Predictors for histological chorioamnionitis among women with preterm premature rupture of membranes after dexamethasone administration:a retrospective study

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Abstract

Objective: To investigate reliable biomarkers for predicting histological chorioamnionitis (HCA). Design: In this retrospective study, PPROM mothers were treated with a course of dexamethasone. Blood tests for serum indictors were conducted continuously after first injection. Setting: One Shanghai hospital Population: PPROM mothers before 34 0/7 weeks of gestation Methods: Data were compared by General Linear Model analysis. The diagnostic accuracy in predicting HCA were evaluated with ROC curve. Main Outcome Measures: The response of infectious indictors to dexamethasone treatment; the diagnostic accuracy for CRP and PCT in predicting HCA. Results: We found 98 HCA women (62.42%) and 59 CON women (37.58%) in 157 PPROM mothers. WBC and neutrophil significantly increased 24 hours after the first injection in both groups, followed by a decrease at 72 hours post first injection ($P<0.05$). No significances were found between two groups in WBC, neutrophil and lymphocyte. Both CRP and PCT were significantly higher in the HCA group after first injection. PCT had both high specificity and sensitivity, especially at the baseline (cutoff, 0.031 ng/ml). Furthermore, the positive predictive values (PPV) of PCT were respectively 0.946 and 0.960 at 48 (cutoff, 0.049 ng/ml) and 72 (cutoff, 0.051 ng/ml) hours, which were better than the corresponding PPV of CRP. Conclusion: The response of WBC, neutrophil and lymphocyte to dexamethasone could be differentiated from uterine infection; PCT could be a reliable biomarker for early diagnosis of HCA. Funding: Shanghai Municipal Commission of Health and Family Planning (GWIV-26, 202040128); Pudong Commission of Health and Family Planning (PW2019D-13).

Predictors for histological chorioamnionitis among women with preterm premature rupture of membranes after dexamethasone administration: a retrospective study

Running title: HCA predictors among PPROM women after dexamethasone administration

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Data were compared by General Linear Model analysis. The diagnostic accuracy in predicting HCA were evaluated with ROC curve.

Main Outcome Measures:

The response of infectious indictors to dexamethasone treatment; the diagnostic accuracy for CRP and PCT in predicting HCA.

Results:

We found 98 HCA women (62.42%) and 59 CON women (37.58%) in 157 PPROM mothers. WBC and neutrophil significantly increased 24 hours after the first injection in both groups, followed by a decrease at 72 hours post first injection ($P<0.05$). No significances were found between two groups in WBC, neutrophil and lymphocyte. Both CRP and PCT were significantly higher in the HCA group after first injection. PCT had both high specificity and sensitivity, especially at the baseline (cutoff, 0.031 ng/ml). Furthermore, the positive predictive values (PPV) of PCT were respectively 0.946 and 0.960 at 48 (cutoff, 0.049 ng/ml) and 72 (cutoff, 0.051 ng/ml) hours, which were better than the corresponding PPV of CRP.

Conclusion:

The response of WBC, neutrophil and lymphocyte to dexamethasone could be differentiated from uterine infection; PCT could be a reliable biomarker for early diagnosis of HCA.

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Keywords:

Preterm premature rupture of membrane, histological chorioamnionitis, dexamethasone, white blood cell count, C-reactive protein, procalcitonin

Tweetable abstract:

HCA might not influence the response of WBC, neutrophil and lymphocyte in PPROM women within 72 hours after first injection; PCT could be a sensitive and reliable marker for early diagnosis of HCA.

Introduction

A high proportion of preterm premature rupture of membranes (PPROM) occurring before 34 weeks of gestation are associated with chorioamnionitis (CA), which is caused primarily by the ascending bacterial invasion of the vagina, leading to infection of fetal membranes, placenta, amniotic fluid, and uterine cavity[1-3]. Chorioamnionitis could be divided into clinical CA (CCA) and histological CA (HCA). CCA is diagnosed based on the presence of clinical evidence before or during labor and delivery; HCA is identified from the evidence of infection and inflammation in the examination of the placenta[4, 5], with its clinical course often asymptomatic and its prevalence higher than CCA[6, 7]. In addition, HCA was associated with early-onset sepsis and combined perinatal comorbidities in infants, which are of more diagnostic importance than CCA alone[8]. However, confirmation of HCA through pathological examination of the placenta is unable to provide an early warning for the treatment of newborns. Therefore, it is vitally important to explore a sensitive and accurate diagnostic biomarker for early detection of histological chorioamnionitis that may allow for early intervention and treatment of newborn infants.

