Accepted: 17 January 2023 | Published Online 13 March 2023

DOI: 10.1111/1471-0528.17431

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

General obstetrics

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

Jing Peng[1,2] | **Ying Chen**[2] | **Sheng Wan**[2] | **Tianfan Zhou**[1] | **Yu-Sin Chang**[3] | **Xiaobo Zhao**[2] | **Xiaolin Hua**[1,2]

[1]Shanghai Key Laboratory of Maternal Fetal Medicine, Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, Shanghai, China

[2]Obstetrics Department, Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, Shanghai, China

[3]Department of Mathematics, Milwaukee School of Engineering, Milwaukee, USA

Correspondence
Xiaobo Zhao and Xiaolin Hua, Obstetrics Department, Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, Shanghai, China.
Email: zhaoxiaobo@51mch.com and xiaolin_hua@tongji.edu.cn

Funding information
Funding for this study was provided by the Shanghai Municipal Commission of Health and Family Planning (202040128), the Pudong Commission of Health and Family Planning (PW2019D-13) and the Shanghai Science and Technology Committee (22Y11906200).

Abstract

Objective: To investigate reliable biomarkers for predicting histological chorioamnionitis (HCA) in women with preterm prelabour rupture of membranes (PPROM).
Design: A retrospective study.
Setting: A maternity care hospital in Shanghai.
Population: Women with PPROM before $34^{+0/7}$ weeks of gestation.
Methods: Mean values of biomarkers were compared by two-way analysis of variance (ANOVA). Log-binomial regression models were used to assess the association between biomarkers and risk of HCA. A stepwise logistic regression model was used to develop a multi-biomarker prediction model and identify the independent predictors. The area under the receiver operating characteristic curve (AUC) was used to assess prediction performance.
Main outcome measures: The ability of the individual biomarker and the combination of multiple biomarkers to predict HCA.
Results: In 157 mothers with PPROM, 98 (62.42%) women had HCA and 59 (37.58%) women did not have HCA. No significant differences were observed between the two groups in white blood cell, neutrophil or lymphocyte counts, whereas both high-sensitivity C-reactive protein (hsCRP) and procalcitonin (PCT) were significantly higher in the HCA group. HsCRP and PCT were found to be independently associated with the risk of HCA, and PCT had a larger AUC value than hsCRP ($p < 0.05$). The optimal multi-biomarker prediction model for HCA (AUC = 93.61%) included hsCRP at 72 hours and PCT at 48 and 72 hours, and PCT had a stronger prediction capacity than hsCRP.
Conclusions: PCT could be a reliable biomarker for the early prediction of HCA in women with PPROM within 72 hours of dexamethasone treatment.

KEYWORDS
high-sensitivity C-reactive protein, histological chorioamnionitis, preterm prelabour rupture of membranes, procalcitonin

1 | INTRODUCTION

A high proportion of preterm prelabour rupture of membranes (PPROM) occurring before 34 weeks of gestation is associated with chorioamnionitis (CA), which is caused primarily by an ascending bacterial invasion of the vagina, leading to the infection of fetal membranes, placenta, amniotic fluid and the uterine cavity.[1–3] Chorioamnionitis includes clinical CA (CCA) and histological CA (HCA). CCA is diagnosed based on the presence of clinical evidence before or during labour and delivery; HCA is identified from the evidence of infection and inflammation in the examination

Jing Peng and Ying Chen contributed equally to this work.

of the placenta,[4,5] with a clinical course that is often asymptomatic and a prevalence that is higher than that of CCA.[6,7] In addition, HCA was associated with early-onset sepsis and combined perinatal comorbidities in infants, which are of greater 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 the early prediction of HCA that may allow for early intervention and treatment of fetuses/newborns.

As is well known, elevated maternal serum infection indicators, including white blood cell (WBC), neutrophil, lymphocyte, high-sensitivity C-reactive protein (hsCRP) and procalcitonin (PCT), may assist in the early diagnosis of infection. However, antenatal corticosteroid therapy, including either betamethasone or dexamethasone for fetal lung maturation for women in preterm labour,[9,10] has shown a transient increase in maternal WBC and neutrophil, which is easily confused with chorioamnionitis and triggers unnecessary early terminations of pregnancy.[11–13] Although some studies have shown that this increase was physiological leucocytosis after corticosteroid administration, most of those results were merely obtained from PPROM patients without chorioamnionitis, lacking the comparison of data from THE HCA group. In addition, PCT, secreted by thyroid C-cells, is markedly elevated in many bacterial infections and can be used as a prognostic infection indicator of sepsis.[14] However, its role as a biomarker for the detection of HCA in PPROM remains controversial.[15–17] Furthermore, the sequential response of PCT after the 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, hsCRP and PCT to antenatal dexamethasone in women with PPROM, compare differences in these circulating indicators between the HCA group and the non-HCA group, and determine the predictive values of these biomarkers for HCA.

