Predictive value of procalcitonin or c-reactive protein for subclinical intrauterine infection in patients with premature rupture of membranes (PROM)

Kemin Li[1,2]
Haiyan Yu[1,2,]
Xiaodong Wang[1,2]
Xinghui Liu[1,2]

[1] The Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China
[2] Laboratory of molecular epidemiology of birth defects of West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China

Corresponding author:
Haiyan Yu
Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University
E-mail: fanjy422@163.com

Abstract

Introduction: **to evaluate the diagnostic value of procalcitonin (PCT) and C-reactive protein (CRP) for the prediction of subclinical intrauterine infection in patients with premature rupture of membranes (PROM).**
Methods: **a retrospective analysis was performed based on patients with PROM admitted into our hospital between January 2011 and January 2016. Using the pathological diagnosis of placenta as the gold standard, the sensitivities, specificities, positive predictive values, and negative predictive values of PCT and CRP for the diagnosis of subclinical intrauterine infection at different gestational weeks were analyzed. Further, the diagnostic accuracies were compared according to their receiver operating characteristic (ROC) curves.**
Results: **276 cases were included. The area under the ROC curve of CRP is 0.632, and it is significantly better than PCT. The sensitivity, specificity, positive predictive value, and negative predictive value of CRP are 0.686, 0.958, 0.501, and 0.765, which are all better than those of PCT. The group analysis according to different gestational weeks demonstrated that for the group of 28-33+6 weeks pregnant women, the area under the ROC curve of CRP and PCT is 0.869, and 0.787. The both test have satisfactory accuracy. But the sensitivity and specificity of PCT is 0.830, and 0.950, respectively. That are significantly better than CRP.**
Conclusion: **both PCT and CRP have good application potential for the diagnostic prediction of subclinical intrauterine infection in <34 gestational weeks pregnant women with PROM, and PCT is more applicable to 28-33+6 gestational weeks pregnant women with PROM.**

Key words: procalcitonin, C-reactive protein, subclinical intrauterine infection, PROM.

Introduction

The premature rupture of membranes (PROM) can lead to maternal puerperal infection, sepsis, and fetal and neonatal infection, which affects the quality of neonatal survival. A significant complication of PROM is chorioamnionitis. The occurrence of chorioamnionitis during premature labor greatly harms both the mother and the newborn. When chorioamnionitis does not occur, PROM patients who are less than 34 weeks pregnant can still expect management. However, most cases with chorioamnionitis do not follow the typical sub-clinical course, and early diagnosis is difficult.
There are many methods for diagnosing PROM associated with chorionic infection; however, each has certain limitations. PROM and infections have reciprocal causation relationships, and the indicators of infection can be used to diagnose chorioamnionitis and amnionitis (1-4). The C-reactive protein (CRP) is an acute phase protein secreted by the liver, and it is part of the non-specific immune mechanisms. The CRP level is very low in normal serum. However, upon an inflammatory response in the body, CRP can be synthesized and released into the blood by the liver within 6 ~ 12 h, with a peak at 48 ~ 72 h. If the infection and the inflammation are under control, then the CRP level may rapidly decrease into the normal range within a short timeframe. The CRP level may increase responsively but nonspecifically through the course of bacterial infections, viral infections, other microbial infections, autoimmune diseases, and cancer (5-7).
Additionally, procalcitonin (PCT) as a biomarker for the detection of bacterial infections has been explored in recent years. It is a hormone activity-free glycoprotein with a serum half-life of 22 h. Under physiological conditions, the PCT concentration in the serum is very low (<0.05 ng/ml), and it is only produced by thyroid C cells. During bacterial infection, PCT may be produced and rapidly released into the blood by various body tissues and cells. Studies have

shown that the blood PCT concentration begins to elevate 3 h after infection, and peaks at 6 ~ 12 h. If the infection is sustained or deteriorates, the PCT concentration can be maintained or further increase. Once the infection is under control and the patient's condition has improved, the PCT concentration drops. Recently, the PCT concentration has been widely used as a standard for bacterial infection detection and as a guideline for antibiotic use (8-10).