As is well known, monitoring of maternal serum infectious indicators including WBC, neutrophil, lymphocyte, CRP and PCT levels may assist in early diagnosis of infection. However, antenatal corticosteroid therapy, including either betamethasone or dexamethasone for women in preterm labor[9, 10] have shown a transient increase in maternal WBC and neutrophil, which is easily confused with chorioamnionitis and induces unnecessary early termination of the pregnancy[11-13]. Although some studies have shown that this increase was physiologic leukocytosis after corticosteroid administration, most of those results were merely obtained from PPROM patients without chorioamnionitis, lacking the comparison of data from a HCA group. In addition, procalcitonin (PCT), secreted by thyroid C-cells, is markedly elevated in many bacterial infections and can be used as a prognostic infectious indicator of sepsis[14]. However, its role as a biomarker for the detection of HCA in PPROM is still controversial[15-17]. Furthermore, the constant response of PCT after injection of corticosteroids has not been fully investigated.

Consequently, this retrospective study was conducted to thoroughly investigate the dynamic responses of maternal WBC, neutrophil, lymphocyte, CRP and PCT to antenatal dexamethasone in PPROM women, compare the differences of the above serum indicators between the CON women and HCA group, and determine the predictive value of CRP and PCT for predicting HCA by analyzing dynamical changes constantly.

Methods

Participants

Patients with preterm premature rupture of membranes (PPROM) admitted into our hospital between January 2019 and December 2021 were included in this study. Inclusion criteria: all patients including single pregnancy or multiple pregnancy met the diagnostic criteria of spontaneous PPROM[18], with gestational age between 26 0/7 and 33 6/7 weeks. After admission (baseline), all women received a single course of

four intramuscular injections of 6 mg dexamethasone at 12-hour intervals to facilitate fetal lung maturity. A 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin for 48 hours followed by oral amoxicillin and erythromycin was given. Tocolytic agent like nifedipine was cautiously administrated for the first 48 hours if contractions were occurring and avoided if there was evidence of infection. Magnesium sulfate treatment was performed as a neuroprotective in pregnancies at less than 32 0/7 weeks of gestation. Culture for group B streptococci (GBS) were performed for all women.

Exclusion criteria: women with the complications of acute rheumatism, other infections, substantial abnormalities in neurological, psychiatric, cardiac, endocrinological, hematologic, hepatic, renal, or metabolic functions as determined by history, physical examination and blood screening tests were all excluded. Women who had an interval of admission to delivery of more than 7 days or less than 3 days during expectant management were also excluded. Prolongation of pregnancy was associated with a higher risk of chorioamnionitis[18] while a 7-day course of therapy of latency antibiotics is recommended during expectant management as discussed in detail above, and a single course of corticosteroids may persist 48 hours. Therefore, we excluded this condition. The study protocol was approved by the hospital's ethics committee (No. KS22218).

Study design

Before dexamethasone was injected, blood was drawn for peripheral WBC, neutrophil, lymphocyte, CRP and PCT. Then the same tests were repeated at 24, 48 and 72 hours after the injection of the first dose of dexamethasone. Delivery was performed (induction or cesarean as appropriate) after 34 0/7 weeks of gestation or after the development of early signs of intraamniotic infection. All patients underwent placenta pathologic examination after birth. HCA is diagnosed in the presence of acute inflammatory changes in any of the tissue samples (amnion, chorion-decidua, umbilical cord, and chorionic plate), using previously published criteria[19], which manifests as neutrophils in the chorion or in the chorion and amnion on the examination of a membrane roll and chorionic plate of the placenta. Two independent pathologists reviewed the histology slides of the placentas for the pregnant women participating in the study. Women confirmed HCA with the pathological diagnosis of placenta were included into the HCA group while others into the non-HCA (CON) group. CCA is diagnosed clinically in accordance with the following signs: fever ([?]38°C orally), vaginal discharge odor, maternal tachycardia (>100 beats per minute), and fetal tachycardia (>160 beats per minute), abdominal pain, uterine tenderness, and leukocytosis. The presence of at least three of these signs has been shown to indicate a strong probability of chorioamnionitis[20].

