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Original Research

Exploratory Study of the Diagnostic Value of Combined Serum β-hCG, Serum Ferritin, and Gestational Age in Intrauterine Infection Among Pregnant Women With Premature Rupture of Membranes

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Abstract

Background: Intrauterine infection poses significant risks to both mother and fetus, especially in cases of premature rupture of membranes (PROM). Early and accurate diagnosis is crucial for timely intervention. **Methods**: This was a prospective study involving 120 patients with PROM, including 32 cases diagnosed with intrauterine infection and 88 non-infected controls. Parameters such as serum beta-human chorionic gonadotropin (β-hCG), serum ferritin (SF), and gestational age (GA) were evaluated for their diagnostic efficacy using logistic regression and receiver operating characteristic (ROC) analysis. **Results**: A total of 120 patients were analyzed, with 32 (26.67%) diagnosed with intrauterine infection. Infected patients exhibited significantly higher median β-hCG (43,104.00 *vs.* 22,375.00 mIU/mL; $p < 0.0001$) and SF (34.14 *vs.* 27.81 ng/mL; $p = 0.0020$), and a shorter mean gestational age (38.63 *vs.* 37.78 weeks; $p = 0.0040$). Furthermore, the logistic regression analysis established these as independent predictors, with significant ORs for $\log_{10}$-β-hCG (22.41; $p = 0.0010$), $\log_{10}$-SF (6.45; $p = 0.0300$), and gestational age (0.61; $p = 0.0300$). The combined testing approach, particularly the integration of $\log_{10}$-β-hCG, $\log_{10}$-SF, and GA, showed superior diagnostic efficacy, achieving an ROC area under the curve of 0.78, with significantly enhanced sensitivity and specificity. **Conclusions**: The combined testing of serum β-hCG, SF, and GA offers a robust tool for the early diagnosis of intrauterine infection in women with PROM. These findings support the use of comprehensive biomarker screening in clinical settings to improve diagnostic accuracy and patient outcomes.

Keywords: intrauterine infection; premature rupture of membranes; beta-human chorionic gonadotropin; serum ferritin; gestational age

1. Introduction

Premature rupture of membranes (PROM) is a common obstetric complication during pregnancy. The earlier it occurs in gestation, the worse the prognosis for the perinatal infant, potentially leading to premature birth, oligohydramnios, placental abruption, umbilical cord prolapse, fetal distress, and neonatal respiratory distress syndrome. This condition significantly increases the rate of intrauterine infection and perinatal mortality for both the mother and fetus [1,2]. Importantly, a spectrum of placental and amniotic fluid pathologies beyond PROM—including placenta accreta spectrum disorders, placental abruption, and amniotic fluid volume abnormalities have been similarly associated with adverse perinatal outcomes through shared pathophysiological mechanisms involving uteroplacental insufficiency and inflammatory cascade activation. These clinical parallels highlight the critical need for reliable biomarkers to predict and stratify infection-related pregnancy complications. It is generally believed that the main causes of PROM are infection, trauma, poor membrane development, cervical incompetence, and abnormal intrauterine pressure, which can lead to the destruction of the maternal membrane structure. As the gestational week progresses, the weaker parts of the membrane may rupture [3–5]. PROM and intrauterine infections are causally linked, with clinical studies confirming an extremely high risk of intrauterine infection among those with premature rupture, with infection rates exceeding 15% [5,6]. This condition is also one of the main causes of poor maternal and infant outcomes.