2 | METHODS

2.1 | Study design and population

This is a retrospective study. Patients with PPROM admitted into Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, between January 2019 and December 2021 were included in this study. The study protocol was approved by the hospital ethics committee (no. KS22218).

Inclusion criteria: all patients, including single pregnancy or multiple pregnancy, that met the diagnostic criteria of spontaneous PPROM between $26^{+0/7}$ and $33^{+6/7}$ weeks of gestation.[18] 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 to all patients. Tocolytic agents like nifedipine were cautiously administered for the first 48 hours if contractions were occurring and were avoided if there was evidence of infection. Treatment with magnesium sulphate was performed as a neuroprotective in pregnancies at $<32^{+0/7}$ weeks of gestation. Culture for Group B streptococci (GBS) was performed for all women. Delivery was performed (with induction or caesarean, as appropriate) after $34^{+0/7}$ weeks of gestation or after the development of early signs of intra-amniotic infection. All patients underwent pathological examination of the placenta after birth.

Exclusion criteria: women with the complications of acute rheumatism, other infections, substantial abnormalities in neurological, psychiatric, cardiac, endocrinological, haematological, hepatic, renal or metabolic functions, as determined by history, physical examination and blood screening tests, were all excluded. Women who had an interval between admission and delivery of more than 7 days or fewer than 3 days during expectant management were also excluded. As prolongation of pregnancy is associated with a higher risk of chorioamnionitis,[18] a 7-day course of therapy with prophylactic antibiotics is recommended as expectant management, discussed in detail above, and a single course of corticosteroids may last for 48 hours.

2.2 | Outcome

The outcome of interest was HCA. HCA is diagnosed by the presence of acute inflammatory changes in any of the tissues sampled (amnion, chorion–decidua, umbilical cord and chorionic plate), using previously published criteria,[19] and manifests as neutrophils in the chorion or in the chorion and amnion on examination of a membrane roll and chorionic plate of the placenta. Two independent pathologists reviewed the histology slides of the placentas. Women confirmed with HCA by pathological diagnosis of the placenta were included in the HCA group, whereas women without confirmed HCA were placed in the non-HCA group. CCA is diagnosed clinically in accordance with the following signs: fever (≥38°C orally), vaginal discharge odour, maternal tachycardia (>100 beats per minute), fetal tachycardia (>160 beats per minute), abdominal pain, uterine tenderness and leucocytosis. The presence of at least three of these signs has been shown to indicate a strong probability of chorioamnionitis.[20]

2.3 | Biomarkers

The biomarkers measured in blood samples were peripheral WBC, neutrophil, lymphocyte, hsCRP and PCT. Before

dexamethasone was injected, blood was drawn for peripheral WBC, neutrophil, lymphocyte, hsCRP and PCT. Then the same tests were repeated at 24, 48 and 72 hours after injection of the first dose of dexamethasone.

2.4 | Statistical analysis

We first described maternal and neonatal characteristics and clinical factors between HCA and non-HCA groups. Continuously distributed variables were presented as mean (standard deviation) and compared using a Student's *t*-test. Categorical variables were displayed by counts (percentages) and compared using a chi-square test or Fisher's exact test, where appropriate. Comparisons of biomarkers between baseline and after treatment periods were analysed by two-way ANOVA (time × group) with Bonferroni post-hoc test.

The receiver operating characteristic (ROC) curve was used to estimate the optimal cut-off values, sensitivity, specificity, positive predictive value and negative predictive value of hsCRP and PCT at baseline, and at 24, 48 and 72 hours after injection of the first dose of dexamethasone (detailed methods and results are available in Table S2). Differences in the area under the curve (AUC) were examined using the DeLong's test.[21] Then these biomarkers were converted to categorical data based on cut-off values.

We then assessed the association between each clinical factor and biomarker and the risk of HCA among women with PPROM. Log-binomial regression models were used to estimate the crude and adjusted relative risks (RRs) with 95% confidence intervals (95% CIs). Confounding factors were carefully selected and adjusted in the multivariable models, based on literature review and review of a directed acyclic graph (DAG), as well as data availability. When assessing the association between a biomarker and the risk of HCA, maternal age, gestational age, assisted reproductive technology, gestational diabetes mellitus and multiple pregnancy were adjusted in the regression model.

To develop the prediction model and identify the predictors, all clinical factors and biomarkers independently associated with the risk of HCA were selected for inclusion in the backward stepwise logistic regression model. Independent predictors with adjusted odds ratios (aORs) and 95% CIs were presented in the final prediction model. The AUC was then used to calculate the accuracy of the prediction model in discriminating between the HCA and non-HCA groups. To estimate the relative contribution of each predictor to the risk of HCA, we further used the multivariable logistic regression model to calculate the standardised coefficient.

All analyses were performed using SPSS 23.0 (IBM, Armonk, NY, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA), with two-tailed tests and a significance level of $p < 0.05$.

3 | RESULTS

3.1 | 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: 98 (62.42%) women with HCA and 59 (37.58%) women without HCA (Figure 1).