Statistical analysis

Comparisons between continuous variables were evaluated by the Student'st -test for independent samples, and proportions were compared with the chi-squared test or the Fisher's exact test. Comparisons between baseline and after-treatment periods were drawn by Repeated Measures of General Linear Model analysis. Outcomes in the CON group and the HCA group were analyzed by the multivariate analysis. ROC curve was used to calculate the cut-off, sensitivity, specificity, positive predictive value, and negative predictive value of the optimal cut-off value, respectively. All analyses were completed with SPSS version 23 software. All tests for statistical significance were two-tailed and were calculated under the assumption of a type I error being smaller than 0.05 ($p<0.05$). Data are presented within one standard deviation of mean.

Results

Maternal and neonatal characteristics

Initially, a total of 380 patients were enrolled in the study; 223 women were removed from the study based on the exclusion criteria stated above. A total of 157 mothers were involved in this study with 98 women (62.42%) detected HCA and 59 women (37.58%) detected non-HCA eventually. The number of patients who met each exclusion criterion is shown in Figure 1. Demographic and clinical characteristics, and the risk factors of the mothers are given in Table 1. Mothers with or without HCA were not significantly different in comparison to age, interval of admission to delivery, incidence of multiple pregnancy, infertility, gestational diabetes mellitus, cesarean delivery rate, culture of vaginal secretion including streptococcus agalactiae

(GBS), mycoplasma and candidiasis ($p>0.05$)). Three characteristics have shown significant, which are gestational age at admission (weeks), gestational age at delivery (weeks), and birth weight (grams). The mean gestational age at admission for the CON group was 32.27 weeks with standard deviation 1.31 weeks, but for the HCA group was 30.09 weeks with standard deviation 1.94 weeks. Both showed very strong significance as the p-value was smaller than 0.001. Interval of admission to delivery did not show significance between two groups as the p-value is 0.31. There were only two women meeting the criteria of CCA in the CON group (3.4%) and 7 women in the HCA group (7.1%), which showed no significant difference with the p-value 0.485. Infants of non-chorioamnionitis mothers were significantly heavier than those of mothers in the HCA with the p-value being smaller than 0.001. Specifically, the mean of the CON (HCA) group was 2052 (1772) grams with standard deviation 284 (317) grams, respectively. Apgar scores in two groups were similar.

The response of WBC to dexamethasone treatment

In Fig. 2A, patients were divided into two groups according to the histological chorioamnionitis. Both groups showed a similar significant increase in mean WBC count. In Table 2, mean WBC count increased from the baseline value of 9.36×10^9 to 12.24×10^9 cell/L by 30.77% ($p<0.001$) in the CON group, and from 9.71×10^9 to 12.30×10^9 cell/L by 26.67% ($p<0.001$) in the HCA group 24 hours after injection of the first dose of dexamethasone. Then the level of mean WBC remained stable in both groups for the next 24 hours, before declining to 11.24×10^9 cell/L in the CON group and to 11.41×10^9 cell/L in the HCA group 72 hours after the first injection, without returning to the baseline level ($p<0.001$ in both groups). The overall analysis with repeated measure ANOVA revealed no significant differences between two treatment groups at all the time points. These results indicate the same physiologic leukocytosis after dexamethasone treatment in both CON and HCA groups.

The response of neutrophil to dexamethasone treatment

Similar to mean WBC count, in Fig. 2B and Table 2, significant rises in mean neutrophil in both groups were noted 24 hours after injection of the first treatment; there was a 44.85% increase in the CON group from 7.18×10^9 to 10.40×10^9 cell/L ($p<0.001$) and a 39.87% increase in the HCA group from 7.45×10^9 to 10.42×10^9 cell/L ($p<0.001$). Declining levels of neutrophil were recorded on day three (72 hours) after the first dexamethasone injection compared to the value at day two (48 hours). There was a 17.45% decline in the CON group from 10.37×10^9 to 8.56×10^9 cell/L ($p<0.001$) and a 16.38% decline in the HCA group from 10.44×10^9 to 8.73×10^9 cell/L ($p<0.001$); these levels remained higher than in the baseline ($p<0.001$ in both groups). At all the time points, no significant difference in mean neutrophil between two groups was found during the process. The above data confirmed HCA might not influence the response of neutrophil to dexamethasone in PPROM women.