Studies have shown that both CRP and PCT have high sensitivities and specificities in PROM associated with intrauterine infection. They can be used to predict asymptomatic intrauterine infection. However, the results have great discrepancy in different studies (5-10). To further investigates the clinical application value of PCT and CRP in the early prediction and diagnosis of subclinical intrauterine infection in patients with premature rupture of membranes (PROM), A retrospective analysis was performed based on 276 patients with PROM during pregnancy that were admitted into our hospital between January 2011 and January 2016. Each patient met the study inclusion criteria.

Materials and Methods

Participants

The retrospective study was used. Patients with PROM admitted into our hospital were included between January 2011 and January 2016.

Inclusion criteria and exclusion criteria: All patients including single pregnancy or multiple pregnancy met the diagnostic criteria of PROM (spontaneous PROM), without gestational weeks limitation. All patients underwent placenta pathologic examination, and were undergone CRP and PCT tests within 12 hours before delivery. The complications of acute rheumatism, liver disease, other infections, and pregnancy-induced hypertension syndrome were all excluded. Acute infection period patients with symptoms including fever, abdominal pain, uterine tenderness, purulent vaginal discharge, or vaginal smell, and so on were all excluded. There is no ethical committee approval because of the retrospective study.

Sample collection

After admission, a sample of 5 mL of peripheral blood was collected from each patient. The blood sample was kept at room temperature for 10 min and then centrifuged at 3,000 rpm for 10 min. The serum was then collected for determining the PCT and CRP levels. The enzyme-linked immunosorbent assay (ELISA) was used for the determinations. All of the pregnant women's placentas after childbirth were sent to pathological exam. Two pathologists are invited.

Diagnostic criteria

The diagnostic criteria for PROM detailed in the 24th edition of "Williams Obstetrics" was applied to all expectant mothers. Before labor, a pregnant woman would suddenly feel more liquid (amniotic fluid) flow out from the vagina. The amniotic fluid may contain vernix and/or meconium, and the pelvic exam would reveal more amniotic fluid with vernix and/or meconium flow out from the cervix. The microscopic examination of a dried vaginal smear would demonstrate fern fronds-like crystallization. The pH for the vaginal fluid was > 6.5. The pathological diagnosis criteria require that inside the placenta and amniotic membrane tissues, the leukocytes of chorionic plate and amnion demonstrate diffuse aggregation and infiltration, with ≥5 neutrophils per view under a light microscope on the highest magnification. Two independent pathologists reviewed the histology slides of the placentas of the included pregnant women.

Data analysis

Spss20.0 was used to analyze the data; The Medcalc software was used to draw the ROC curves of CRP and PCT; and calculate the cut-off of CRP and PCT, and the sensitivities, specificities, positive predictive values, and negative predictive values of the optimal cut-off value, respectively. Logistics regression was used to analyze the CRP and PCT values on the prediction of intrauterine infection for different gestational age groups. $P < 0.05$ was considered statistically significant.

Results

The characteristics of the patients

As shown in Table 1, there were 276 cases of PROM pregnant women, aged 27.6 ± 8.4, with a pathological positive rate of 37.0% (102/276). There were 24 cases of <28 weeks of pregnancy, aged 27.5 ± 8.6 years old, with a pathological positive rate of 50.0% (12/24);

Table 1. Characteristics of the patients included in the study

Gestational age	Number of cases	Age	Pathologic positive rate (%)
< 28	24	27.5 ± 8.6	50.0 (12/24)
28-33+6	152	27.8 ± 8.5	47.4 (72/152)
34-36+6	42	28.2 ± 7.8	19.0 (8/42)
≥ 37	58	27.9 ± 8.0	17.2 (10/58)
Total	276	27.6 ± 8.4	37.0 (102/276)

152 cases of 28-33+6 weeks of pregnancy, aged 27.8 ± 8.5, with a pathological positive rate of 47.4% (72/152); 42 cases of 34-36+6 weeks of pregnancy, aged 28.2 ± 7.8, with a pathological positive rate of 19.0% (8/42); and 58 cases of ≥ 37 weeks of pregnancy, aged 27.9 ± 8.0, with a pathological positive rate of 17.2% (10/58).

