

**Maternal risk score for the prediction of fetal inflammatory response syndrome
after preterm premature rupture of membranes**

Mariko Nakahara^{a*}, Shunji Goto^b, Eiji Kato^b, Shuko Nojiri^c Atsuo Itakura^a, Satoru
Takeda^a

*^aDepartment of Obstetrics and Gynecology, Juntendo University Faculty of Medicine,
Bunkyo-ku, Tokyo, Japan*

*^bPerinatal Center for Maternity and Neonate, Japan Community Health Care
Organization Funabashi Central Hospital, Funabashi, Chiba, Japan*

*^cMedical Technology Innovation Center Clinical Research and Trial Center Juntendo
University Faculty of Medicine, Bunkyo-ku, Tokyo, Japan*

Running Title: Maternal risk score of FIRS

***Corresponding Author:** Mariko Nakahara

ORCID ID: 0000-0001-5187-2624

Department of Obstetrics and Gynaecology

Juntendo University Faculty of Medicine

2-1-1 Hongo Bunkyo-ku, Tokyo 113-8421, Japan

Phone: +81-3-5802-1100

Fax: +81-3-5689-7460

E-mail: mrnakaha@juntendo.ac.jp

Abstract

Aim: Preterm premature rupture of membranes (PPROM) is common in preterm births. Fetal inflammatory response syndrome (FIRS) is present in nearly 50% of PPRM cases. We created a risk score to predict FIRS using maternal factors after PPRM.

Methods: We conducted a retrospective study of singleton pregnancies complicated by PPRM that resulted in delivery at 23 to 35 weeks of gestation. Antepartum maternal factors and umbilical cord blood interleukin-6 (IL-6) data were analysed. FIRS was defined as IL-6 >11 pg/mL.

Results: Umbilical cord blood IL-6 and maternal blood data within 24 hours before parturition were available for 158 cases; 66 were diagnosed with FIRS (41.8%; median IL-6, 57.55 pg/mL). We created a risk score (FIRS score) comprising expected delivery weeks (≤ 30 weeks), maternal C-reactive protein (≥ 1.2 mg/dl), maternal white blood cell count ($\geq 13000/\mu\text{l}$), corticosteroid use (none) and PROM latency period (≥ 3 days) from the multivariate logistic regression model predicting FIRS. Receiver operating characteristic curve analysis of the score produced the following results: area under the curve, 0.82; 95% CI, 0.76-0.89; cut-off value, 7.5; sensitivity, 89%; specificity, 63%; positive predictive value, 63%; and negative predictive value, 89%. The probability of FIRS according to the categories of the FIRS score was 11% for those with a score of 0-7, 50% for a score of 8-15, and 88% for a score of 16-22.

Conclusions: The devised maternal risk score could predict FIRS and be helpful to decide the delivery timing for the cases of PPRM.

Keywords: Chorioamnionitis, C-reactive protein, Fetal membranes, Premature rupture, prenatal care

Introduction

Preterm premature rupture of membranes (PPROM) accounts for approximately one-third of preterm births and is closely related to bacterial products and pro-inflammatory cytokines.¹

The fetal inflammatory response syndrome (FIRS) was first proposed by Gomez *et al.* (1998) as an amniotic fluid infection or inflammatory process leading to a systemic inflammatory response syndrome with increased fetal blood interleukin-6 (IL-6). In about 50% of PROM cases, the foetus will undergo FIRS.² Several reports have defined FIRS as having a fetal blood IL-6 >11 pg/mL. It is associated with bronchopulmonary dysplasia, intraventricular haemorrhage, and periventricular leukomalacia in children, as well as cerebral palsy and other developmental disorders.²⁻⁸

There are only a few sufficient maternal parameters to predict FIRS. Several studies have utilised cytokine levels and other biomarkers to predict histological chorioamnionitis (HCA) and microbial invasion of the amniotic cavity (MIAC) before delivery in cases with amniotic fluid infection by amniocentesis.^{8,9} However, routine amniocentesis can present difficulties because sometimes patients can refuse this treatment, the physician can decline to perform the procedure, and patients may not have enough fluid to safely perform the procedure.¹⁰ Therefore, it is important to establish a less invasive and accurate method of diagnosis. We evaluated antepartum maternal factors related to FIRS in women with PPRM and attempted to develop a risk score that can predict FIRS in this population.