The response of lymphocyte to dexamethasone treatment

24 hours after the initial treatment (Fig. 2C and Table 2), lymphocyte in the CON group descended significantly by 16.34% ($p<0.001$); lymphocyte in the HCA group also declined significantly by 16.78% ($p<0.001$). At 48 hours, mean lymphocyte levels in both groups returned to their baseline levels. At 72 hours after first injection, a significant increase in lymphocyte levels was recorded. Lymphocyte levels went from 1.51×10^9 to 1.91×10^9 cell/L, an increase of 26.49% ($p<0.001$) in the CON group, and a similar elevation was found from 1.42×10^9 to 1.81×10^9 cell/L, an increase of 27.46% ($p<0.001$) in the HCA group. There was no significance in mean lymphocyte levels between the HCA and CON groups during the process. These results demonstrate that both groups had similar physiologic response to dexamethasone whether they had HCA or not.

The response of CRP to dexamethasone treatment

CRP level changes were quite different between the CON and HCA groups after the injection of dexamethasone (Fig. 2D and Table 2). In the CON group, CRP levels began to decline significantly by 31.71% from the baseline of 1.64 to 1.12 mg/L at 48 hours after the initial treatment ($p=0.024$) and went on to reach the lowest level of 1.06 mg/L at 72 hours post initial treatment (by 35.37%, $p=0.045$). In contrast, in the

HCA group, a significant increase in mean CRP levels of 58.82% was found from the baseline of 2.38 to 3.78 mg/L at 24 hours after treatment (p=0.013) and the CRP levels steeply dropped to 2.81mg/L at 48 hours, this level was similar to the baseline (p=0.403). When comparing the CRP levels between the two groups, results showed significant difference at 24 hours (1.46 vs. 3.78 mg/L, p=0.018), 48 hours (1.12 vs. 2.81 mg/L, p=0.018) and 72 hours (1.06 vs. 2.23 mg/L, p=0.001). The response of CRP to dexamethasone injection might be more likely associated with HCA.

The response of PCT to dexamethasone treatment

PCT levels in the CON group (Fig. 2E and Table 2) increased from the baseline value of 0.024 to 0.030 ng/ml (p<0.001) when measured at 24 hours post injection, and then remained at the same level for the next 48 hours. Similarly, PCT levels in the HCA group increased from 0.040 to 0.058 ng/ml (p=0.016) 24-hours after the injection of dexamethasone. The difference was that PCT levels continued to increase in the HCA group to a peak of 0.110 ng/ml at 72 hours (p=0.001). Comparing the two groups, PCT levels in the HCA group were consistently higher than those in the CON group 72 hours after the first injection (p<0.05). These results indicate that HCA instead of dexamethasone might influence the response of PCT in PPROM women less than 34 gestational weeks. Due to this evidence, we analyzed the diagnostic values of PCT and CRP in the next step of our research.

The diagnostic values of PCT and CRP

As shown in Figure. 3 and Table. 3, for women at baseline and different times after their initial treatments (24, 48 and 72 hours), the areas under ROC curves of CRP were 0.588, 0.788 ,0.701, and 0.714, respectively, with statistically significant differences only in 24, 48 and 72 hours (p<0.001). As for PCT, the areas under ROC curves of the same time point were 0.763, 0.730, 0.901, and 0.902, respectively, with statistically significant differences in all the time points (p<0.001). Meanwhile, the areas of PCT were significantly better than those of CRP at baseline, 48 and 72 hours after the first injection (p<0.05).