The diagnostic PCT and CRP values in the pregnant women with PROM

As shown in Figure 1 and Table 2, without grouping, the areas under the ROC curves of PCT and CRP are 0.493 and 0.632, respectively. As shown in Table 3, using the optimal cutoff value as the positive threshold, the sensitivity, specificity, positive predictive value, and negative predictive value of CRP are 0.686, 0.958, 0.501, and 0.764, respectively. The area under the ROC curve <0.5 was negative, thus, without grouping, the diagnostic value of CRP for subclinical intrauterine infection is better than that of PCT.

The diagnostic values of PCT and CRP in the pregnant women with PROM at different gestational weeks

As shown in Figure 2 and Table 3, for women pregnant <28 weeks, the areas under the ROC curves of PCT and CRP are 0.625 and 0.944, respectively, with statistically significant differences between the both test and the gold standard (P <0.05). Using the optimal cutoff value as the positive threshold, the sensitivity, specificity, positive predictive value, and negative predictive value of CRP are 1.000, 0.833, 0.857, and 1.000, respectively. All of the CRP values are significantly better than those of PCT (P <0.05). Thus, for women pregnant <28 weeks, the diagnostic value of CRP for subclinical intrauterine infection is better than that of PCT.

For women pregnant from 28-33+6 weeks, the areas under the ROC curves of PCT and CRP are 0.787 and 0.869, respectively, and the difference is statistically significant between the both test and the gold standard (P <0.05). Using the optimal cutoff value as the positive threshold, the sensitivity, specificity, positive predictive value, and negative predictive value of PCT is better than CRP (<0.05). Thus, for women pregnant from 28-33+6 weeks, the diagnostic value of PCT for subclinical intrauterine infection is comparable to that of CRP.

For women pregnant from 34-36+6 weeks, the areas under the ROC curves of PCT and CRP are 0.459 and 0.550, respectively, and For women pregnant from ≥37 weeks, the areas under the ROC curves of PCT and CRP are 0.308 and 0.558, respectively. The area under the ROC curve <0.5 was negative, thus, the diagnostic value of CRP for subclinical intrauterine infection is better than that of PCT in ≥34 weeks patients with PROM.

Logistics regression analysis

As shown in Table 4, according to the logistics regression analysis, because of the inclusion of two continuous quantitative variables (PCT and CRP), the results are not statistically significant. Only the p value of PCT for the third group (34-36+6 weeks) is less than 0.05. However, with a large standard error, this value is not actually meaningful. Therefore, it is indeterminable whether the risk of intrauterine infection increased as CRP and PCT levels increased.

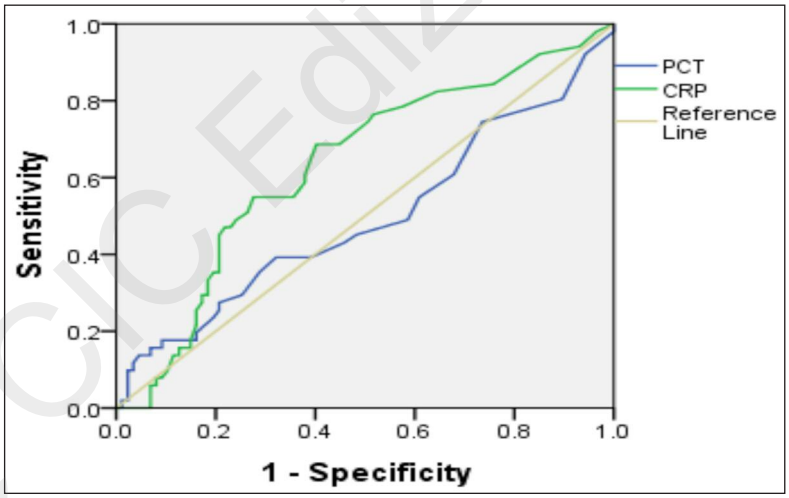

Figure 1. The ROC curves of PCT and CRP for all pregnant women.