There were no significant differences between the two groups in age, time interval from admission to delivery, incidence of multiple pregnancy, infertility, gestational diabetes mellitus, rate of caesarean delivery, time interval from admission to delivery, culture of vaginal secretions including *Streptococcus agalactiae* (GBS), mycoplasma and candidiasis (all $p > 0.05$). The mean gestational age at admission and delivery in the non-HCA group were greater than those in the HCA group (Table 1).

As some of the newborns were transferred to other hospitals after birth, neonatal data were recorded for 42 (36.84%) neonates in the non-HCA group and 72 (63.16%) neonates in the HCA group (Table 1). Infants of mothers in the non-HCA group were significantly heavier than infants of mothers in the HCA group ($p < 0.001$), whereas the Apgar scores were similar ($p > 0.05$). There were more admissions to a neonatal intensive care unit (NICU), more cases of late sepsis and more cases of respiratory distress syndrome (RDS) in the HCA group, compared with the non-HCA group ($p < 0.05$). Definitive cases of sepsis were recorded for infants with positive blood cultures. Sepsis cases in the first 7 days were defined as early sepsis and sepsis cases after the seventh day were defined as late sepsis.

3.2 | The response of serum indicators to dexamethasone treatment

There were no significant differences between non-HCA and HCA groups in WBC, neutrophil and lymphocyte ($p > 0.05$). No significant interaction between group and time was found in the above indictors ($p > 0.05$). The mean WBC

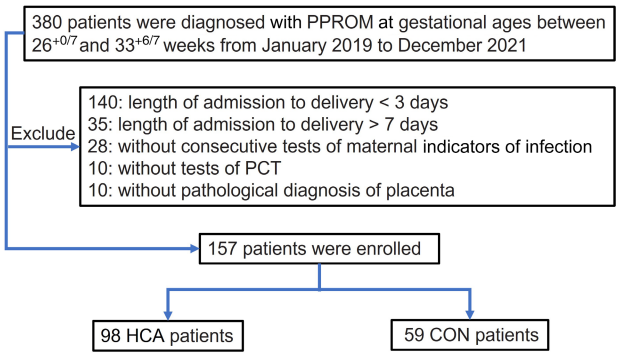

FIGURE 1 Flowchart and study design.

TABLE 1 Characteristics of women with PPROM and their neonates in the non-HCA and HCA groups.

	Non-HCA	HCA	*p*
Maternal features	(*n* = 59)	(*n* = 98)	
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)	<0.001
Culture of vaginal secretion			
GBS+	1 (1.7%)	2 (2.0%)	1.000
Mycoplasma+	6 (10.2%)	10 (10.2%)	1.000
Candidiasis+	5 (8.5%)	4 (4.1%)	0.298
CCA	2 (3.4%)	7 (7.1%)	0.485
Length of admission to delivery (days)	4.29 (1.54)	4.52 (1.28)	0.310
Gestational age at delivery (weeks)	32.88 (2.55)	31.52 (3.02)	<0.001
Caesarean delivery	28 (47.5%)	49 (50.0%)	0.869
Neonatal features	(*n* = 42)	(*n* = 72)	
Birthweight (g)	2052 (284)	1772 (317)	<0.001
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
NICU	24 (57.1%)	64 (88.9%)	<0.001
Early sepsis	0	1 (1.4%)	0.445
Late sepsis	0	7 (9.7%)	0.038
Mechanical ventilator treatment	2 (4.8%)	9 (12.5%)	0.179
Respiratory distress syndrome	21 (50%)	56 (77.8%)	0.002
Neonatal pneumonia	1 (2.4%)	9 (12.5%)	0.134
Necrotising enterocolitis	2 (4.8%)	3 (3.2%)	0.882
Retinopathy of prematurity	0	2 (2.8%)	0.278
Intraventricular haemorrhage	3 (7.1%)	6 (5.7%)	1.000
Neonatal mortality	0	0	–

Note: Continuously distributed variables were presented as means (standard deviations) and compared using a Student's *t*-test. Categorical variables were presented as counts (percentages) and compared using a chi-square test or Fisher's exact test, where appropriate.

Abbreviations: ART, assisted reproductive technology; CCA, clinical chorioamnionitis; GBS, Group B streptococci; GDM, gestational diabetes mellitus; HCA, histological chorioamnionitis; NICU, neonatal intensive care unit.

increased 24 hours after the first injection of dexamethasone and dropped at 72 hours, without returning to the baseline level (time effect, $p < 0.001$; Figure 2A). A similar response to dexamethasone treatment was found in the mean neutrophil count (Figure 2B). The lymphocyte count decreased significantly at 24 hours after the initial treatment, returned to baseline at 48 hours and then rose at 72 hours (time effect, $p < 0.001$; Figure 2C). Detailed results are presented in Table S1.