Clinically, women with PROM often exhibit no obvious symptoms early on, such as fever, fetal tachycardia, or uterine tenderness, which complicates prenatal diagnosis. Laboratory tests and biomarkers are critical for early detection of intrauterine infection, including amniotic fluid culture, placental pathology, and the testing of serum procalcitonin (PCT), interleukin-6 (IL-6), and C-reactive protein (CRP) [5,7]. However, traditional testing methods have limitations. For example, amniotic fluid cultures require several days, which may delay diagnosis. Some pathogens are anaerobic and difficult to culture, leading to a high rate of false negatives [8]. Pathological examinations are only available post-delivery and cannot predict early outcomes effectively. Serum markers like PCT, IL-6, and CRP are susceptible to stress and other interfering factors, making their results less stable [9,10]. Thus, there is a need for a simple, reliable, non-invasive, and accurate method for

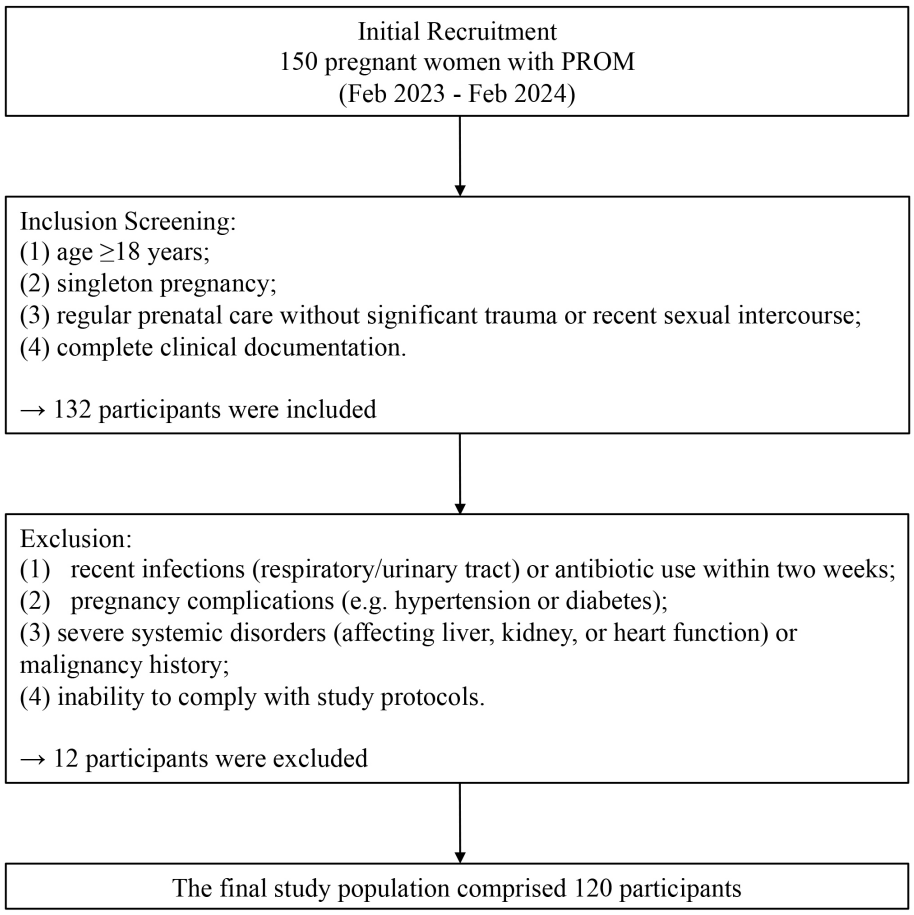

Fig. 1. The study flow chart. PROM, premature rupture of membranes.

early diagnosis of intrauterine infection in cases of PROM, warranting further clinical research.

β-human chorionic gonadotropin (β-hCG) is a glycoprotein hormone secreted upon implantation of the fertilized egg, which primarily aids in transitioning the corpus luteum from the menstrual to the early pregnancy phase, stimulates the secretion of progesterone, and enhances the production of progesterone in the placental trophoblasts [11,12]. Previous study has shown that serum β-hCG level may rise in cases of intrauterine infection, possibly due to anoxic conditions stimulating the trophoblast to synthesize and release more β-hCG [13]. Although it can reflect intrauterine infection, its diagnostic efficacy alone is limited. Serum ferritin (SF), which stores excess iron in ferritin within the protein shell to prevent high levels of free iron inside cells, is vital for meeting the iron needs of bone marrow in hemoglobin production [14,15]. A previous study has found that SF, an acute-phase protein, significantly increases during infections and is closely related to infection [16]. While serum β-hCG and SF testing have found some clinical application in assessing infectious diseases, their use in diagnosing intrauterine infection in cases of PROM is still limited, suggesting further research is needed. Clinical studies indicate that the rate of intrauterine infection in cases of PROM between 20 to 27 weeks is around 70%, whereas it drops below 30% between 33 to 35 weeks. As gestation progresses, the fetus matures, and the outcomes of premature rupture or preterm birth may more closely resemble those of normal labor in terms of immune status [17].

