement between the nomogram-predicted probabilities and the actual observed outcomes, with the curve closely following the ideal calibration line (Figure 3B). The Hosmer-Lemeshow goodness-of-fit test yielded a *p*-value of 0.841 (> 0.05), demonstrating no significant deviation between the model's predictions and the actual observations and indicating excellent fit. Furthermore, ROC curve analysis revealed that the AUC of this nomogram for predicting SPTD within 14 days after sampling was 0.829 (Figure 3C), demonstrating excellent predictive performance and potential clinical application value.

DISCUSSION

PPROM is a major cause of preterm birth, posing significant challenges to maternal and neonatal health [30]. Accurately predicting the occurrence of SPTD following PPROM is crucial for securing timely clinical intervention and improving neonatal outcomes [31]. This study is the first to investigate the value of maternal peripheral blood PAF and sFlt-1 levels in predicting SPTD subsequent to PPROM. The results confirmed that women with iSPTD exhibited elevated peripheral blood levels of both PAF and sFlt-1, and that both were independent risk factors for SPTD within 14 days after sampling. More importantly, the nomogram prediction model combining these two biomarkers demonstrated excellent discriminatory performance (AUC = 0.829), suggesting its potential as a novel biomarker combination

Table 1. Demographic and clinical characteristics of the study population.

Variables	iSPTD (n = 45)	non-iSPTD (n = 40)	p-value
Maternal age (years)	31.40 ± 3.80	32.10 ± 3.70	0.393
Nulliparity	15 (33.33%)	17 (42.50%)	0.502
Previous preterm birth (< 37 weeks)	4 (8.89%)	3 (7.50%)	0.816
Gestational age at sampling (weeks)	28.20 ± 2.00	26.60 ± 1.50	< 0.001
Body mass index at admission (kg/m ²)	24.62 ± 4.10	23.85 ± 3.02	0.332
Diabetes (gestational or overt)	4 (8.89%)	2 (5.00%)	0.679
Cesarean section	24 (53.33%)	19 (47.50%)	0.666
Male fetus	25 (55.56%)	21 (52.50%)	0.830
Use of tocolytic agents	37 (82.22%)	23 (57.50%)	0.017
Use of antibiotics	42 (93.33%)	37 (92.50%)	0.881
Use of antenatal corticosteroids	42 (93.33%)	33 (82.50%)	0.179

Table 2. Multivariable logistic regression analysis of factors associated with spontaneous preterm birth within 14 days after sampling.

Variables	OR	95% CI	p-value
PAF (ng/mL)	1.272	1.094 - 1.480	0.002
sFlt-1 (pg/mL)	1.179	1.058 - 1.315	0.003