The changes in hsCRP level differed between the non-HCA and HCA groups after the injection of dexamethasone (interaction effect, $p = 0.029$; Figure 2D). In the non-HCA group (time effect: $p = 0.036$), hsCRP levels began to decline significantly 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 at 72 hours (by 35.37%, $p = 0.045$). In contrast, in the HCA group (time effect, $p = 0.027$) a significant increase in mean hsCRP levels of 58.82% was found at 24 hours after treatment ($p = 0.013$), and then dropped significantly to 2.81 mg/L at 48 hours after treatment, a level similar to that of the baseline ($p = 0.403$). When comparing the hsCRP levels between the two groups, results showed significant differences at 24 hours (1.46 vs 3.78 mg/L; $p = 0.017$) and 48 hours (1.12 vs 2.81 mg/L; $p = 0.012$; Table S1).

The increases in PCT level in two groups after dexamethasone treatment differ significantly (interaction effect, $p = 0.037$; Figure 2E). PCT levels in the non-HCA group (time effect, $p = 0.025$) increased from the baseline value of 0.024 to 0.030 ng/mL ($p < 0.001$) at 24 hours post-injection, and then remained at the same level for the next 48 hours. Similarly, PCT levels in the HCA group (time effect, $p < 0.001$) increased from 0.040 to 0.058 ng/mL ($p = 0.016$) 24 hours after injection and continued to increase 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 non-HCA group after the first injection (Table S1).

3.3 | The association between clinical characteristics, biomarkers and the risk of HCA

Univariable log-binomial regression analysis (Table 2) found that the gestational week of admission and several biomarkers (hsCRP and PCT at baseline, and at 24, 48 and 72 hours after the initial treatments) were associated with the risk of HCA. After adjusting for confounding factors, admissions at <28 weeks of gestation (aRR 1.66, 95% CI 1.07–2.57) and at 28–32 weeks of gestation (aRR 1.54, 95% CI 1.10–2.15) were associated with the risk of HCA, compared with gestational ages of >32 weeks, and all the biomarkers above were significantly and independently associated with the risk of HCA (hsCRP at baseline, aRR 1.62, 95% CI 1.13–2.33; hsCRP at 24 hours, aRR 2.30, 95% CI 1.58–3.36; hsCRP at 48 hours, aRR 1.95, 95% CI 1.34–2.83; hsCRP at 72 hours, aRR 2.51, 95% CI 1.56–4.04; PCT at baseline, aRR 1.34, 95% CI 1.10–1.63; PCT at 24 hours, aRR 1.44, 95% CI 1.14–1.82; PCT at 48 hours, aRR 1.40, 95% CI 1.01–1.93; PCT at 72 hours, aRR 1.42, 95% CI 1.14, 1.77). WBC, neutrophil and lymphocyte were not associated with risk of HCA.