Therefore, this study proposes to conduct a prospective analysis by enrolling pregnant women with PROM who meet the criteria, as well as healthy pregnant women. The study will measure levels of serum β-hCG and SF, and combine these with the gold standard of pathological examination to explore the predictive value of combined serum β-hCG and SF tests with gestational age indicators for intrauterine infection in cases of PROM. The aim is to establish a simple, effective, non-invasive, and highly repeatable early diagnostic method for intrauterine infections in PROM, with the further goal of developing a predictive model for clinical application and widespread use.

2. Methods

2.1 Study Participants

This prospective study enrolled 150 pregnant women diagnosed with PROM according to the 2015 Guidelines for Diagnosis and Management of PROM [18] from Chongqing University Central Hospital and the People's

Hospital of Yubei District between February 2023 and February 2024. Initial screening identified 132 eligible participants meeting all inclusion criteria: (1) age $\geq$18 years; (2) singleton pregnancy; (3) regular prenatal care without significant trauma or recent sexual intercourse; and (4) complete clinical documentation. Subsequently, we excluded 12 participants based on predefined exclusion criteria: (1) recent infections (respiratory/urinary tract) or antibiotic use within two weeks; (2) pregnancy complications (e.g., hypertension or diabetes); (3) severe systemic disorders (affecting liver, kidney, or heart function) or malignancy history; and (4) inability to comply with study protocols. The final study population comprised 120 participants. The procedure for participant recruitment is summarized in the flow chart of Fig. 1.

Participants were stratified based on the degree of neutrophil infiltration in placental membrane tissues under high magnification into non-infection, mild infection, moderate infection, and severe infection categories. The Ethics Committee of Chongqing University Central Hospital approved the study protocol (2023-8). All participants were fully briefed on the study's objectives and procedures, from which informed consent was voluntarily obtained.

2.2 Data Collection and Biochemical Measurements

Participant data collected included age, gestational age, length of hospital stay, parity, delivery mode, sex of the fetus, and newborn weight. On admission, 3 mL of venous blood was drawn, stored in dry vacuum coagulation tubes, and centrifuged at 3000 rpm for 15 minutes. The serum was then transferred to Eppendorf tubes and stored at –80 °C. Placental and membrane tissues were collected within 10 minutes post-delivery from near the rupture site for pathological analysis, fixed in formaldehyde, and processed with hematoxylin and eosin staining.

Serum β-hCG levels were measured using the electrochemiluminescence method on a Roche Cobas e411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany), and SF levels were assessed with the chemiluminescence method on a DiaSorin LIAISON XL analyzer 2210 (DiaSorin S.p.A., Saluggia, Italy), following all manufacturer instructions for calibration and quality control.

2.3 Definitions of Intrauterine Infection Severity

The placental membranes collected postpartum were fixed in formalin, processed into pathological sections, and stained with hematoxylin and eosin for microscopic examination. The severity was determined by examining placental membrane tissue slices for neutrophil infiltration per high-power field: none (<5 neutrophils), mild (5–10 neutrophils), moderate (11–30 neutrophils), and severe (>30 neutrophils) [19].

2.4 Statistical Analysis

Participants were categorized into non-infected and infected groups, and then further subdivided by infection severity. Data are presented as mean $\pm$ SD or median values (25th–75th percentile) as appropriate. Group comparisons were made using one-way ANOVA for continuous variables. Variables with skewed distributions, like serum β-hCG and ferritin levels, were logarithmically transformed before analysis.