Using the optimal cutoff value as the positive threshold, the sensitivities of CRP at baseline and different time after treatment (24, 48 and 72 hours) were 0.837, 0.918, 0.837, 0.786 and the specificities were 0.373, 0.542, 0.542, 0.644, respectively. As for PCT, the sensitivities at the same time were 0.765, 0.765, 0.796, and 0.816; the specificities were 0.746, 0.678, 0.932, and 0.949, respectively. Generally, CRP had high sensitivity but low specificity while PCT had high specificity and modest sensitivity. It is worth noting that both sensitivity and specificity of PCT were prominent initially at the baseline (cutoff, 0.031ng/ml), not to mention 48 hours (cutoff, 0.048 ng/ml) and 72 hours (cutoff, 0.051 ng/ml), which indicated PCT might be more sensitive for early diagnosis of HCA than CRP.

The positive predictive values (PPV) of PCT at the baseline and different times after initial treatment (24, 48, and 72 hours) were 0.819, 0.781, 0.946, and 0.960, all of which were better than the corresponding negative predictive values (NPV) (0.679, 0.657, 0.753, and 0.775). In contrast, the PPV and NPV of CRP seemed to have no advantage in comparison with those of PCT at the same time; the PPV of PCT were especially prominent at 48 and 72 hours. These results demonstrated that PCT might be a reliable candidate for HCA diagnosis.

Discussion

This study retrospectively analyzed 157 cases of PPROM women with gestational age between 26 0/7 and 33 6/7 weeks and investigated the dynamic responses of maternal WBC, neutrophil, lymphocyte, CRP and PCT to antenatal dexamethasone. We found both CON and HCA groups had similar physiologic response to dexamethasone in WBC, neutrophil, and lymphocyte whether they had HCA or not. On the contrary, HCA might influence the response of CRP and PCT in PPROM women, and notably PCT had better predictive values of HCA when compared with those of CRP.

Membrane rupture may occur for a variety of reasons and intraamniotic infection has been shown to be commonly associated with preterm PROM, especially at earlier gestational ages[6, 21]. Previous studies which have shown HCA occurred in approximately 50–60% of women with PPROM[22, 23]. Consistent with

those data, a total of 157 mothers were involved in this study and 98 women (62.42%) were identified as HCA. Only 5 patients (5.75%) presenting positive symptoms were diagnosed with CCA, of whom 4 were proven to have HCA, which suggests that diagnosis of CA solely based on clinical manifestation may underestimate the true risks to the offspring. Hence, it is vital for detection of HCA in PPROM women, especially in those with younger gestational ages who were more prone to greater incidence of HCA[6]. Furthermore, limitations on the timeliness of placenta pathological examination urges the value of early diagnosis of HCA that may help provide timely intervention to newborn infants.

Antenatal corticosteroid therapy has shown a transient physiologic response including an increase in maternal WBC and neutrophil, which is caused by increasing leukocyte extravasation from bone marrow and decreasing their clearance from blood vessels[11-13]. Some study demonstrated WBC increased from a baseline value of $11.3x10^9$ to $16.2x10^9$ cell/L 24 hours after treatment and normalized thereafter[24]. Voon et al. found mean WBC in a preterm subgroup was initially $10.65x10^9$cell/L, then rose to $11.99x10^9$ cell/L at 36 hours after dexamethasone injection, and finally returned to baseline level[13]. Our study confirmed the physiologic leukocytosis after administration of dexamethasone in PPROM which could differentiate from uterine infection. In comparison, mean WBC and neutrophil counts in our study did not return to their initial baseline levels even at 72 hours after treatment, which is different from the aforementioned studies. This may be explained by the fact that the preterm women recruited by prior studies included both PPROM patients and those with intact membranes, while women in our study only included PPROM mothers. The results indicate the responses of maternal WBC and neutrophil in the first 72 hours after dexamethasone injection might not be influenced by HCA; hence they could not predict HCA in PPROM women.

Different from WBC, neutrophil and lymphocyte, CRP and PCT levels in the HCA group were consistently higher than those in the CON group at different time points after patients received their first injection, indicating the responses of CRP and PCT to dexamethasone injection might be associated with HCA. When it comes to analysis of diagnostic value, this study showed that PCT is better than that of CRP for early prediction of HCA. The areas under ROC curves of PCT were significantly better than those of CRP at baseline, 48 and 72 hours, which indicate that PCT had greater predictive value than CRP. Similarly, some scholars found that both CRP and PCT had satisfactory accuracy, and the diagnostic value of PCT is better than CRP for women pregnant for 28-34 weeks[17]. PCT also had both high specificity and sensitivity even at the initial baseline, whereas CRP had high sensitivity but low specificity, which meant PCT might be more sensitive for early diagnosis of HCA than CRP. A previous study found PCT inversely had a poor sensitivity and a modest specificity compared with CRP[15], but the author included all the intrauterine infectious patients without distinction between CCA and HCA. In the HCA group, mean CRP showed a significant rise only at 24 hours after initial treatment before dropping to the baseline vale where it remained stable. PCT levels increased continually from baseline to the peak at 72 hours post first treatment, which reflected the dynamic response of CRP and PCT after dexamethasone and required constantly monitoring of trends.

