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Original Research

Prediction of intrauterine inflammation in patients with preterm premature rupture of membranes at 28 to 34 weeks of gestation

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Abstract

Background: To analyze the influence of white blood cells (WBC), serum C-reactive protein (CRP), procalcitonin (PCT), and other risk factors on the prognosis of patients with preterm premature rupture of membranes (PPROM) from 28 to 34 weeks of gestation. **Methods**: We performed a retrospective study of 425 patients with PPROM from 28 to 34 weeks of gestation who delivered infants at Shandong Provincial Hospitals between January 1, 2013 and December 31, 2019. Risk factors for puerperal infection were analyzed using a logistic regression model. A receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) was estimated. **Results**: Of the 425 patients (mean $\pm$ SD age, 34.69 $\pm$ 5.55 years), 104 (24.47%) had chorioamnionitis. The CRP level (odds ratio [OR], 1.009; 95% Confidence Interval (CI), 1.003–1.014; $P = 0.002$), WBC count (OR, 1.170; 95% CI, 1.092–1.254; $P < 0.001$) and gestational age (OR, 0.772; 95% CI, 0.648–0.921; $P = 0.004$) were risk factors of chorioamnionitis. Patients who did not undergo previous cesarean section had twice the risk of developing chorionic inflammation ($P = 0.022$). The cut-off value of CRP level for prediction of chorioamnionitis was 19.69 mg/L with a sensitivity of 65.4%, a specificity of 75.7%, a positive predictive value (PPV) of 46.58%, and a negative predictive value (NPV) of 90.24%. The cut-off value of WBC count was 12.99 $\times$ 10^9/L with a sensitivity of 62.4%, a specificity of 65.8%, a PPV of 36.65%, and an NPV of 84.61%. The cut-off value of PCT level was 0.054 ng/mL with a sensitivity of 81.0%, a specificity of 75.7%, a PPV of 32.08%, and an NPV of 90.67%. The AUC for CRP was 0.731. **Conclusions**: Study results suggested that CRP level (<19.69 mg/L), WBC count (<12.99 $\times$ 10^9/L) and PCT level (<0.054 ng/mL) had good NPVs for chorioamnionitis, whereas their PPVs were low. The CRP level was found to have the most accurate prediction of chorioamnionitis among patients with PPROM from 28 to 34 weeks of gestation.

Keywords: Preterm premature rupture of membranes; Chorioamnionitis; C-reactive protein; White blood cell count; Procalcitonin

1. Introduction

Preterm premature rupture of membranes (PPROM) is a common complication during pregnancy. It occurs in approximately 3% of all pregnancies and 25% to 33% of preterm infants [1]. Because the fetal lung is immature before 34 weeks of pregnancy, premature delivery due to PPROM can lead to increased complications in newborns. At present, it is suggested that expectant management should be performed if there is no contraindication for the mother and fetus [2]. However, prolonged pregnancy time significantly increases maternal and neonatal risk of infection [3]. When combined with intrauterine infection, the risk of nervous system injury, respiratory distress syndrome, necrotizing enterocolitis and sepsis in preterm infants increases [4,5]. The detection of the indicators of intrauterine infection is particularly important to the prognosis of both mother and infant.

The association of C-reactive protein (CRP), procalcitonin, and other related infectious indexes with intrauterine infection of PPROM have been reported. Asadi *et al.* [6] analyzed 75 cases of patients, and serum CRP was found to be the most accurate predictor of chorioamnionitis among patients with PPROM. Li *et al.* [7] analyzed 152 patients at 28 to 34 weeks of gestation and found both procalcitonin (PCT) and CRP to have good application potential for the diagnostic prediction of subclinical intrauterine infection in patients with PPROM at less than 34 weeks of gestation.

In the process of expectant management, different regions and hospitals may vary in terms of latency time and treatment measures. Between January 1, 2013 and December 31, 2019, 425 patients with PPROM at 28 to 34 weeks of gestation delivered in our hospital. In this study, the infection index, complications, and incidence of chorionic inflammation in these patients with the aim to further elucidate associations that may minimize the risk of maternal and infant infection and provide a reference for clinical treatment.