Spearman's rank correlation analysis was conducted to evaluate the association between risk factors and intrauterine infection. Logistic regression analyses were performed to identify the risk factors for intrauterine infection. Two logistic regression models were developed: Model 1 adjusted for age, hospital stay, white blood cells (WBCs), neutrophils, and hemoglobin; Model 2 adjusted for gestational age and log-transformed serum levels. Multinomial logistic regression was used to assess the predictive value of serum markers and gestational age.

The C-statistics were calculated to measure the concordance between model-based risk estimates and intrauterine infection in PROM. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were determined to measure the incremental prognostic effect of adding β-hCG, serum ferritin, and gestational age to conventional risk factors. The basic prediction model included conventional risk factors for intrauterine infection in PROM, such as age, length of hospital stay, white blood cell count, neutrophil count, hemoglobin, and newborn weight.

The gold standard for diagnosis was pathological examination. The efficacy of combined serum β-hCG, SF levels, and gestational age as predictors of intrauterine infection in PROM was analyzed using receiver operating characteristic (ROC) curves, evaluating the area under the curve (AUC).

All statistical analyses were conducted by using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), or SPSS version 22.0 (IBM Corp., Armonk, NY, USA), with significance set at a two-sided p-value of <0.05.

3. Results

3.1 Basic Characteristics

The study included 120 patients with PROM, among whom 32 (26.67%) were diagnosed with intrauterine infection. The infected patients exhibited significantly higher median levels of serum β-hCG and SF compared to non-infected patients (serum β-hCG: 43,104.00 *vs.* 22,375.00 mIU/mL, $p < 0.0001$; SF: 34.14 *vs.* 27.81 ng/mL, $p = 0.0020$). Additionally, gestational age was significantly shorter in the infected group (38.63 *vs.* 37.78 weeks, $p = 0.0040$) (Table 1). Table 2 presents the basic characteristics of patients stratified by intrauterine infection levels in cases of PROM. Significant trends were observed with shorter gestational age, increasing levels of SF and β-hCG related

Table 1. Basic characteristics of patients with intrauterine infection and non-infected patients in PROM.

	Non-infected patients	Infected patients	*p* value*
Number (%)	88 (73.33)	32 (26.67)	/
Age (years)	28.97 ± 4.41	28.81 ± 3.53	0.8400
Length of hospital stay (days)	4.17 ± 1.36	3.91 ± 1.20	0.3300
WBC count ($\times 10^9$/L)	8.62 ± 1.89	8.87 ± 2.03	0.5300
Neutrophil ratio (%)	73.94 ± 5.33	75.09 ± 6.34	0.3200
Hemoglobin (g/L)	122.51 ± 10.72	119.36 ± 10.91	0.1500
Newborn weight (g)	3188.00 ± 366.00	3150.00 ± 402.00	0.6200
β-hCG (mIU/mL)	22,375.00 (14,610.00, 38,357.00)	43,104.00 (27,867.00, 65,027.00)	<0.0001
SF (ng/mL)	27.81 (15.73, 42.72)	34.14 (23.19, 72.79)	0.0020
Gestational age (weeks)	38.63 ± 1.41	37.78 ± 1.28	0.0040

Data are expressed as mean ± standard deviation, number (percentage), or median (interquartile range). *p values were calculated using ANOVA for continuous variables and $p < 0.05$ was considered that the difference is statistically significant. β-hCG, beta-human chorionic gonadotropin; SF, serum ferritin; WBC, white blood cell. "/" indicates not applicable.

Table 2. Basic characteristics of patients stratified by intrauterine infection levels in PROM.