Table 2. The areas under the ROC curves of PCT and CRP for different gestational age groups.

	< 28 weeks	28-33+6 weeks	34-36+6 weeks	≥ 37 weeks	All
CRP	0.944	0.869	0.550	0.558	0.632
PCT	0.625	0.787	0.459	0.308	0.493

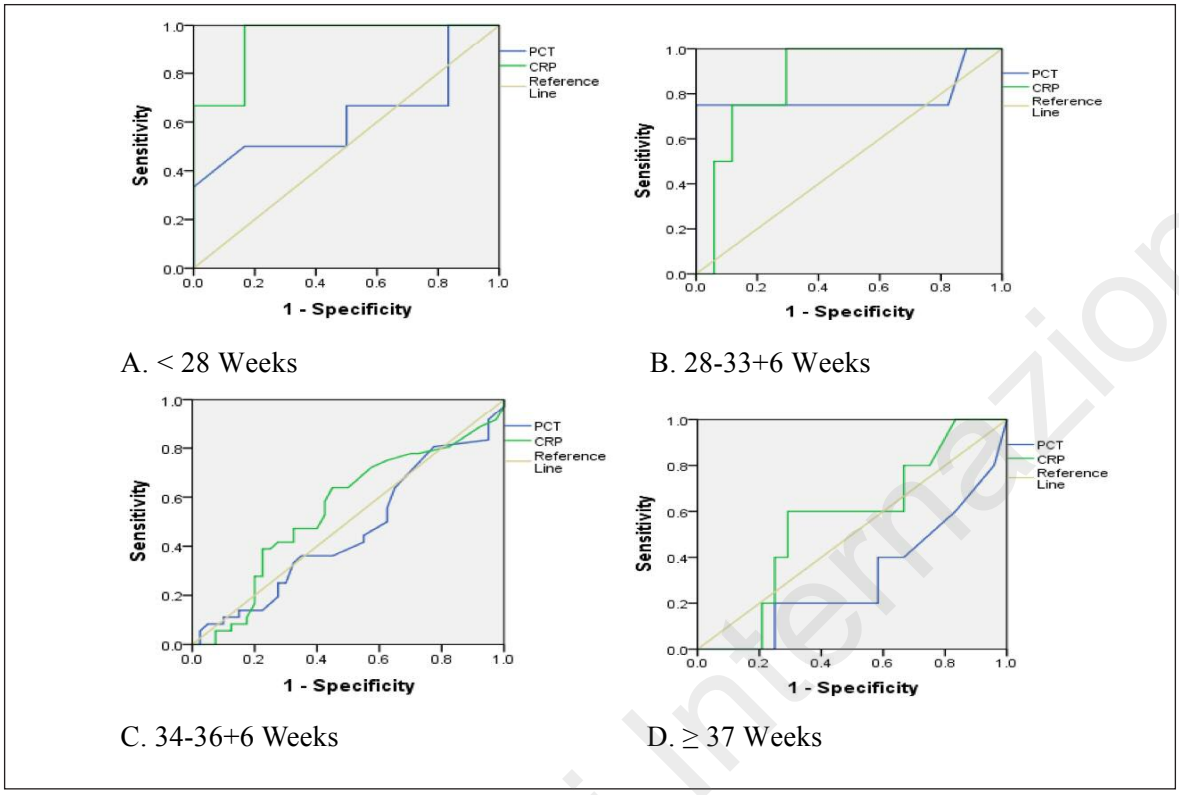

Figure 2. The ROC curves of PCT and CRP for pregnant women at different gestational ages.

Table 3. The sensitivity analysis for PCT and CRP for different gestational age groups.

