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*Original Article*

# A clinical predictive model of intrauterine inflammation for early single preterm birth

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**Abstract:** Objective: To develop clinical predictive model of intrauterine inflammation for single preterm births ≤ 34 weeks gestational age. Methods: Clinical parameters and placental pathology of 240 pregnant women were collected. According to placenta pathology, intrauterine inflammation was divided into maternal inflammatory response (MIR) and fetal inflammatory response (FIR). We used logistic regression to establish predictive models for MIR and FIR. Results: Among 240 births, 119 (49.58%) had MIR, while 54 (22.5%) presented FIR. The logistic model for MIR was: logit P = (0.133 × neutrophile counts) + (-1.473 × pregnancy hypertension) + (-1.302 × cesarean section) + (1.510 × prenatal antibiotics) - 1.389, which yielded the area under the ROC curve of 0.845. The logistic model for predicting FIR was: logit P = (-0.703 × lymphocyte counts) + (0.193 × neutrophile counts) + (2.349 × PPROM) - 3.951, and the AUC was 0.852. Conclusion: These predictive models are easily established and have much better performance than single factors.

**Keywords:** Intrauterine inflammation, preterm birth, clinical prediction

## Introduction

Preterm labor, defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation, represents a significant perinatal health problem across the globe, in terms of associated mortality and morbidity [1]. Intrauterine inflammation, such as chorioamnionitis, is an important mechanism of preterm labor. Up to 50% of extremely preterm births is concerned with intrauterine inflammation [2]. Studies have demonstrated that intrauterine inflammation/infection not only is associated with significant maternal adverse outcomes, including postpartum infections, sepsis, disseminated intravascular coagulation, and even death [3], but also has comprehensive impact on neonatal outcomes, including brain injury [4], bronchopulmonary dysplasia [5, 6] necrotizing enterocolitis [7, 8], retinopathy of prematurity [9], transient hypothyroxinaemia of prematurity [10] and thymus involution [11]. Furthermore, intrauterine inflammation exposure could alter neonatal response to clinical treatment. There are different responses in surfactant supplement [12], ventilation time [13] and postnatal corticosteroid administration [14] between premature infants of mothers with and without chorioamnionitis. Therefore, the timely estimation of intrauterine inflammation could not only guide prenatal management but also facilitate the early intervention strategies for preterm infants and improve their clinical outcomes.

Pathogens in the uterus related to the preterm birth are often low virulence, such as Ureaplasma urealyticum, Chlamydia trachomatis, Mycoplasma hominis, and Trichomonas vaginalis. Therefore, most cases of histological chorioamnionitis are subclinical, and merely 10% have obvious clinical manifestations of infection [15]. Placental pathologic examination is still the golden standard for diagnosing intrauterine inflammation, but it is posteriori and time-consuming. Procedures to detect intrauterine infection at present include amniotic fluid examination via amniocentesis and fetal blood test via cordocentesis. Yet these two methods are invasive and risky. For these rea-

sons, it is necessary to establish a predictive model for intrauterine inflammation using easily available clinical parameters, for example maternal hematology and medical records.

In this study, we explored meaningful factors of intrauterine inflammation and developed prediction models for early preterm birth using maternal clinical parameters. Hopefully these results will facility clinical management preterm birth.

## Materials and methods

### *Study population*

This study was performed in accordance with relevant guidelines and regulations. Ethical approval for this project was granted by the Ethics Committee of International Peace Maternity & Child Health Hospital, School of Medicine, Shanghai Jiao Tong University. A written informed consent was obtained from each subject before sample collection. We recruited preterm infants born at gestational age of 34 weeks or less and their mothers at the hospital between January 2008 and October 2010. Subjects were not eligible if the pregnancy was multiple, or infants had major birth defects. A total of 240 pairs of eligible mothers and preterm infants were enrolled in the study.

### *Assessment of maternal inflammatory response (MIR) and fetal inflammatory response (FIR)*

After delivery, placentas and membranes were immediately fixed in formalin. Tissues included two membrane rolls, four full-thickness blocks of the placental disk and two cross-sections (the placental and fetal ends) of the umbilical cord were embedded in paraffin. All of the placental pathologies were examined according to the Amniotic Fluid Infection Nosology Committee [16] by a pathologist who was blinded about maternal and neonatal characteristics. The maternal inflammatory response (MIR) and fetal inflammatory response (FIR) were defined based on infiltration of polymorphonuclear leukocytes. The MIR contains subchorion (the presence of polymorphonuclear leukocytes underneath the chorionic membrane), chorion (the presence of polymorphonuclear leukocytes inside the chorionic layer), or amnion (the presence of polymorphonuclear leukocytes in both chorion and amnion). The FIR was defined as chorionic vasculitis/umbilical phlebitis, umbilical arteritis, umbilical perivasculitis or funisitis/perivasculitis [17]. According to placental pathology, we divided subjects into MIR- group and MIR+ group on the basis of maternal inflammatory response without regard to fetal inflammatory response, or FIR- group and FIR+ group on the basis of fetal inflammatory response without regard to maternal inflammatory response.