	Non-infected patients	Mildly infected patients	Moderately infected patients	Severely infected patients	*p* value*
Number, (%)	88 (73.33)	11 (9.17)	9 (7.50)	12 (10.00)	/
Age (years)	28.97 ± 4.41	29.45 ± 3.04	27.11 ± 3.62	29.50 ± 3.72	0.5500
Length of hospital stay (days)	4.17 ± 1.36	3.72 ± 1.27	3.33 ± 0.70	4.50 ± 1.24	0.1500
WBC count ($\times 10^9$/L)	8.62 ± 1.89	8.07 ± 1.90	9.96 ± 2.77	8.78 ± 1.09	0.1500
Neutrophils (%)	73.94 ± 5.33	74.79 ± 4.10	75.43 ± 8.91	75.11 ± 6.33	0.7900
Hemoglobin (g/L)	122.51 ± 10.71	119.30 ± 5.59	119.91 ± 14.12	118.99 ± 12.71	0.5600
Newborn weight (g)	3188.00 ± 366.00	3304.00 ± 387.00	3060.00 ± 324.00	3077.00 ± 454.00	0.3800
β-hCG (mIU/mL)	22,375.00 (14,610.00, 38,357.00)	31,333.00 (25,060.00, 45,892.00)	43,258.00 (26,210.00, 74,641.00)	45,070.00 (39,599.00, 71,859.00)	<0.0001
SF (ng/mL)	27.81 (15.73, 42.72)	22.98 (17.70, 48.10)	26.67 (23.80, 45.22)	61.78 (34.14, 84.97)	0.0010
Gestational age (weeks)	38.62 ± 1.41	38.49 ± 1.02	37.52 ± 1.51	37.34 ± 1.12	0.0050

Data are expressed as mean ± standard deviation, number (percentage), or median (interquartile range). *p values were calculated using ANOVA for continuous variables. Bonferroni adjusted for 6 tests, which confirmed significant differences among groups for all biomarkers ($p < 0.008$). "/" indicates not applicable.

to the severity of infection (p values were 0.01, 0.001, and <0.0001, respectively).

3.2 Risk Factors for Intrauterine Infection and Severity in PROM Patients

In the correlation analysis (Table 3), $\log_{10}$-β-hCG and $\log_{10}$-SF demonstrated significant positive correlations with intrauterine infection (correlation coefficients of 0.39, $p < 0.0001$, and 0.23, $p = 0.0100$, respectively). In contrast, gestational age showed a negative correlation with intrauterine infection (correlation coefficient of –0.26, $p = 0.0020$). Similarly, when analyzing the severity of infections, $\log_{10}$-β-hCG (correlation coefficient of 0.41, $p < 0.0001$), $\log_{10}$-SF (correlation coefficient of 0.26, $p = 0.0030$), and gestational age (correlation coefficient of –0.29, $p = 0.0010$) remained significant predictors.

For the logistic regression analysis (Table 4), elevated $\log_{10}$-β-hCG and $\log_{10}$-SF levels, as well as lower gestational age, were significantly associated with a higher risk of intrauterine infection. In Model 1, after adjusting for age, hospital stay, WBC count, neutrophil ratio, hemoglobin levels, and newborn weight, the odds ratio (OR) for $\log_{10}$-β-hCG was 31.42 (95% confidence interval [CI]: 5.11–193.23, $p = 0.0002$), for $\log_{10}$-SF was 13.45 (95% CI: 2.79–64.72, $p = 0.0010$), and for gestational age was 0.54 (95% CI: 0.36–0.81, $p = 0.0020$). In Model 2, after further adjustment for gestational age, $\log_{10}$-β-hCG, and $\log_{10}$-SF, the associations remained significant, with ORs of 22.41 (95% CI: 3.39–148.19, $p = 0.0010$) for $\log_{10}$-β-hCG, 6.45 (95% CI: 1.10–37.81, $p = 0.0300$) for $\log_{10}$-SF, and 0.61 (95% CI: 0.39–0.97, $p = 0.0300$) for gestational age.

When analyzing infection severity (non-infected, mildly, moderately, severely), the risk increased significantly with higher $\log_{10}$-β-hCG and $\log_{10}$-SF levels, and shorter gestational age. In Model 1, $\log_{10}$-β-hCG had an OR of 16.88 (95% CI: 4.47–63.53, $p < 0.0001$), while

Table 3. Spearman's rank correlation analysis for intrauterine infection and intrauterine infection levels in PROM patients.