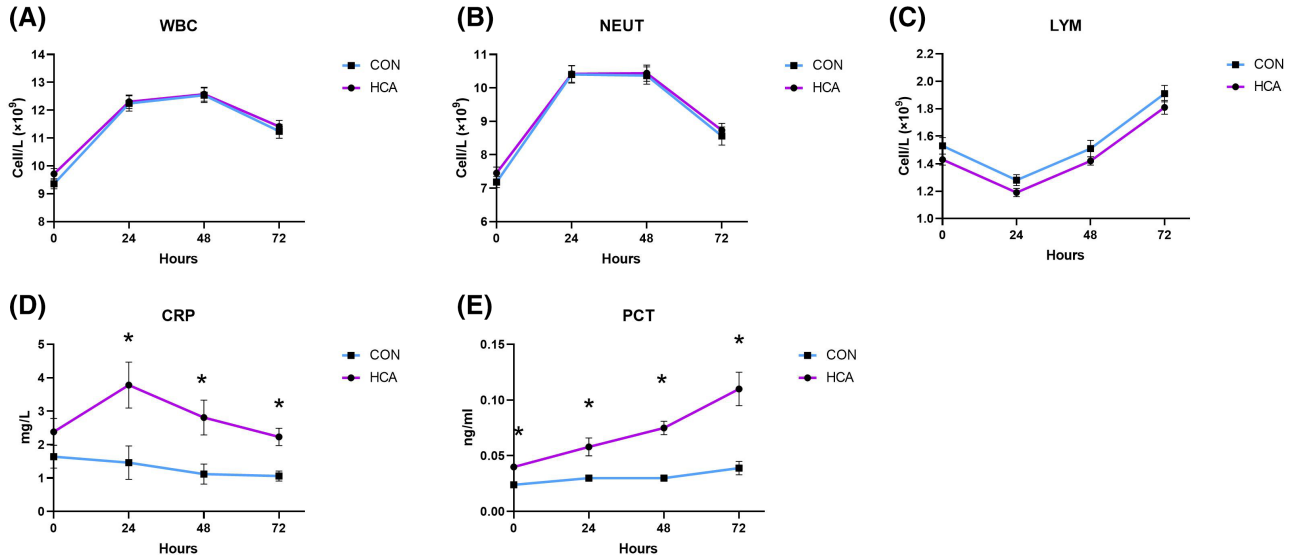

FIGURE 2 The responses of infection indicators to dexamethasone in women with PPROM. Comparisons of biomarkers between baseline and in periods after treatment were analysed by two-way ANOVA (time × group) with the Bonferroni post hoc test. (A, B) No significant interaction between group and time was found in relation to WBC ($p = 0.719$) or neutrophil ($p = 0.908$) counts. WBC and neutrophil counts increased at 24 hours after the first injection in both groups, followed by a decrease at 72 hours after first injection to levels that remained higher than at baseline. No significance was found between the two groups for WBC ($p = 0.189$) or neutrophil ($p = 0.191$) counts. (C) The mean lymphocyte count decreased at 24 hours but ultimately peaked at 72 hours. There was no significance between the two groups ($p = 0.116$). (D, E) In the HCA group, hsCRP temporarily increased at 24 hours after treatment before dropping to the baseline and remaining at a stable level (time effect, $p = 0.036$); PCT increased continually to a peak at 72 hours after treatment (time effect, $p < 0.001$). Both hsCRP and PCT were significantly higher in the HCA group. Significance (non-HCA vs HCA): $^*p < 0.05$.

3.4 | Predictors for HCA

The final prediction model included three biomarkers: PCT at 72 hours (aOR 34.11, 95% CI 5.45–213.42), PCT at 48 hours (aOR 5.51, 95% CI 1.07–28.36) and hsCRP at 72 hours (aOR 5.08, 95% CI 1.59–16.02). The prediction performance reached 93.61%.(AUC = 93.61%). Of these three biomarkers, PCT at 72 hours was the strongest predictor for HCA (standardised coefficient, 0.9745), followed by PCT at 48 hours (standardised coefficient, 0.4716) and hsCRP at 72 hours (standardised coefficient 0.4358) (Table 3).

4 | DISCUSSION

4.1 | Main findings

This study retrospectively analysed 157 cases of women with PPROM at $26^{+0/7}$ and $33^{+6/7}$ weeks of gestation and investigated the sequential responses of maternal WBC, neutrophil, lymphocyte, hsCRP and PCT to antenatal dexamethasone. We found that both non-HCA and HCA groups had similar physiological responses to dexamethasone in WBC, neutrophil and lymphocyte. By contrast, the response of hsCRP and PCT differed between the two groups, and PCT had a better predictive value for HCA, compared with hsCRP. A combination of hsCRP at 72 hours, PCT at 48 hours and PCT at 72 hours showed good predictive performance for HCA.

4.2 | Interpretation

Intrauterine infection has been shown to be commonly associated with PPROM.[6,22] Microorganisms may gain access to the amniotic cavity and fetus by ascending from the vagina and cervix.[23] The most common organisms isolated from the amniotic cavity of women with very early preterm deliveries are *Ureaplasma parvum* and *Mycoplasma hominis*.[24] The lower the gestational age at delivery, the greater the frequency of intrauterine infection.[25] This study also showed that the gestational week of admission was significantly negatively correlated with the risk of HCA ($p < 0.05$). Moreover, chorioamnionitis may be associated with severe RDS, probably through the combination of surfactant deficiency and diffuse pneumonia/inflammation with a non-culturable organism.[26] We observed highly frequent NICU admission (88.9%) and RDS (77.8%) in the HCA group. Hence, it is vital to detect suspected HCA in women with PPROM, especially at early gestational ages, which may help to facilitate timely interventions to safeguard fetuses/newborns.[6]

Antenatal corticosteroid therapy has shown a transient physiological response, including an increase in maternal WBC and neutrophil, which is caused by increasing leucocyte extravasation from bone marrow and decreasing leucocyte clearance from blood vessels.[11–13] A previous study demonstrated that WBC increased from the baseline at 24 hours after treatment and normalised thereafter.[27] This study confirmed physiological leucocytosis after the administration of dexamethasone, and further showed that the similar responses of maternal WBC and neutrophil in both

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 2 Associations between clinical factors and biomarkers and the risk of HCA.