Conclusion

Our results confirmed HCA might not influence the response of WBC, neutrophil, and lymphocyte in PPROM women before 34 0/7 gestational weeks within 72 hours after first injection, which could be differentiated from uterine infection. Moreover, PCT could be a sensitive and reliable biomarker for early diagnosis of HCA.

Acknowledgements

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Declaration of Competing Interest

The authors report no declarations of interest.

Author Roles

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Ethics approval

The study protocol was approved by the hospital's ethics committee (No. KS22218).

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Legend:

Fig. 1. Flowchart and study design

Fig. 2: The response of different infectious indicators to dexamethasone in PPROM women

A and B: WBC and neutrophil increased 24 hours after the first injection in both groups, followed by a decrease at 72 hours post first injection to levels that remained higher than the baseline. No significance was found between two groups. C: Mean lymphocyte declined at 24 hours whereas peaked ultimately at 72 hours. There was no significance between the two groups. D and E: In the HCA groups, CRP temporarily increased at 24 hours before dropping to the baseline and remaining at stable level; PCT increased continually to the peak at 72 hours. Both CRP and PCT were significantly higher in HCA group after first injection.

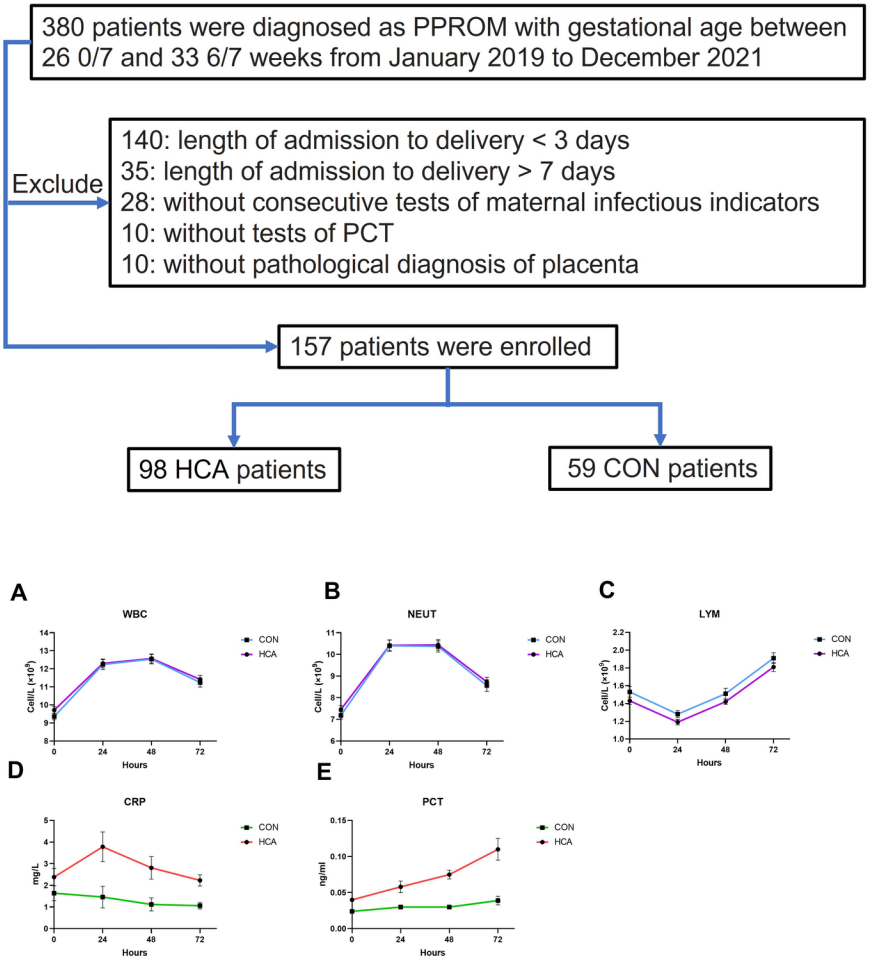
Fig. 3: The ROC curves of CRP and PCT for HCA after administration of dexamethasone