	Intrauterine infection		Intrauterine infection levels (non-, mildly, moderately, severely)	
	correlation coefficient	*p* value	correlation coefficient	*p* value
Age	–0.01	0.8500	–0.01	0.8500
Length of hospital stay	–0.08	0.3200	–0.06	0.4800
WBC count	0.04	0.6600	0.05	0.5300
Neutrophile	0.06	0.4800	0.06	0.4600
Hemoglobin	–0.12	0.1700	–0.11	0.1900
Newborn weight	–0.03	0.7300	–0.04	0.5900
Log_{10}-β-hCG	0.39	<0.0001	0.41	<0.0001
Log_{10}-SF	0.23	0.0100	0.26	0.0030
Gestational age	–0.26	0.0020	–0.29	0.0010

Table 4. Logistics regression analysis for risk of intrauterine infection in PROM.

	Model 1	*p* value	Model 2	*p* value
Intrauterine infection				
Log_{10}-β-hCG	31.42 (5.11, 193.23)	0.0002	22.41 (3.39, 148.19)	0.0010
Log_{10}-SF	13.45 (2.79, 64.72)	0.0010	6.45 (1.10, 37.81)	0.0300
Gestational age	0.54 (0.36, 0.81)	0.0020	0.61 (0.39, 0.97)	0.0300
Intrauterine infection levels (non-, mildly, moderately, severely)				
Log_{10}-β-hCG	16.88 (4.47, 63.53)	<0.0001	13.56 (3.51, 52.92)	0.0001
Log_{10}-SF	10.74 (3.49, 33.05)	<0.0001	5.47 (1.70, 17.52)	0.0040
Gestational age	0.59 (0.43, 0.81)	0.0010	0.71 (0.52, 0.97)	0.0300

Model 1 was adjusted for age, length of hospital stay, WBC, neutrophil number, hemoglobin, and newborn weight.

Model 2 was further adjusted for gestational weeks, log_{10}-SF, and log_{10}-β-hCG based on model 1.

log_{10}-SF had an OR of 10.74 (95% CI: 3.49–33.05, $p <$ 0.0001), and gestational age had an OR of 0.59 (95% CI: 0.43–0.81, $p = 0.0010$). After full adjustment in Model 2, the ORs were 13.56 (95% CI: 3.51–52.92, $p = 0.0001$) for log_{10}-β-hCG, 5.47 (95% CI: 1.70–17.52, $p = 0.0040$) for log_{10}-SF, and 0.71 (95% CI: 0.52–0.97, $p = 0.0300$) for gestational age (Table 4).

3.3 Diagnostic Efficacy and Predictive Value of Biomarkers in PROM Patients

Fig. 2 presents the receiver operating characteristic (ROC) curves, illustrating the diagnostic performance of these biomarkers. The combined approach using log_{10}-β-hCG, log_{10}-SF, and gestational age significantly enhanced diagnostic accuracy, as evidenced by the highest area under the curve (AUC) of 0.78 (Table 5). These findings underscore the value of integrating multiple biomarkers to improve the early diagnosis and management of intrauterine infection in PROM patients.

Next, we compared the predictive performance of β-hCG, SF, and gestational age, alongside basic risk factors, in forecasting incident intrauterine infection in patients with PROM. Incorporating β-hCG, SF, and gestational age into the conventional risk models significantly improved C-statistics, IDI, and NRI, compared to adding each variable individually to the models (all p values < 0.05, except for NRI in the models that included gestational age alone, or both gestational age and SF) (Table 6).

4. Discussion

This study emphasizes the significant role of integrating SF, β-hCG, and gestational age as diagnostic biomarkers in managing PROM with suspected intrauterine infection. The combination of these biomarkers offers a robust method for early diagnosis of intrauterine infections, which is crucial for the effective management of PROM and the prevention of adverse outcomes for both mother and fetus.

The adoption of a multi-marker strategy in obstetric care, particularly for conditions like PROM, offers a more dynamic and sensitive approach to diagnosing intrauterine infections. Gestational age is a pivotal factor in maternal health, and its correlation with increased inflammatory responses at advanced stages can indicate higher risks of complications [20,21]. The present study found that the shorter the gestational age, the higher the risk of intrauterine infection in patients with PROM. This finding aligns closely with previous studies [22,23].