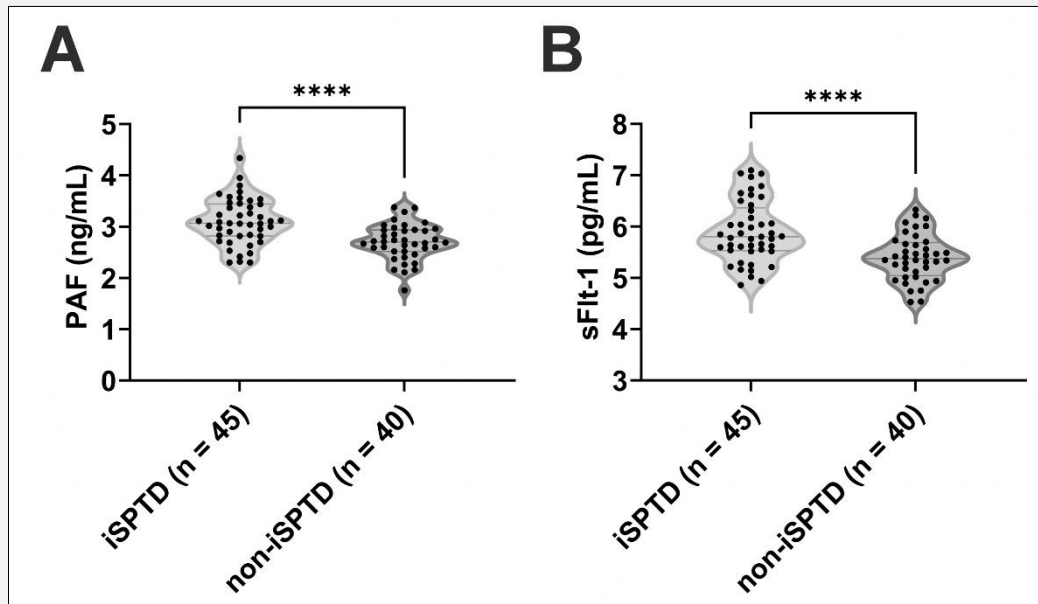


Figure 1. Peripheral blood PAF and sFlt-1 levels were higher in the iSPTD group than in the non-iSPTD group.

A, B: Serum levels of (A) PAF and (B) sFlt-1 were measured using ELISA kits. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

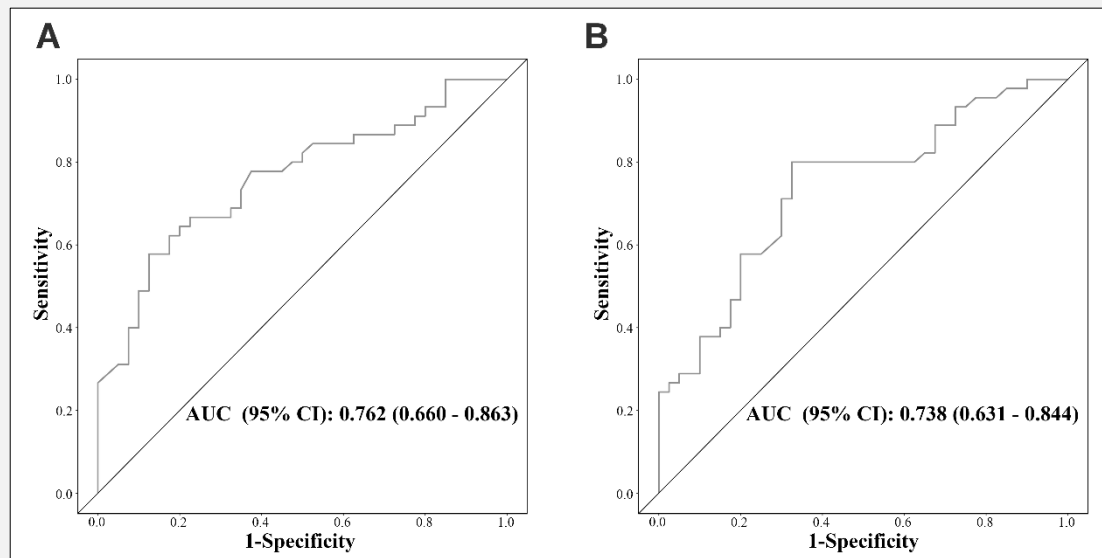


Figure 2. Peripheral blood PAF and sFlt-1 levels have predictive value for SPTD within 14 days after sampling.

A: ROC curve analysis of peripheral blood PAF level for predicting SPTD within 14 days.

B: ROC curve analysis of peripheral blood sFlt-1 level for predicting SPTD within 14 days.