Methods

Study design

We performed a retrospective study of singleton pregnancies complicated by

PPROM that resulted in delivery at 23 to 35 weeks of gestation at the Japan Community Health Care Organization Funabashi Central Hospital between January 2009 and December 2014. All data were obtained from patients' medical records. Cases involving maternal malignancy, child chromosome abnormalities, and intrauterine fetal death were excluded. We also excluded cases in which umbilical cord blood IL-6 was not measured and patients who did not undergo a laboratory examination within 24 hours before parturition.

The Institutional Review Committee of Japan Community Health Care Organization of Funabashi Central Hospital approved this study (22 March 2018; no. H 30-5). All patients included in the study provided informed consent for scientific analysis of their data in an anonymised form. Additionally, this study does not violate the policies and/or procedures described in the Specific Inappropriate Acts In Publication Process and conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Patient management

Premature rupture of membranes (PROM) was defined as watery leakage from the vagina that was confirmed by sterile speculum examination and by the observation of either fluid accumulation in the posterior vaginal fornix or direct leakage from the cervical canal.¹ We managed PPRM expectantly until week 35 of gestation by performing vital sign evaluations and laboratory monitoring for infection or inflammation. We prescribed a 7-day course of intravenous antibiotics (sulbactam/ampicillin, cloxacillin/ampicillin, or clindamycin). Women who were already on tocolytics before admission to our hospital had their tocolytics discontinued after we made the diagnosis of PROM. If a patient was not in labour, then we

administered dexamethasone (12 mg/day) to improve fetal lung maturity. In cases of spontaneous labour, non-reassuring fetal status, or clinical chorioamnionitis, the foetus was delivered immediately.

Clinical chorioamnionitis was diagnosed using the following criteria: maternal fever, maternal blood test results, vaginal discharge, tenderness of the uterus (Lencki criteria)¹¹, and fetal tachycardia. After 35 weeks of gestation, we induced vaginal delivery with oxytocin administration if the patient had no history of uterine incisional surgery or other contraindications.

Outcome definitions

Pathologists performed a histopathologic examination of formalin-fixed, paraffin-embedded placental tissue. The Blanc classification was used to stage each case according to the degree of neutrophil infiltration as follows: stage I, intervillitis; stage II, chorionitis; and stage III, chorioamnionitis. We defined stage II or higher as HCA.¹²

Umbilical cord blood IL-6 was measured in the umbilical artery or vein blood sample collected at the time of delivery. We performed an umbilical cord blood gas analysis, cell counts, and biochemical and immunological studies at the time of delivery, and we prioritised the blood gas analysis results, cell counts, and biochemical examination results. Immunological tests were not conducted if a small amount of blood was collected, and umbilical cord blood IL-6 was not measured in all cases. IL-6 was analysed using the Human Interleukin-6 CLEIA (Fujirebio, Tokyo, Japan) chemiluminescent enzyme immunoassay according to the manufacturer's instructions. The upper and lower detection limits were 1000 and 0.2 pg/mL, respectively, and IL-6 >11 pg/mL was defined as FIRS.

Predictive factors

We calculated the maternal non-pregnant body mass index (BMI) (weight [kg]/height [m²]) and recorded the body temperature (°C). We frequently evaluated fetal well-being before delivery. Cases of corticosteroid use included all cases who used corticosteroid during pregnancy. Venous blood evaluations, including white blood cell count (WBC) and C-reactive protein (CRP) levels, were performed every few days. We used antepartum WBC and CRP in our calculations, which were the results within 24 hours before delivery. The delivery route was classified as vaginal delivery or caesarean delivery. We also recorded and defined the PROM latency period as the number of days from membrane rupture to delivery.

Perinatal outcomes

The perinatal outcome was composited by adverse perinatal outcomes including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), pulmonary hypertension (PH), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), culture-proven sepsis, necrotizing enterocolitis (NEC), and perinatal death. RDS was defined as the presence of respiratory symptoms (e.g. tachypnoea and retraction) requiring respiratory support and surfactant administration and findings of reticulogranular patterns and air bronchograms on chest x-ray. BPD was defined by following the international consensus guideline.¹³ NEC was defined as Bell > Stage 1.¹⁴ PVL >grade 1 and IVH >grade 1 were diagnosed by repeated neonatal cranial ultrasound or magnetic resonance imaging by the neonatologist.^{15,16} We analysed the correlation between FIRS and each outcome adjusted for delivery weeks and calculated a cut-off value of IL-6 at our hospital to predict the composite perinatal outcome.