SF, recognized for its role as an acute-phase reactant, shows a strong correlation with the presence of intrauterine infection, supporting the findings of other stud-

Table 5. The area under the curve of SF, β-hCG, and gestational age for intrauterine infection.

	Area under the curve (95% CIs)	*p* value
β-hCG	0.75 (0.66–0.85)	<0.0001
SF	0.65 (0.55–0.76)	0.0100
Gestational age	0.67 (0.57–0.77)	0.0030
β-hCG + SF	0.77 (0.67–0.86)	<0.0001
β-hCG + Gestational age	0.78 (0.69–0.87)	<0.0001
SF + Gestational age	0.69 (0.58–0.79)	0.0020
β-hCG + SF + Gestational age	0.78 (0.69–0.88)	<0.0001

Abbreviation: 95% CIs, 95% confidence intervals.

Table 6. Improvement in the prediction of intrauterine infection in PROM by adding β-hCG, SF, and gestational age to conventional risk factors.

	ΔC-statistics (95% CIs)	*p* values	IDI, % (95% CIs)	*p* values	NRI, % (95% CIs)	*p* value
β-hCG *vs.* risk factors	0.17 (0.05, 0.28)	0.0040	0.13 (0.06, 0.21)	0.0001	0.61 (0.22, 1.00)	0.0030
SF *vs.* risk factors	0.12 (0.01, 0.23)	0.020	0.10 (0.04, 0.17)	0.0010	0.43 (0.04, 0.83)	0.0300
Gestational age *vs.* risk factors	0.11 (0.01, 0.22)	0.0300	0.07 (0.02, 0.13)	0.0040	0.31 (–0.08, 0.71)	0.1200
β-hCG + SF *vs.* risk factors	0.19 (0.07, 0.32)	0.0010	0.22 (0.12, 0.31)	<0.0001	0.59 (0.20, 0.97)	0.0040
β-hCG + Gestational age *vs.* risk factors	0.22 (0.11, 0.34)	<0.0001	0.21 (0.12, 0.29)	<0.0001	0.80 (0.43, 1.17)	<0.0001
Gestational age + SF *vs.* risk factors	0.16 (0.04, 0.27)	0.0100	0.15 (0.07, 0.23)	0.0003	0.29 (–0.10, 0.69)	0.1500
β-hCG + SF + Gestational age *vs.* risk factors	0.22 (0.10, 0.33)	0.0002	0.25 (0.15, 0.35)	<0.0001	0.65 (0.27, 1.04)	0.0010

Basic risk factors: age, length of hospital stay, WBC, neutrophil, hemoglobin, and newborn weight.