### *Maternal hematologic parameters and clinical characteristics*

The maternal hematologic parameters within 24-72 h before delivery were obtained from medical records, i.e. white blood cell counts and differential leukocyte proportion. In addition, we obtained maternal and infant information from medical record, including maternal age, delivery mode, preterm premature rupture of membranes, prenatal antibacterial use, pregnancy hypertension, gestational age, birth weight, sex, Apgar score at 1 min and 5 min.

### *Statistical analysis*

We used the packages in Statistical Product and Service Solutions (Version. 13.0, SPSS) to analyze data. Continuous data were expressed as means ± SD, and the differences between groups were assessed by Student's t test or Mann-Whitney U test. For categorical data, we summarized them by frequency and used chi-square tests or Fisher's exact test to the difference among groups. We used multiple logistic regression models with stepwise forwards method to investigate the relationship between potential predictors and intrauterine inflammation. Hosmer-Leme show test was used to assess the goodness-of-fit of logistic regression models. Factors in the final regression models were used to develop regression equations for MIR or FIR, and predicted probabilities were calculated. Receivers operating characteristic (ROC) curves were employed to estimate the diagnostic specificity and sensitivity of different single predictors and logistic models in the prediction of either MIR or FIR. We employed MedCalc software to compare the discriminatory ability of regression model with different single factors at the same time to determine its superiority. $P < 0.05$ (two-sided) was considered statistically significant.

**Table 1.** Placental pathology and perinatal characteristics

| | MIR- (n = 121) | MIR+ (n = 119) | P | FIR- (n = 186) | FIR+ (n = 54) | P |
|---|---|---|---|---|---|---|
| Maternal age (y) | 30.04±4.51 | 29.56±4.44 | 0.406 | 29.97±4.31 | 29.23±5.01 | 0.288 |
| Gestational age (d) | 223.61±11.80 | 220.71±11.26 | 0.043 | 223.04±11.70 | 219.20±10.87 | 0.032 |
| Birth weight (g) | 1703.95±442.04 | 1728.87±372.95 | 0.638 | 1723.60±414.09 | 1691.19±391.70 | 0.609 |
| Male (%) | 68 (56.2%) | 68 (57.1%) | 0.883 | 109 (58.6%) | 27 (50%) | 0.261 |
| Apgar score ≤ 7 at 1 min | 25 (20.7%) | 16 (13.4%) | 0.138 | 32 (17.2%) | 9 (16.7%) | 0.926 |
| Apgar score ≤ 7 at 5 min | 7 (5.8%) | 6 (5.0%) | 0.799 | 9 (4.8%) | 4 (7.4%) | 0.463 |
| PROM | 34 (28.1%) | 82 (68.9%) | < 0.0001 | 69 (37.1%) | 47 (87.0%) | < 0.0001 |
| Caesarean section | 90 (74.4%) | 41 (34.5%) | < 0.0001 | 111 (59.7%) | 20 (37.0%) | 0.003 |
| Pregnancy hypertension | 54 (45.6%) | 4 (3.4%) | < 0.0001 | 56 (30.1%) | 2 (3.7%) | < 0.0001 |
| Antenatal steroids | 105 (86.8%) | 105 (88.2%) | 0.733 | 161 (86.6%) | 49 (90.7%) | 0.413 |
| Prenatal antibiotics | 47 (38.8%) | 94 (79.0%) | < 0.0001 | 93 (50%) | 48 (88.9%) | < 0.0001 |

Data were expressed as n (%) or mean ± SD. Premature Rupture of Membranes, PROM; Maternal Inflammatory Response, MIR; Fetal Inflammatory Response, FIR.