2. Materials and methods

2.1 Methods

Data were taken from patients who delivered infants at Shandong Provincial Hospital Affiliated to Shandong First Medical University between January 1, 2013 and December 31, 2019. A total of 425 patients with PPROM (28 to 34 weeks) were enrolled. Exclusion criteria included abnormal placentation, cervical incompetence, and other diseases that may affect the level of WBCs and CRP (e.g., sexually transmitted diseases, diseases of immune system, infectious diseases of other systems, etc.). Patients admitted to hospital due to severe intrauterine infection and those experiencing regular contractions were also excluded. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Biomedical Research Ethic Committee of Shandong Provincial Hospital before commencing (SLYY-NO-2020-121).

The diagnosis of PPROM was based on the patient history, physical examination, and laboratory studies [8]. Evidence of membrane rupture included a report of watery leakage from the vagina (confirmed by sterile speculum examination) and observation of either fluid accumulation in the posterior vaginal fornix or direct leakage from the cervical canal after pressure on the uterine fundus with a cough attempt [9]. A positive nitrazine test was performed or fern-ing of the vaginal fluid was observed, or both. We included patients for whom at least two of these examinations were positive.

After the patients were admitted to the hospital, antibiotics (cefuroxime, 1.5 g, administered two times a day or Clindamycin phosphate, 0.6 g, administered two times a day) were routinely used to prevent infection within 12 hours, and uterine contraction inhibitors (ritodrine hydrochloride or atosiban) and glucocorticoids (dexamethasone, 5 mg, four times) were used for treatment. Close monitoring of maternal temperature, WBC count (nucleic acid fluorescence staining technology), CPR (immunoturbidimetry), PCT (electrochemiluminescence) level and fetal status (non-stress test) was performed. The pregnancy was terminated if fetal distress, frequent contractions, and suspected intrauterine infection were found. On the day of pregnancy termination, WBC, CRP and PCT levels were drawn. If not detected, take the values of the last test.

The patients were divided into two groups according to the presence or absence of chorioamnionitis, which was diagnosed on pathology or clinically (body temperature $\geq$38 °C on two occasions at least 4 hours apart, and more than two of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leukocytosis, maternal tachycardia, and fetal tachycardia).

2.2 Statistical analyses

Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY, USA). Continuous data are presented as mean $\pm$ SD. Differences of nominal data were analyzed with the χ^2 test or Fisher' exact test. The risk factors of puerperal infection were analyzed using a logistic regression model.

A receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) was estimated. An AUC value of 1 indicated a perfect test, a value of greater than >0.9 indicated high accuracy, and a value of 0.7 to 0.9 indicated moderate accuracy. Values less than 0.7 indicated low accuracy. Significance was accepted at $P < 0.05$.

3. Results

3.1 Characteristics of the participants

Of the 425 patients (mean $\pm$ SD age, 34.69 $\pm$ 5.55 years) with PPROM at 28 to 34 weeks of gestation in the studied period, 104 (24.47%) had chorioamnionitis. The mean $\pm$ SD gestational age was 30.47 $\pm$ 1.40 weeks. A total of 327 patients (76.9%) had cesarean section delivery, 115 (27.06%) had undergone previous cesarean section, and 17 (4.00%) had twin pregnancies. 19 (4.47%) patients had hypertensive disorder complicating pregnancy (HDCP), 94 (22.12%) had abnormal presentation, 6 (1.41%) had neonatal asphyxia, and 45 (10.59%) had gestational diabetes (GDM) or pre-gestational diabetes (PGDM).