Factors	Non-HCA *n*	HCA *n*	Crude RR (95% CI)	Adjusted RR (95% CI)
Clinical factors[a]				
Age (years)				
<35	47 (41.2%)	65 (58.8%)	Ref.	Ref.
≥35	12 (27.9%)	31 (72.1%)	1.23 (0.98–1.57)	1.17 (0.88–1.54)
Gestational age at admission (weeks)				
<28	2 (18.2%)	9 (81.8%)	1.91 (1.22–2.77)	1.66 (1.07–2.57)
28–32	25 (27.8%)	65 (72.2%)	1.68 (1.19–2.28)	1.54 (1.10–2.15)
>32	32 (57.1%)	24 (42.9%)	Reference	Reference
ART (yes)	9 (28.1%)	23 (71.9%)	1.17 (0.90–1.52)	1.06 (0.79–1.43)
GDM (yes)	3 (50%)	3 (50%)	0.91 (0.46–1.95)	0.91 (0.43–1.89)
Multiple pregnancy (yes)	2 (14.3%)	12 (85.7%)	1.40 (1.09–1.80)	1.21 (0.88–1.66)
Biomarkers[b]				
HsCRP at baseline > 0.52	35 (30.2%)	81 (69.8%)	1.89 (1.27–2.82)	1.62(1.13–2.33)
HsCRP at 24 hours > 0.895	25 (22.1%)	88 (77.9%)	3.57 (2.43–5.23)	2.30 (1.58–3.36)
HsCRP at 48 hours > 0.53	25 (23.8%)	80 (76.2%)	2.74 (1.83–4.09)	1.95 (1.34–2.83)
HsCRP at 72 hours > 0.975	19 (20.2%)	75 (79.8%)	3.12 (2.00–4.89)	2.51 (1.56–4.04)
PCT at baseline > 0.031	14 (15.7%)	75 (84.3%)	2.49 (1.73–3.56)	1.34 (1.10–1.63)
PCT at 24 hours > 0.039	17 (18.5%)	75 (81.5%)	2.29 (1.60–3.27)	1.44 (1.14–1.82)
PCT at 48 hours > 0.048	3 (3.8%)	76 (96.2%)	3.46 (2.38–5.03)	1.40 (1.01–1.93)
PCT at 72 hours > 0.051	2 (2.5%)	78 (97.5%)	3.85 (2.58–5.74)	1.42 (1.14–1.77)
WBC at baseline	9.4 (1.4)	9.7 (1.9)	1.06 (0.98–1.15)	1.05 (0.96–1.10)
WBC at 24 hours	12.4 (2.2)	12.3 (2.4)	1.01 (0.95–1.06)	1.02 (0.94–1.10)
WBC at 48 hours	12.5 (2.0)	12.6 (2.5)	1.01 (0.94–1.07)	1.01 (0.95–1.09)
WBC at 72 hours	11.2 (1.9)	11.4 (2.1)	1.02 (0.96–1.08)	1.03 (0.92–1.10)
Neutrophil at baseline	7.2 (1.3)	7.4 (1.8)	1.05 (0.97–1.14)	1.02 (0.95–1.10)
Neutrophil at 24 hours	10.4 (2.0)	10.4 (2.5)	1.01 (0.94–1.07)	1.01 (0.95–1.09)
Neutrophil at 48 hours	10.4 (2.0)	10.4 (2.4)	1.01 (0.95–1.07)	0.98 (0.92–1.08)
Neutrophil at 72 hours	8.6 (2.1)	8.7 (2.1)	1.01 (0.96–1.07)	0.99 (0.92–1.12)
Lymphocyte at baseline	1.5 (0.5)	1.4 (0.4)	0.82 (0.62–1.08)	0.75 (0.61–1.10)
Lymphocyte at 24 hours	1.3 (0.3)	1.2 (0.3)	0.65 (0.43–1.01)	0.58 (0.40–1.02)
Lymphocyte at 48 hours	1.5 (0.5)	1.4 (0.3)	0.83 (0.62–1.09)	0.76 (0.55–1.08)
Lymphocyte at 72 hours	1.9 (0.4)	1.8 (0.5)	0.84 (0.65–1.09)	0.85 (0.58–1.12)

Note: Log-binomial regression models were used to estimate the risk ratios and 95% confidence intervals. HsCRP and PCT were converted to categorical data based on cut-off values. Categorical variables were displayed by counts (percentages). Continuously distributed variables were presented as means (standard deviations). hsCRP (mg/L); PCT (ng/ml).

Abbreviations: ART, assisted reproductive technology; GDM, gestational diabetes mellitus; HCA, histological chorioamnionitis; LYM, lymphocyte count ($\times 10^9$ cell/L); NEUT, neutrophil count ($\times 10^9$ cell/L); WBC, white blood cell count ($\times 10^9$ cell/L).

[a]Models were adjusted for all other clinical factors listed in the table if one clinical factor was treated as the main interest.

[b]Models were adjusted for maternal age, gestational age, ART, gestational diabetes mellitus and multiple pregnancy.

groups could not differentiate between HCA and non-HCA groups of women with PPROM.

Both hsCRP and PCT levels in the HCA group were consistently higher than those in the non-HCA group at different time points after patients received the first injection, indicating that the responses of hsCRP and PCT might be associated with HCA. Accordingly, hsCRP and PCT at baseline, and at 24, 48 and 72 hours after treatment, were found to be independently related to the risk of HCA. The AUCs of PCT were significantly better than those of hsCRP at baseline, and at 48 and 72 hours after treatment, which indicated that PCT had a greater predictive value than hsCRP. Furthermore, the optimal multi-biomarker model for predicting HCA (AUC = 93.61%) indicated that PCT had a stronger prediction capacity than hsCRP. Similarly, some scholars found that both CRP and PCT had satisfactory accuracy, and that the diagnostic value of PCT is better than that of CRP.[17] Another study reported that

TABLE 3 Final prediction model for risk of HCA (stepwise logistic regression model).