**Table 2.** Characteristics of hematologic parameters

| | MIR- (n = 121) | MIR+ (n = 119) | P | FIR- (n = 186) | FIR+ (n = 54) | P |
|---|---|---|---|---|---|---|
| RBC ($10^{12}$/L) | 3.72±0.49 | 3.60±0.39 | 0.033 | 3.68±0.46 | 3.60±0.40 | 0.247 |
| Hb (g/L) | 113.85±16.23 | 109.80±12.98 | 0.038 | 112.48±15..46 | 109.69±12.29 | 0.234 |
| WBC ($10^9$/L) | 11.50±3.66 | 14.63±4.60 | < 0.0001 | 12.30±4.26 | 15.60±4.07 | < 0.0001 |
| Platelet ($10^9$/L) | 205.07±71.13 | 223.76±51.74 | 0.024 | 213.18±66.45 | 218.25±49.06 | 0.61 |
| Neutrophile ($10^9$/L) | 9.03±3.56 | 12.05±4.01 | < 0.0001 | 9.70±3.71 | 13.33±4.01 | < 0.0001 |
| Neutrophile (%) | 76.88±8.60 | 82.22±7.32 | < 0.0001 | 78.06±8.57 | 84.50±5.48 | < 0.0001 |
| Monocyte ($10^9$/L) | 0.62±0.28 | 0.75±0.30 | 0.0001 | 0.66±0.30 | 0.77±0.28 | 0.021 |
| Monocyte (%) | 5.44±2.01 | 5.37±1.89 | 0.78 | 5.52±2.04 | 5.01±1.55 | 0.096 |
| Lymphocyte ($10^9$/L) | 1.75±0.85 | 1.49±0.76 | 0.017 | 1.70±0.87 | 1.34±0.49 | 0.005 |
| Lymphocyte (%) | 15.64±6.89 | 11.18±5.89 | < 0.0001 | 14.66±6.89 | 9.24±4.33 | < 0.0001 |

Data were expressed as mean ± SD. Red Blood Cell, RBC; Haemoglobin, Hb; White Blood Cell, WBC; Maternal Inflammatory Response, MIR; Fetal Inflammatory Response, FIR.

## Results

*Placental pathology and perinatal characteristics*

A total of 240 pairs of mothers and their early preterm infants were included in the study. Placental pathologic examination revealed that 119 (49.58%) cases showed MIR, while 54 (22.5%) cases presented FIR. **Table 1** showed the perinatal clinical characteristics of groups for MIR- versus MIR+ and for FIR- versus FIR+. Compared with MIR- group, newborns of MIR+ group were born at lower gestational age, and less often by caesarean, but there were no difference in birth weight and Apgar score between two groups. Mothers in MIR+ group had more PPROM and prenatal antibacterial use, and less pregnancy hypertension. There was no significant difference in maternal age and the use of antenatal steroids between two groups. The similar differences were present between FIR+ and FIR- group.

*Characteristics of hematologic parameters*

**Table 2** presents the maternal characteristics of hematologic parameters for MIR- versus MIR+ and for FIR- versus FIR+ group. There were higher white blood cell counts (WBC), neutrophile proportion and platelet counts, and lower lymphocyte proportion, red blood cell counts (RBC) and hemoglobin (Hb) concentration for MIR+ versus MIR- group, as well as for women with FIR+ versus FIR- with the exception of platelet counts, RBC and Hb concentration, of which differences between groups were not significant.

*Logistic regression analyses of independent variables in predicting MIR (Test A) and FIR (Test B) after adjusted*

After the descriptive univariate analysis, we used the multivariable logistic regression models to investigate the relationship between vari-

**Table 3.** Logistic regression analyses of independent variables in predicting MIR (Test A) and FIR (Test B) after adjusted

| | | OR (95% CI) | Coefficient | P |
|---|---|---|---|---|
| Test A | Neutrophile counts | 1.142 (1.042~1.253) | 0.133 | 0.005 |
| | Pregnancy hypertension | 0.229 (0.068~0.775) | -1.473 | 0.018 |
| | Caesarean section | 0.272 (0.134~0.553) | -1.302 | < 0.0001 |
| | Prenatal antibacterial | 4.525 (2.079~9.851) | 1.510 | < 0.0001 |
| Test B | Neutrophile counts | 1.213 (1.100~1.338) | 0.193 | < 0.0001 |
| | Lymphocyte counts | 0.495 (0.251~0.976) | -0.703 | 0.042 |
| | PROM | 10.478 (4.042~27.158) | 2.349 | < 0.0001 |

Premature Rupture of Membranes, PROM.