3.2 Risk factors of chorioamnionitis

Comparison of maternal characteristics is shown in Table 1. There were no significant differences between the two groups in terms of maternal age, BMI (Body Mass Index), twin pregnancies, HDCP, abnormal presentation, and GDM/PGDM ($P > 0.05$). The mean CRP, and WBC levels of patients with chorioamnionitis were higher than those of patients without chorioamnionitis (50.16 $\pm$ 51.88 vs 22.52 $\pm$ 38.85 mg/L; $P < 0.001$; 14.90 $\pm$ 4.42 vs 12.37 $\pm$ 3.31 $\times$ 10^9/L, $P < 0.001$). Gestational age of patients with chorioamnionitis was less than that of patients without chorioamnionitis (30.15 $\pm$ 1.40 vs 30.57 $\pm$ 1.39 weeks; $P = 0.009$). The rate of cesarean section in chorioamnionitis group was higher than that of the group without chorioamnionitis ($P = 0.001$). The rate of previous cesarean section was lower in patients with chorioamnionitis than that of the patients without chorioamnionitis ($P = 0.022$).

The variables of CRP, WBC, gestational age, cesarean section delivery, and previous cesarean section were subject to stepwise backward logistic regression analysis. Binary logistic regression analysis showed that CRP level (OR, 1.009; 95% Confidence Interval (CI), 1.003–1.014; $P = 0.002$), WBC (OR, 1.170; 95% CI, 1.092–1.254; $P < 0.001$) and gestational age (OR, 0.772; 95% CI, 0.648–0.921; $P = 0.004$) were risk factors of chorioamnionitis. Patients who did not undergo previous cesarean section had twice the risk of developing chorioamnionitis ($P = 0.022$). The risk of chorioamnionitis in the vaginal delivery group was 0.29 times higher than that of the cesarean section group ($P = 0.01$) (Table 2).

Table 1. Characteristics and outcomes between two groups according to the presence or absence of chorioamnionitis.

Variables	Chorioamnionitis		*P*
	Absent (n = 321)	Present (n = 104)	
Age (y)	34.76 ± 5.54	34.47 ± 5.61	0.647
Gestational age (w)	30.57 ± 1.39	30.15 ± 1.40	0.009
BMI	23.29 ± 2.92	23.85 ± 2.87	0.089
GDM	33 (10.28%)	12 (11.54%)	0.716
HDCP	14 (4.36%)	1 (0.96%)	0.131
previous cesarean section	96 (29.91%)	19 (18.27%)	0.022
twin pregnancies	12 (3.74%)	5 (4.81%)	0.576
abnormal presentation	67 (20.87%)	27 (25.96%)	0.280
CRP (mg/L)	22.52 ± 38.85	50.16 ± 51.88	<0.001
WBC (10^9/L)	12.37 ± 3.31	14.90 ± 4.42	<0.001
Cesarean section delivery	235 (73.2%)	92 (88.50%)	0.001

Table 2. Binary regression analysis and risk of chorioamnionitis.

	OR	95% CI	*P*
WBC (thousand/mm^3)	1.170	1.092–1.254	<0.001
CRP (mg/L)	1.009	1.003–1.014	0.002
Gestational age (w)	0.772	0.648–0.921	0.004
Vaginal delivery	0.286	0.140–0.585	0.001
Previous cesarean section	2.034	1.108–3.731	0.022

3.3 Prediction of CRP, WBC, and PCT levels for chorioamnionitis

The accuracy of each parameter to predict chorioamnionitis was evaluated by ROC curve analysis (Fig. 1). The CRP level was found to have moderate accuracy to predict chorioamnionitis with an AUC of 0.731 (95% CI, 0.676–0.787). The AUC for WBC count was 0.672 (95% CI, 0.611–0.732), indicating a low accuracy. As shown in Table 3, the cut-off value of CRP for prediction of chorioamnionitis was 19.69 mg/L with a sensitivity of 65.4%, a specificity of 75.7%, a positive predictive value (PPV) of 46.58%, and a negative predictive value (NPV) of 90.24%. The cut-off value of WBC counts was 12.99 $\times$ 10^9/L with a sensitivity of 62.4%, a specificity of 65.8%, a PPV of 36.65%, and an NPV of 84.61%. The PCT values were measured before delivery in 186 patients, and the accuracy of PCT was evaluated by ROC curve analysis. The cut-off value of PCT was 0.054 ng/mL with a sensitivity of 81.0%, a specificity of 75.7%, a PPV of 32.08%, and an NPV of 90.67%. The AUC for PCT was 0.683 (95% CI, 0.591–0.774), indicating a low accuracy.