A: For women at baseline, the area under ROC curve of PCT was significantly better than that of CRP (0.763 vs. 0.588; $p<0.05$). B: The areas under ROC curve of CRP and PCT were 0.788 and 0.730, respectively. No significance was found between them. C: The area under ROC curve of PCT was significantly better than that of CRP at 48 hours (0.901 vs. 0.701; $p<0.05$). D: The area under ROC curve of PCT was significantly better than that of CRP at 48 hours (0.902 vs. 0.714; $p<0.05$).

Table. 1: Characteristics of PPROM women in CON and HCA group

Table. 2: Laboratory tests at baseline and after administration of dexamethasone

Table. 3: The predictive analysis for CRP and PCT for HCA after administration of dexamethasone



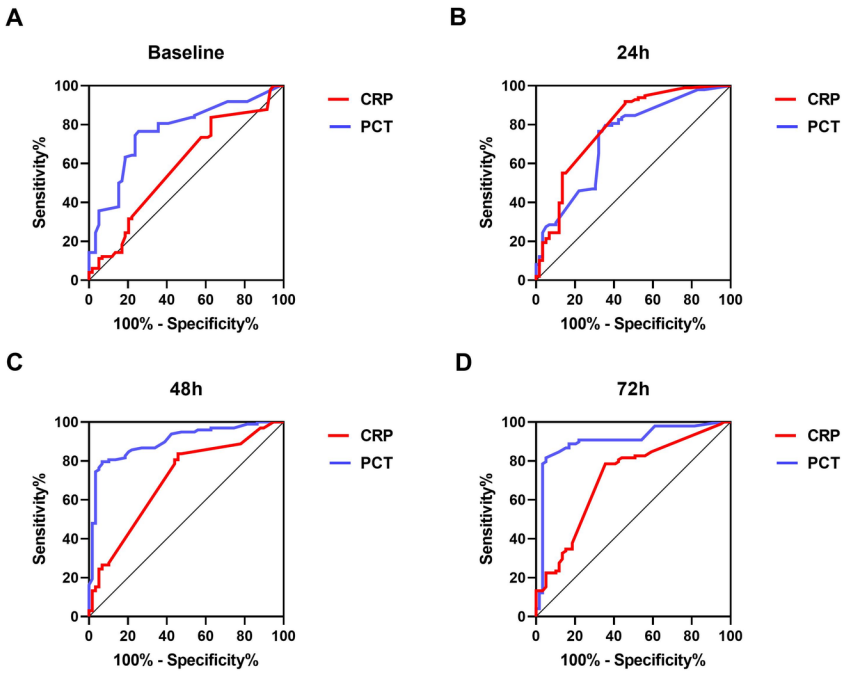


Table 1: Characteristics of PPROM women in CON and HCA group

	CON (n=59)	HCA (n=98)	p
Maternal age (years)	32.03 (3.29)	32.00 (3.39)	0.951
ART	9 (15.3%)	23 (23.5%)	0.306
Multiple pregnancy	2 (3.4%)	12 (12.2%)	0.082
GDM	3 (5.1%)	3 (3.1%)	0.673
Gestational age at admission (weeks)	32.27 (1.31)	30.90 (1.94)***	0
Culture of vaginal secretion			
GBS+	1 (1.7%)	2 (2.0%)	1
Mycoplasma+	6 (10.2%)	10 (10.2%)	1
Candidiasis+	5 (8.5%)	4 (4.1%)	0.298
CCA	2 (3.4%)	7 (7.1%)	0.485
Interval of admission to delivery (days)	4.29 (1.54)	4.52 (1.28)	0.31
Gestational age at delivery (weeks)	32.88 (2.55)	31.52 (3.02)***	0
Cesarean delivery	28 (47.5%)	49 (50.0%)	0.869
Birth weight (g)	2052 (284)	1772 (317)***	0
1-min Apgar score	8.66 (0.93)	8.66 (0.52)	0.997
5-min Apgar score	9.22 (0.75)	9.19 (0.62)	0.756

Data are presented as mean (standard deviation) or n (%) as appropriate.