Predictor	Adjusted OR (95% CI)	Standardised coefficient
PCT at 72 hours > 0.051 ng/mL	34.11 (5.45–213.42)	0.9745
PCT at 48 hours > 0.048 ng/mL	5.51 (1.07–28.36)	0.4716
HsCRP at 72 hours > 0.975 mg/L	5.08 (1.59–16.02)	0.4358
AUC	93.61%	–

Abbreviations: AUC, area under curve; hsCRP, high-sensitivity C-reactive protein; PCT, procalcitonin.

PCT had a poor sensitivity and a modest specificity compared with CRP,[15] but the author included all patients with intrauterine infections, without any distinction between CCA and HCA.

4.3 | Strengths and limitations

Our study may have potential important implications for clinical practice. When expectant management is chosen for women with PPROM, it should include the careful monitoring of symptoms and signs of infection. Elevated levels of hsCRP and PCT might be a high index of suspicion of intra-amniotic infection when there is no clinical evidence. As these biomarkers are easily measured and routinely available in the hospital, the serial monitoring of hsCRP and PCT is suggested for women with PPROM.

Several limitations of this analysis should be acknowledged. The retrospective design raises the possibility of biases inherent to such investigations. Further longitudinal studies with large sample sizes evaluating the multi-biomarker model for HCA prediction could bring interesting information and potentially help alert clinicians and facilitate early interventions. In addition, recent proteomic and other studies suggest the potential predictive value of other biomarkers, such as plasma C4a, serum amyloid A4 (SAA4),[28] matrix metallopeptidase 9 (MMP-9), interleukin 6 (IL-6), insulin-like growth factor-binding protein 1 (IGFBP-1), S100A8/A9, E-selectin and kallistatin.[29,30] Further studies are warranted to assess whether adding these new biomarkers may improve the prediction for HCA.

5 | CONCLUSION

Both hsCRP and PCT were found to be independently associated with the risk of HCA. Moreover, the optimal multi-biomarker prediction model for HCA indicated that PCT had a stronger prediction capacity than hsCRP. Therefore, PCT could be a sensitive and reliable biomarker for the early prediction of HCA in women with PPROM at $34^{+0/7}$ weeks of gestation within 72 hours of the first dexamethasone treatment, by alerting clinicians and facilitating early interventions.

AUTHOR CONTRIBUTIONS

JP: study design, data analysis, interpretation and writing the article. YC: study design, data abstraction and writing the article. SW: data acquisition and interpretation. TZ: data acquisition, data interpretation and revision of the article. Y-SC: critical revision of the article. XZ: study design, data interpretation and revision of the article. XH: study design, data analysis, data interpretation and revision of the article.

ACKNOWLEDGEMENTS

We thank Yingying Yang, Yanfang Guo and Zhongcheng Luo for their contributions to the data analysis.

CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

All authors agree with the final version, and agree to be accountable to the integrity of the data published

ETHICS APPROVAL

The study protocol was approved by the hospital ethics committee (no. KS22218).

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

ORCID

Xiaolin Hua https://orcid.org/0000-0003-1098-5010

REFERENCES

1. Lu HY, Zhang Q, Wang QX, Lu JY. Contribution of histologic chorioamnionitis and fetal inflammatory response syndrome to increased risk of brain injury in infants with preterm premature rupture of membranes. Pediatr Neurol. 2016;61:94–98.e1.
2. Lorthe E, Ancel PY, Torchin H, Kaminski M, Langer B, Subtil D, et al. Impact of latency duration on the prognosis of preterm infants after preterm premature rupture of membranes at 24 to 32 Weeks' gestation: a National Population-Based Cohort Study. J Pediatr. 2017;182:47–52.e2.
3. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010;37(2):339–54.
4. Been JV, Rours IGIJG, Kornelisse RF, Lima Passos V, Kramer BW, Schneider TAJ, et al. Histologic chorioamnionitis, fetal involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. Am J Obstet Gynecol. 2009;201(6):587.e1–8.
5. Park CW, Moon KC, Park JS, Jun JK, Romero R, Yoon BH. The involvement of human amnion in histologic chorioamnionitis is an indicator that a fetal and an intra-amniotic inflammatory response is more likely and severe: clinical implications. Placenta. 2009;30(1):56–61.
6. Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. Am J Obstet Gynecol. 2004;190(1):147–51.
7. Edwards RK, Duff P. Single additional dose postpartum therapy for women with chorioamnionitis. Obstet Gynecol. 2003;102(5 Pt 1):957–61.
8. Kim SA, Park KH, Lee SM. Non-invasive prediction of histologic chorioamnionitis in women with preterm premature rupture of membranes. Yonsei Med J. 2016;57(2):461–8.

9. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.
10. Goldenberg RL, Wright LL. Repeated courses of antenatal corticosteroids. Obstet Gynecol. 2001;97(2):316–7.
11. Danesh A, Janghorbani M, Khalatbari S. Effects of antenatal corticosteroids on maternal serum indicators of infection in women at risk for preterm delivery: a randomized trial comparing betamethasone and dexamethasone. J Res Med Sci. 2012;17(10):911–7.
12. Bauer ME, Price LK, MacEachern MP, Housey M, Langen ES, Bauer ST. Maternal leukocytosis after antenatal corticosteroid administration: a systematic review and meta-analysis. J Obstet Gynaecol. 2018;38(2):210–6.
13. Voon HY, Leong MS, Li CW, Bujang A, Suharjono H. Corticosteroid-induced leukocytosis in pregnancy: a prospective observational study. Med J Malaysia. 2017;72(5):259–63.
14. Hu Y, Yang M, Zhou Y, Ding Y, Xiang Z, Yu L. Establishment of reference intervals for procalcitonin in healthy pregnant women of Chinese population. Clin Biochem. 2017;50(3):150–4.
15. Areia AL, Areia M, Mota-Pinto A. Procalcitonin in preterm rupture of membranes: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021;303(4):917–24.
16. Thornburg LL, Queenan R, Brandt-Griffith B, Pressman EK. Procalcitonin for prediction of chorioamnionitis in preterm premature rupture of membranes. J Matern Fetal Neonatal Med. 2016;29(13):2056–61.
17. Li K, Yu H, Wang X, Liu X. Predictive value of procalcitonin or c-reactive protein for subclinical intrauterine infection in patients with premature rupture of membranes (PROM). J Prenat Med. 2016;10(3–4):23–8.
18. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Prelabor rupture of membranes: ACOG practice bulletin, number 217. Obstet Gynecol. 2020;135(3):e80–97.
19. Yoon BH, Romero R, Kim CJ, Jun JK, Gomez R, Choi JH, et al. Amniotic fluid interleukin-6: a sensitive test for antenatal diagnosis of acute inflammatory lesions of preterm placenta and prediction of perinatal morbidity. Am J Obstet Gynecol. 1995;172(3):960–70.
20. Asadi N, Faraji A, Keshavarzi A, Akbarzadeh-Jahromi M, Yoosefi S. Predictive value of procalcitonin, C-reactive protein, and white blood cells for chorioamnionitis among women with preterm premature rupture of membranes. Int J Gynaecol Obstet. 2019;147(1):83–8.
21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
22. Erdemir G, Kultursay N, Calkavur S, Zekioğlu O, Koroglu OA, Cakmak B, et al. Histological chorioamnionitis: effects on premature delivery and neonatal prognosis. Pediatr Neonatol. 2013;54(4):267–74.
23. Romero R, Espinoza J, Chaiworapongsa T, Kalache K. Infection and prematurity and the role of preventive strategies. Semin Neonatol. 2002;7(4):259–74.
24. Oh KJ, Lee KA, Sohn YK, Park CW, Hong JS, Romero R, et al. Intraamniotic infection with genital mycoplasmas exhibits a more intense inflammatory response than intraamniotic infection with other microorganisms in patients with preterm premature rupture of membranes. Am J Obstet Gynecol. 2010;203(3):211.e1–8.
25. Watts DH et al. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. Obstet Gynecol. 1992;79(3):351–7.
26. Jobe AH. Effects of chorioamnionitis on the fetal lung. Clin Perinatol. 2012;39(3):441–57.
27. Denison FC, Elliott CL, Wallace EM. Dexamethasone-induced leucocytosis in pregnancy. Br J Obstet Gynaecol. 1997;104(7):851–3.
28. Lee JE, Dan K, Kim HJ, Kim YM, Park KH. Plasma proteomic analysis to identify potential biomarkers of histologic chorioamnionitis in women with preterm premature rupture of membranes. PLoS One. 2022;17(7):e0270884.
29. Cho I, Lee KN, Joo E, Kim YM, Kim TE, Park KH. Plasma E-selectin and kallistatin as predictive markers of histologic chorioamnionitis in women with preterm premature rupture of membranes. Am J Reprod Immunol. 2022;88(3):e13584.
30. Park JW, Park KH, Lee JE, Kim YM, Lee SJ, Cheon DH. Antibody microarray analysis of plasma proteins for the prediction of histologic chorioamnionitis in women with preterm premature rupture of membranes. Reprod Sci. 2019;26(11):1476–84.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Peng J, Chen Y, Wan S, Zhou T, Chang Y-S, Zhao X, et al. Predictors for histological chorioamnionitis among women with preterm prelabour rupture of membranes after dexamethasone treatment: a retrospective study. BJOG. 2023;130(9):1072–1079. https://doi.org/10.1111/1471-0528.17431