Pregnancy duration in weeks		Optimal cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
< 28	CRP (mg/l)	12.500	1.000	0.833	0.857	1.000
	PCT (ng/ml)	0.140	0.500	0.833	0.750	0.625
28-33+6	CRP (mg/l)	12.500	0.639	0.550	0.557	0.632
	PCT (ng/ml)	0.445	0.830	0.950	0.597	0.539
34-36+6	CRP (mg/l)	8.500	1.000	0.706	0.444	1.000
	PCT (ng/ml)	0.375	0.75	1.000	1.000	0.945
≥ 37	CRP (mg/l)	18.500	0.600	0.708	0.296	0.896
	PCT (ng/ml)	0.600	0.000	0.958	0.000	0.824
All	CRP (mg/l)	12.500	0.686	0.958	0.501	0.764
	PCT (ng/ml)	0.445	0.137	0.954	0.636	0.653

Discussion

An intrauterine infection in pregnant women can result in an infection to both the mother and fetus at the same time. Furthermore, it is one of the main causes of maternal morbidity and mortality, perinatal infection, and death. If an early intrauterine infection is not treated in a timely manner, fever can result in fetal tachycardia or bradycardia, decreased or increased fetal movement, fetal hypoxia, or even fetal death (11-14). In the case of fetal hypoxia, the fetus suffers different degrees of asphyxia, which threatens its health and even life. Thus, it is critical to establish a rapid, accurate means for the early diagnosis of fever and infection in pregnant women.

Some scholars systematically compared inflammation-related indicators, such as IL-6, CRP, white blood cell (WBC) count, and N, (1-4) and their results indicated that serum PCT could be used to monitor the inflammation process. It was a superior indicator

because of its sensitivity and specificity.

This study retrospectively analyzed 276 cases of pregnant women with PROM that had been admitted into our hospital between January 2011 and January 2016 who had underwent placental pathological examinations as well as CRP and PCT tests results. It was found that, without grouping, the diagnostic value of CRP for subclinical intrauterine infection is better than that of PCT.

Additionally, the subjects were divided into four groups according to different gestational ages: women pregnant for <28 weeks, 28-33+6 weeks, 34-36+6 weeks, and full term. The ROC curves and the hypothesis tests demonstrated that for women pregnant <28 weeks, the diagnostic effect of CRP is statistically better than the gold standard, the diagnostic effect of PCT is statistically comparable to the gold standard. And the sensitivity of the CRP values are significantly better than that of PCT, and the specificity of the both is the same. Thus the both test have satisfactory accuracy, and the diagnostic value of CRP is better than that of PCT. For women pregnant for 28-33+6 weeks, the diagnostic effect of CRP and PCT is statistically better than the gold standard. And the sensitivity and specificity of the PCT are significantly better than that of CRP. Thus the both test have satisfactory accuracy, and the diagnostic value of PCT is better than CRP. However, there is not significant statistical differences between testes and the gold standard in the groups (34-36+6, and ≥ 37), so, the both test have unsatisfactory accuracy in the groups.

Studies have previously shown that the diagnostic values of PCT and CRP for intrauterine infections were positively correlated with their levels. In contrast, our study via logistics regression analyses showed that the risk of intrauterine infection did not increase as the levels of PCT and CRP increased. This result might be due to the small sample size and to large error; thus, further study is necessary.

In summary, both PCT and CRP are good predictive and diagnostic indicators for PROM associated with chorioamnionitis, and PCT is more suitable for 28-33+6 weeks pregnant women. The pathogens that may cause secondary infection after PROM are not limited to bacteria, they also include chlamydia trachomatis, ureaplasma urealyticum, mycoplasma genitalium, and toxoplasma gondii, all of which are beyond the concentration range of PCT. Therefore, further studies with high quality randomized controlled trials with large samples are necessary to determine whether the diagnostic values of PCT and CRP for intrauterine infection are positively correlated with their levels and whether there is a better combination method that could improve the diagnosis value for PROM associated with intrauterine infection.

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