HCA: histological chorioamnionitis; CON: non-HCA.

ART: assisted reproductive technology; GDM: gestational diabetes mellitus; GBS: group B streptococci; CCA: clinical chorioamnionitis.

* p<0.05; ** p<0.01; ***p<0.001.

Table 2: Laboratory tests at baseline and after administration of dexamethasone

	Baseline	24h after first injection	48h after first injection	72h after first injection
WBC (n=157)				
CON (n=59)	9.36 (1.39)	12.24 (2.15)^{aaa}	12.54 (2.01)^{aaa}	11.24 (1.94)^{aaa}
HCA (n=98)	9.71 (1.87)	12.30 (2.38)^{aaa}	12.57 (2.50)^{aaa}	11.41 (2.13)^{aaa}
NEUT (n=157)				
CON (n=59)	7.18 (1.32)	10.40 (1.99)^{aaa}	10.37 (2.01)^{aaa}	8.56 (2.07)^{aaa}
HCA (n=98)	7.45 (1.81)	10.42 (2.47)^{aaa}	10.44 (2.36)^{aaa}	8.73 (2.11)^{aaa}
LYM (n=157)				
CON (n=59)	1.53 (0.45)	1.28 (0.28)^{aaa}	1.51 (0.46)	1.91 (0.48)^{aaa}
HCA (n=98)	1.43(0.35)	1.19 (0.28)^{aaa}	1.42 (0.34)	1.81 (0.49)^{aaa}
CRP (n=157)				
CON (n=59)	1.64 (2.59)	1.46 (3.84)	1.12 (2.27)^{a}	1.06 (1.12)^{a}
HCA (n=98)	2.38 (3.99)	3.78 (6.80)^{a,b}	2.81 (5.15)^{b}	2.23 (2.54)^{bb}
PCT (n=157)				
CON (n=59)	0.024 (0.012)	0.030 (0.016)^{aaa}	0.030 (0.015)^{aa}	0.039 (0.048)^{a}
HCA (n=98)	0.040 (0.021)^{bbb}	0.058 (0.082)^{a,b}	0.075 (0.056)^{aaa,bbb}	0.110 (0.148)^{aaa,bbb}

Values are in mean (standard deviation); HCA: histological chorioamnionitis; CON: non-HCA.

WBC: white blood cell count ($\times 10^9$ cell/L); NEUT: neutrophil count ($\times 10^9$ cell/L); LYM: lymphocyte count ($\times 10^9$ cell/L); CRP (mg/L); PCT (ng/ml).

[a] Significant change ($p<0.05$) vs. baseline level; [aa] significant change ($p<0.01$) vs. baseline level; [aaa] significant change ($p<0.001$) vs. baseline level.

[b] Significant change ($p<0.05$) vs. CON; [bb] significant change ($p<0.01$) vs. CON; [bbb] significant change ($p<0.001$) vs. CON.

Table 3: The predictive analysis of CRP and PCT for HCA after administration of dexamethasone

Time after treatment	Areas under ROC curves	Optimal cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Baseline						
CRP (mg/L)	0.588	0.520	0.837	0.373	0.667	0.604
PCT (ng/ml)	0.763*	0.031	0.765	0.746	0.819	0.679
24h after first injection						
CRP (mg/L)	0.788	0.895	0.918	0.542	0.750	0.815
PCT (ng/ml)	0.730	0.039	0.765	0.678	0.781	0.657
48h after first injection						
CRP (mg/L)	0.701	0.530	0.837	0.542	0.739	0.689
PCT (ng/ml)	0.901*	0.048	0.796	0.932	0.946	0.753
72h after first injection						
CRP (mg/L)	0.714	0.975	0.786	0.644	0.786	0.667
PCT (ng/ml)	0.902*	0.051	0.816	0.949	0.960	0.775

* $p<0.05$: significant change of PCT vs. CRP.