4. Discussion

It is the consensus of most scholars that expectant treatment can reduce the incidence and mortality of newborn respiratory distress syndrome in the immature fetus within 34 weeks of gestation without signs of infection or fetal distress [2,10]. It is very important to monitor for subclinical infection of the mother in the process of expectant treatment using the indicators of heart rate, body temperature, WBC count, CRP level, etc. [10,11]. In the present study, the association of WBC count, serum CRP, and PCT level with chorioamnionitis among patients with PPROM between 28 to 34 weeks of gestation was investigated. The cut-off values selected in this study had certain guiding significance for the expectant treatment of PPROM. The negative predictive values of PCR and PCT were greater than 90%, and the risk of chorioamnionitis was low when the detected levels were less than those values. PCR level was more accurate in predicting chorioamnionitis.

The maternal serum level of CRP was found to be the most accurate test for the diagnosis of chorioamnionitis among patients with PPROM between 28 to 34 weeks of gestation. The ROC curve analysis showed that CRP concentration of 19.69 mg/L predicted chorioamnionitis with an NPV of 90.90%. The clinical practice guideline of premature rupture of fetal membranes issued by the French College of Gynecologists and Obstetricians (CNGOF, 2018) pointed out that if the plasma CRP of asymptomatic patients is less than 5 mg/L, intrauterine infection can be excluded [12]. However, in patients with PPROM, with a delay in the time for expectant treatment, the CRP gradually increased. In this study, a CRP level less than 19.69 mg/L still has a good NPV for chorioamnionitis. Musilova *et al.* [13] found the maternal serum CRP cutoff value of 17.5 mg/L was the best level to identify the presence of both microbial invasion of the amniotic cavity and intra-amniotic inflammation. Perrone *et al.* [14] reported that A maternal CRP level greater than 20 mg/L was an appropriate index for predicting acute funisitis. In this study, a PPV of CRP level greater than 19.69 mg/L for chorioamnionitis was only 46.58%.

In this study, WBC and PCT levels were found to have low accuracy to predict chorioamnionitis. For a WBC count of 12.99 $\times$ 10^9/L, NPV was 84.61% and PPV was only

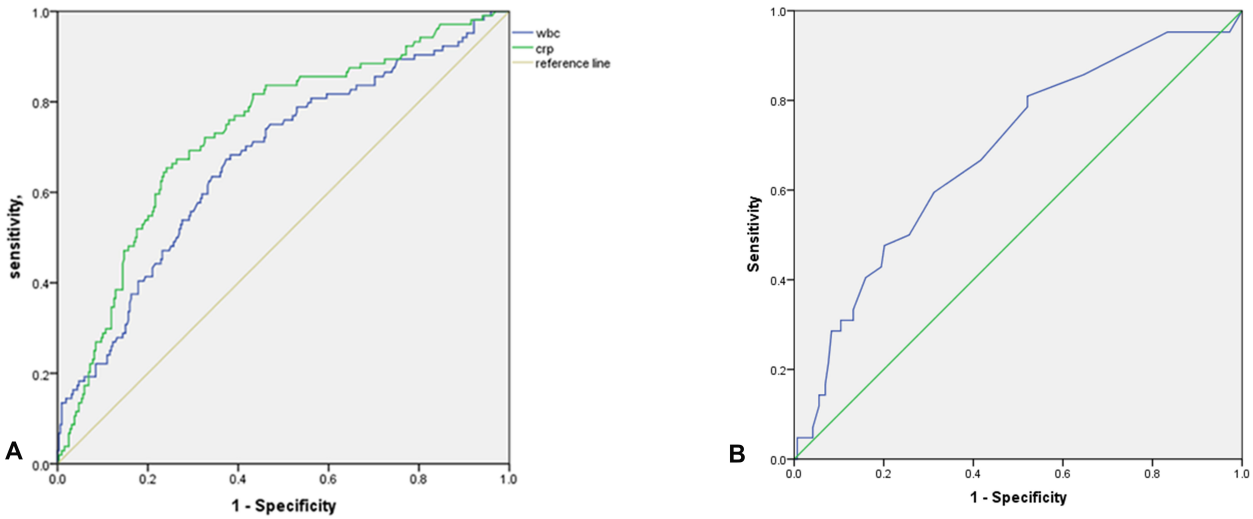

Fig. 1. Receiver operating characteristic (ROC) curves for serum CRP, WBC, and PCT. (A) ROC curves for CRP (AUC, 0.731; $P < 0.001$) and WBC (AUC, 0.672; $P < 0.001$). (B) ROC curves for PCT (AUC, 0.683; $P < 0.001$).