**Table 4.** Diagnostic indices of different indicators in the prediction of MIR and FIR

| | | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| MIR | WBC | 0.712 (0.648~0.770)* | 12.4 | 65.49 (56.0~74.2) | 67.83 (58.5~76.2) | 66.7 (57.1~75.3) | 66.7 (57.3~75.1) |
| | Neutrophile counts | 0.727 (0.661~0.793)* | 9.38 | 73.21 (64.0~81.1) | 62.83 (53.2~71.7) | 66.1 (57.0~74.4) | 70.3 (60.4~79.0) |
| | Lymphocyte proportion | 0.704 (0.640~0.763)* | 12.8 | 71.68 (62.4~79.8) | 65.79 (56.3~74.4) | 67.5 (58.3~75.8) | 70.1 (60.4~78.6) |
| | Test A | 0.845 (0.791~0.890) | 0.45 | 84.82 (76.8~90.9) | 68.14 (58.7~76.6) | 72.5 (64.0~80.0) | 81.9 (72.6~89.1) |
| FIR | WBC | 0.731 (0.668~0.787)§ | 14.0 | 71.15 (56.9~82.9) | 71.59 (64.3~78.1) | 42.5 (32.0~53.6) | 89.4 (83.1~93.9) |
| | Neutrophile counts | 0.753 (0.692~0.808)§ | 12.17 | 71.15 (56.9~82.9) | 77.46 (70.5~83.5) | 48.7 (37.0~60.4) | 89.9 (83.9~94.3) |
| | Neutrophile proportion | 0.723 (0.660~0.780)§ | 81.1 | 78.85 (65.3~88.9) | 60.00 (52.3~67.3) | 36.9 (28.0~46.6) | 90.5 (83.7~95.2) |
| | Lymphocyte proportion | 0.747 (0.685~0.802)§ | 10.9 | 76.92 (63.2~87.5) | 69.14 (61.7~75.9) | 42.6 (32.4~53.2) | 91.0 (84.7~95.3) |
| | Test B | 0.852 (0.799~0.856) | 0.25 | 82.69 (69.7~91.8) | 75.72 (68.6~81.9) | 50.6 (39.5~61.7) | 93.6 (88.1~90.7) |

*, Compared with Test A, $P < 0.05$; §, Compared with Test B, $P < 0.05$. White Blood Cell, WBC; Maternal Inflammatory Response, MIR; Fetal Inflammatory Response, FIR.

ous factors and intrauterine inflammation. In the end, variables in the predict model for MIR were neutrophile counts, pregnancy hypertension, prenatal antibacterial and caesarean section (Test A), as shown in **Table 3**. And we generated the formula to predict MIR: logit $P_{(MIR)}$ = ln ($P_{(MIR)}$/(1 - $P_{(MIR)}$) = (0.133 × neutrophile counts) + (-1.473 × pregnancy hypertension) + (-1.302 × cesarean section) + (1.510 × prenatal antibiotics) - 1.389. Furthermore, lymphocyte counts, neutrophile counts and PPROM were in logistic regression model to predict FIR (Test B), and the formula to predict FIR was: logit $P_{(FIR)}$ = ln ($P_{(FIR)}$/(1 - $P_{(FIR)}$) = (-0.703 × lymphocyte counts) + (0.193 × neutrophile counts) + (2.349 × PPROM) - 3.951. In these formulas, lymphocyte and neutrophile counts were given in $10^9$/L, and we assigned "yes" to 1, "no" to 0 for cesarean, prenatal antibiotics and PPROM.

*Diagnostic indices of different indicators in the prediction of MIR and FIR*

Next, we constructed receiver operator characteristic curves (ROC) to assess the diagnostic indices of single factors, and selected the ones with better predictive performance (WBC, neutrophile counts and lymphocyte proportion for MIR, and WBC, neutrophile counts, lymphocyte and neutrophile proportion for FIR whose AUC > 0.7). We compared single factors and predictive equations (Test A and B) in prediction of MIR and FIR respectively, and compared their predictive performance to determine optimal choice (**Table 4**). As we can see from **Figure 1**, the area under the ROC curves for the MIR predictive equation Test A and for FIR predictive equation Test B were significantly higher than any single factors (P < 0.01 for all). But the prediction differences between any of these single factors were not significant. **Table 4** showed the diagnostic indices for optimal sensitivity and specificity. Cut-off values were selected from the ROC curves to predict MIR and FIR.

## Discussion

It has been acknowledged that intrauterine inflammation is closely related to preterm, especially early preterm births. Our study showed that 49.58% of early preterm infants had evidence of intrauterine inflammation, close to previous findings [18]. There were significant differences in hematological parame-