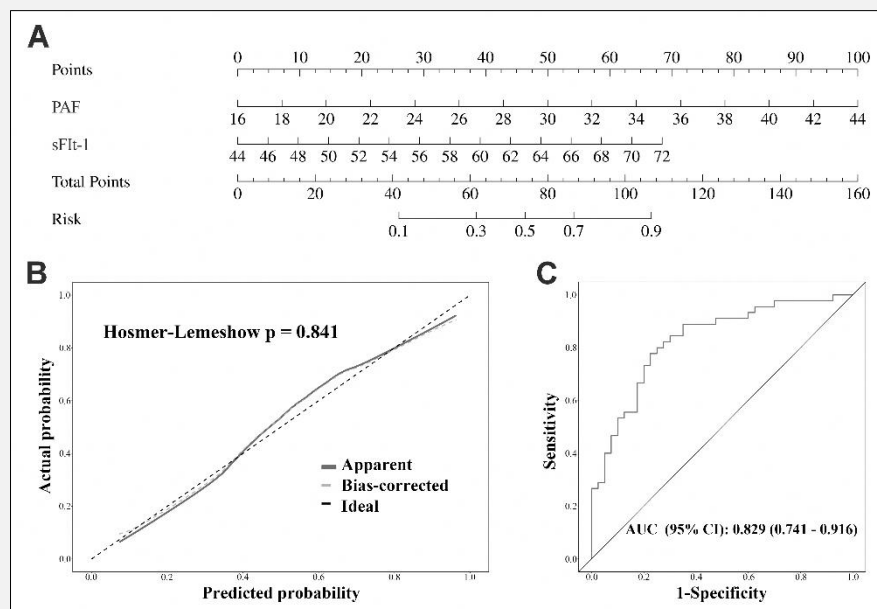


Figure 3. Development of the nomogram prediction model.

A: The nomogram prediction model.

B: The calibration curve of the model.

C: ROC curve analysis of the nomogram.

and a practical predictive tool.

Inflammatory signaling is a key mechanism in the process of parturition, capable of triggering both preterm and term labor [32,33]. Multiple lines of evidence indicate that PAF is a key effector molecule driving the inflammatory cascade associated with parturition [34,35]. This role is not unexpected, given its potent ability to induce and amplify pathological mechanisms in various acute and chronic inflammatory diseases [36]. In this study, elevated peripheral blood PAF levels were observed in women with PPROM and iSPTD, and elevated PAF was identified as an independent risk factor for SPTD within 14 days.

Disruption of the normal angiogenic process in early pregnancy may also contribute to SPTD by altering the balance between pro-angiogenic and anti-angiogenic factors necessary for normal placental vascular remodeling and fetal growth [37]. Histopathological evidence indicates impaired placentation in cases of SPTD [38]. Abnormal placentation, inadequate vascular development, and disruption of the normal transformation of uterine arteries can lead to increased placental vascular resistance accompanied by reduced intervillous blood flow [39]. The resulting limitation in fetal nutrient supply may ultimately trigger SPTD, as the placenta becomes unable to support fetal growth in late gestation [40]. In this study, elevated peripheral blood sFlt-1 levels were demonstrated in women with PPROM and iSPTD, and elevated sFlt-1 was established as an independent risk factor for SPTD within 14 days.

Furthermore, ROC curve analysis revealed that PAF had high sensitivity but moderate specificity, while sFlt-1 offered better specificity but slightly lower sensitivity, making them complementary. Consequently, a nomogram prediction model was constructed. This model not only demonstrated superior predictive accuracy compared to any single indicator (AUC = 0.829), but its good calibration also indicated a high concordance between the predicted risks and the actual observed outcomes.

Several limitations should be considered. The study's single-center design and modest cohort size may limit the extrapolation of findings. Furthermore, biomarker levels were measured only at a single time point, precluding insight into their dynamic changes during the course of PPROM and their precise temporal relationship with the initiation of parturition. The study also did not explore potential interactions between PAF and sFlt-1 or common upstream regulatory mechanisms. Future research should focus on external validation through multi-center, large-scale prospective cohorts and incorporate more frequent longitudinal sampling to map the dynamic trajectories of these biomarkers. Concurrently, utilizing cell and animal models to deeply investigate the specific molecular mechanisms of PAF and sFlt-1 in membrane stability and parturition initiation will provide a theoretical basis for further understanding the etiology of PPROM and developing novel intervention targets.

CONCLUSION

In conclusion, this study demonstrates for the first time that maternal peripheral blood PAF and sFlt-1 levels are independent predictors of SPTD within 14 days after sampling in patients with PPROM. The nomogram model constructed based on these biomarkers shows good calibration and discrimination, providing a promising objective basis and practical tool for the early clinical identification of high-risk patients and individualized risk management, which indicates potential clinical utility.

Data Available:

Data is available from the corresponding author on request.

Ethics Statement:

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by Ganzhou Hospital-Nanfeng Hospital, Southern Medical University (Ganzhou People's Hospital).

Declaration of Generative AI in Scientific Writing:

No artificial intelligence-assisted technologies were used in the production of this manuscript.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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