Table 3. Predictive value of the model of CRP, WBC, and PCT for chorioamnionitis.

Factor	AUC	95% CI	Sensitivity %	Specificity %	PPV %	NPV %	*P*
CRP (19.69 mg/L)	0.731	0.676–0.787	65.4	75.7	46.58	90.24	<0.001
WBC (12.99 $\times 10^9$/L)	0.672	0.611–0.732	62.4	65.8	36.65	84.61	<0.001
PCT (0.054 ng/mL)	0.683	0.591–0.774	81.0	75.7	32.08	90.67	<0.001

36.65% for chorioamnionitis. However, in clinical practice, changes in WBC count can be nonspecific, particularly in patients who are concurrently treated with glucocorticoids. When judging the level of WBCs in patients' plasma, clinicians should focus on the time relationship between blood sample collection and glucocorticoid use. The PCT level as a biomarker for the detection of bacterial infections is superior to other inflammatory factors, such as CRP and cytokines, and is an objective and easy to detect indicator with unique diagnostic advantages. It is a hormone activity free glycoprotein with a serum half-life of 22 hours. Kemin *et al.* [7] analyzed 152 patients with PPROM at 28 to 34 weeks of gestation and reported that the optimal cutoff values for PCT was 0.445 ng/mL, PPV and NPV were 59.7% and 53.9%, respectively. In this study, the NPV of PCT less than 0.054 ng/mL reached 90.67%.

The cesarean section rate in this study was 76.9%, which was higher than that reported by Lee *et al.* (34.31%) [15], Faucett *et al.* (18.9%) [16], and Drassinower *et al.* (36.9%) [5], because patients with previous cesarean section and suspected intrauterine infection tended to choose cesarean section delivery. The risk of chorionic inflammation in vaginal delivery was 0.29 times higher than that in cesarean section delivery; this also might be related to the fact that patients suspected of chorioamnionitis were more likely to choose cesarean delivery. Gestational age of patients with chorioamnionitis was less than that of patients without chorioamnionitis, which might be because the expectant treatment time of patients with smaller gestational age was prolonged, which leaded to the increased risk of infection.

There were some limitations in this study. Because of the difficulty in data acquisition, we did not analyze the correlation between latency time and clinical chorioamnionitis. Patients with clinical or pathological diagnosis of chorioamnionitis were not grouped for discussion. As for the relationship between previous cesarean section and chorioamnionitis, we reviewed the literature and found no relevant reports. In this study, patients who had undergone previous cesarean section were less likely to develop chorioamnionitis. It is not clear whether this was related to immune factors or other reasons.

5. Conclusions

The CRP level (<19.69 mg/L), WBC count (<12.99 $\times$ 10^9/L), and PCT level (<0.054 ng/mL) had good NPV for chorioamnionitis, while their PPVs were low. The CRP level was found to have the most accurate prediction of chorioamnionitis among patients with PPROM from 28 to 34 weeks gestation. As for the correlation between chorioamnionitis and previous cesarean section, we look forward to relevant reports from other scholars in the future.

Author contributions

YZG and YZ conceived and designed this retrospective analysis; YXW and YYX analyzed the data; SW and XLW collected the data; YXW wrote the paper; YYX proofread the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Biomedical Research Ethic Committee of Shandong Provincial Hospital before commencing (approval number: SLYY-NO-2020-121). Our study was retrospective with data from the medical record system, and it was applicated for waiers of informed consent.

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Conflict of interest

The authors declare no conflict of interest.

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