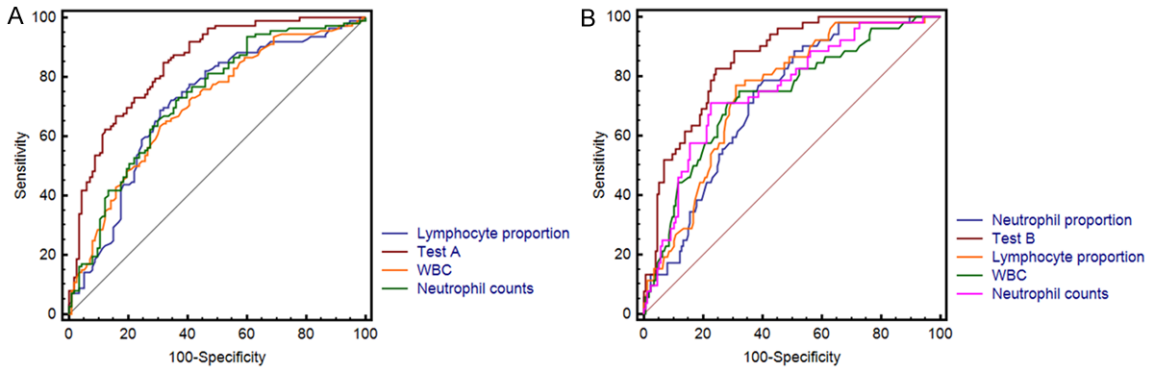


**Figure 1.** Receiver-operator characteristics curves comparing the predictors and logistic models for MIR (A) and FIR (B).

ters for MIR+ versus MIR- group and for FIR+ versus FIR- group, as well as other clinical variables, including the presence of PPROM and caesarean section, etc. Combining these variables which were easily available in the clinical setting, both MIR and FIR could be predicted before birth reasonably. The regression models present here would provide a potential convenience in performing early intervention strategies for mothers and fetus/neonates.

Our innovations consist in the use of combinations of hematologic and clinical data, which are routine examinations and records. By means of these parameters, we worked out predictive regression model with good performance of diagnosing intrauterine inflammation, significantly superior to any single factors. The predict models whose area under the ROC curve were respectively 0.845 for MIR and 0.852 for FIR, have significantly improved discrimination power than single factors.

In fact, some of above single factors have been reported as biomarkers of intrauterine inflammation. Some investigators used WBC as independent indicator to predict intrauterine infection. As well known, maternal WBC will increase in response to intrauterine inflammation. It has been demonstrated that increased WBC in maternal circulation are associated with the presence of intrauterine infection [19]. Actually, with regard to the role of WBC in detecting intrauterine inflammation, previous results were inconsistent [20]. In a cohort study including 126 pregnant women after at least 28 weeks of gestation with premature rupture of membranes, researchers investigated WBC and neutrophile counts taken at delivery, and results indicated their poor diagnostic performance for histological chorioamnionitis [21]. Furthermore, Amirabi et al. suggested measuring WBC in women with PROM wasn't supportive in the prediction of chorioamnionitis [22]. However, Bartkeviciene proposed leukocytes in maternal blood could be the possible indicators of fetal inflammatory response syndrome (FIRS) [20]. In our study, we noticed that mothers with intrauterine inflammation had higher WBC and neutrophile counts, lower lymphocyte proportion, and revealed that these factors had certain predictive value for MIR and FIR. But the differences between different factors were not significant.

Most previous researches focused on single factor, and neglected interactions of multi-factors. Only a few studies synthetically considered different factors. Park et al. built a model based on maternal blood CRP, WBC, parity, and gestational age, which had good diagnostic performance of intra-amniotic infection (IAI) in women with PPROM [23]. However, a retrospective cohort study containing 73 patients from 20 to 37 weeks of gestation demonstrated that predictive logistic model including CRP level, WBC before delivery and temperature at onset of delivery was not significantly better than CRP level alone in predicting chorioamnionitis [24].

The current study investigated the predict value of WBC, neutropile counts and proportion, lymphocyte proportion for MIR and FIR at first, then described logistic models for MIR and FIR respectively adjusting for gestational age, birth weight, administration of antibiotics. We com-

bined hematological and clinical data and draw a conclusion that combination model has the best predictive function, by means of which we can obtain a higher discrimination power than any single parameters. The prediction models are convenient to use, and the results are readily available. Nevertheless, our study existed limitations. First, this is a retrospective cohort study. But our data was collected from clinical database directly, so the results should close to clinical practice. Second, this is a single center study. We should enlarge the sample size and examine the power of this model.

In conclusion, WBC, neutrophile counts and proportion, lymphocyte proportion during 24~72 h before delivery may be handy indicators of intrauterine inflammation in early preterm birth. Furthermore our study established the logistic models with combination of hematologic and clinical data, which have significant better performance of detecting MIR and FIR, and have the advantages of convenience and low-cost. With no doubt, the diagnostic efficiency of the models needs further evaluation so as to guide clinical decisions about diagnosis and treatment.

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## Disclosure of conflict of interest

None.

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