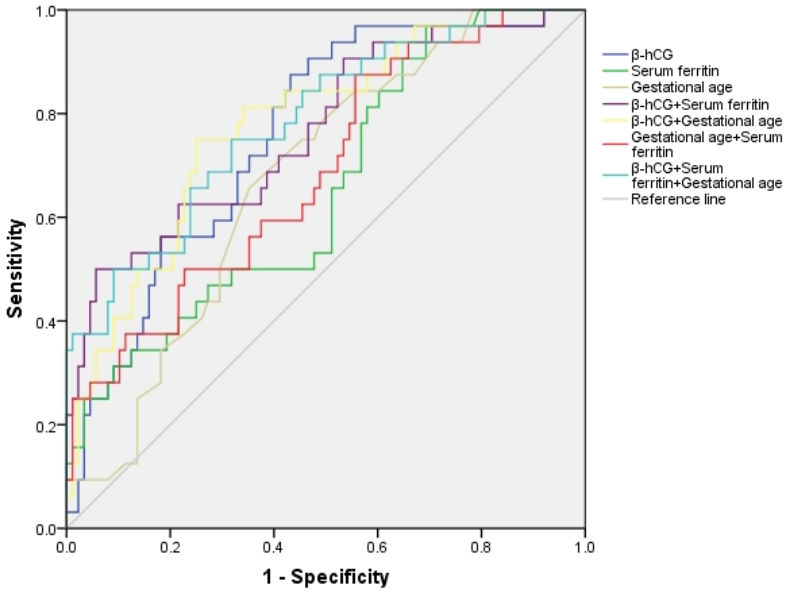

Fig. 2. The receiver operating characteristic analysis for the risk of intrauterine infection. This figure displays the ROC curve, plotted using sensitivity (true positive rate) against 1-specificity (false positive rate) based on the data from the predictive model. The AUC value included in the figure quantifies the model's accuracy in distinguishing cases with and without the risk of intrauterine infection, reflecting its diagnostic ability. AUC, area under the curve; ROC, receiver operating characteristic.

ies that have used SF as a marker for systemic inflammation and infection in pregnant women [16,21]. Ferritin is involved in iron metabolism, and during infection, it is synthesized in greater amounts to limit the availability of iron to pathogens, a process known as nutritional immunity [24]. Elevated SF levels provide a quantifiable measure that can be crucial in the early detection of subclinical infections.

Similarly, abnormal β-hCG levels, often associated with trophoblastic disease, have been noted in our study to indicate placental stress, which may be due to, or result in, intrauterine infections [5]. The diagnostic relevance of β-hCG as a biomarker for assessing placental health underlines its utility, as discussed by Schmitz *et al.* [5], who found that β-hCG levels could serve as an indicator of placental inflammation and subsequent fetal risk.

Our findings support the literature advocating for the use of multiple diagnostic indicators to improve sensitivity and specificity in the detection of intrauterine infections [25,26]. The use of a combined biomarker approach, yielding an AUC of 0.78, demonstrates a significant improvement over traditional single-marker methods and suggests potential changes in standard screening protocols for PROM.

Implementing a multi-marker strategy could lead to earlier and more accurate diagnoses, allowing healthcare providers to initiate appropriate and timely interventions. This proactive approach aligns with guidelines from major health organizations, including World Health Organization (WHO) and American College of Obstetricians and Gynecologists (ACOG), which emphasize the need for precise and proactive management in cases of PROM to mitigate risks of infection and preterm labor [3,25]. By integrating these biomarkers into routine prenatal care, we can potentially lower the incidence of adverse neonatal outcomes and improve maternal health.

Limitations

This study has several limitations that should be acknowledged. Firstly, although participants were enrolled from two medical centers, the sample size remains relatively modest, which may limit the statistical power and the generalizability of the findings. Expanding the sample size in future studies could enhance the robustness of the conclusions. Secondly, while serum β-hCG, SF, and gestational age demonstrated strong diagnostic value, variations in clinical protocols, diagnostic thresholds, and testing equipment across different institutions may influence the reproducibility of results. Additionally, some potential confounding variables, such as CRP, procalcitonin, maternal microbiome profiles or environmental factors, were not included in the analysis and may contribute to variability in outcomes. Finally, emerging biomarkers such as the neutrophil-to-lymphocyte ratio [27] were not included in this study but could be valuable additions to future investigations. Future research should prioritize larger, multicenter trials to validate these findings and improve diagnostic models for intrauterine infections in PROM cases. Incorporating genetic, immunological, and microbial assessments may further enhance diagnostic precision and support the development of personalized management strategies for high-risk patients.

5. Conclusions

In conclusion, the integration of gestational age, SF, and β-hCG as biomarkers significantly enhances the diagnostic landscape for intrauterine infections in PROM. This approach not only improves diagnostic accuracy but also provides a basis for more effective clinical management, thereby enhancing maternal and neonatal health outcomes.

Availability of Data and Materials

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (YD) upon reasonable request.

Author Contributions

YD designed the research study. YD and SY performed the research and analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. We used a database started after ethical approval by the Ethics Committee of Chongqing University Central Hospital (2023-8), and all participants had provided written informed consent to have their data anonymously used in future research.

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Conflict of Interest

The authors declare no conflict of interest.

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