Statistical analysis

Statistical analyses were performed using R version 3.6.3 (R Foundation, Vienna, Austria). First, we performed a univariate analysis comparing patients with and without FIRS. Continuous variables were compared using the non-parametric Mann-Whitney U test, and the results are presented as medians (interquartile range). Categorical variables were compared using the Chi-squared test and are presented as numbers and percentages. Secondly, we created a multivariate logistic regression model to predict FIRS. The variables were selected from our univariate analysis and previous reports^{2,7,17-19} to become Akaike information criterion (AIC) and area under curve (AUC) best. The model included CRP, WBC, corticosteroid use, PROM latency period, and gestational age (GA) at delivery. The Youden index, the maximum potential effectiveness of a biomarker, is a measure of the receiver-operator characteristic (ROC) curve.²⁰ In our study, we evaluated the cut-off values of CRP, WBC, PROM latency period, and gestational age by the Youden index. The numeric variables were converted to factor variables with a pre-selected cut-off point in the same manner done in a prior publication, in which each variable was fitted in the logistic model. The coefficient of regression model was rounded off to the nearest integer. The scores were further divided into those for factor variable and those used for developing the scoring system. Finally, we summed all component points into a total score that could be used for risk stratification. The score was converted to a probability score of FIRS and compared to an observed number of FIRS.²¹ ROC curve analysis was used to display the relationship between sensitivity and specificity and to select the best cut-off value for the FIRS score to predict FIRS. Differences were considered statistically significant at a confidence level of $p < 0.05$ (two-sided alternative hypothesis).

Results

During the study period, 309 singleton pregnancies met our study criteria. Of these, we excluded 151 cases (cases without umbilical cord blood IL-6 measurements and/or no examination within 24 hours before parturition, n=144; trisomy 21 [child], n=4; maternal malignancy, n=1; both trisomy 18 [child] and intrauterine fetal death, n=1; multiple malformations [child], n=1;), and 158 women were analysed (median GA at PROM, 31 weeks [range, 22-35 weeks]; median GA at delivery, 31 weeks [range, 23-35 weeks]) (Figure 1).

We diagnosed FIRS (umbilical cord blood IL-6 > 11 pg/mL) in 66 out of 158 patients (42%; median 57.6 pg/mL [range, 11.1-33,100 pg/mL]). Table 1 shows the demographic characteristics and laboratory findings of patients with and without FIRS. Mann-Whitney U testing demonstrated that the cervical length at admission, GA at PROM, PROM latency period, GA at delivery, antepartum WBC and CRP, incidence of caesarean delivery, placental weight, birth weight, incidence of HCA, incidence of funisitis, neonatal sex, and 5-minute Apgar scores varied significantly between groups (Table 1). The neonatal outcomes was as follows: RDS, n=54, Clude OR [cOR], 2.10; 95% confidence interval [CI], 1.07-4.10, p=0.03, Adjusted OR [aOR], 0.67; 95% CI, 0.28-1.62, Adjusted p=0.37; PH, n=4, cOR, 4.33, 95% CI, 0.44-42.6, p=0.21, aOR, 1.48; 95% CI, 0.13-16.60, p=0.75; culture-proven sepsis, n=8, cOR, 2.43, 95% CI, 0.56-10.6, p=0.24, aOR, 1.28; 95% CI, 0.25-6.44, p=0.77; Composite perinatal outcome, n=22, cOR, 4.59, 95% CI, 1.69-12.5, p<0.0001, aOR, 1.55; 95% CI, 0.52-4.64, p=0.43. Our cut-off value of IL-6 predicting composite perinatal outcome, which included RDS, BPD, PH, IVH, PVL, culture-proven sepsis, NEC, and perinatal death, was 7.2 pg/mL with a sensitivity of 82% and specificity of 59%.

Firstly, we calculated the AUC of each variable of maternal factor; PROM latency period, 0.62, 95% CI, 0.53-0.71, GA at delivery, 0.76, 95% CI, 0.68-0.84, antepartum CRP, 0.77, 95% CI, 0.69-0.85, antepartum WBC, 0.67, 95% CI, 0.58-0.76. Because the administration of corticosteroids increases the number of circulating WBC, we added corticosteroid use as a covariate of WBC. A multivariate logistic regression model for predicting FIRS using related maternal factors included the PROM latency period (OR; 1.05, $p=0.012$), antepartum WBC (OR; 1.03, $p=0.65$), antepartum CRP (OR; 1.77, $p=0.002$), GA at delivery (OR; 0.76, $p<0.001$), and corticosteroid use (OR; 0.84, $p=0.70$) (AIC, 167.02 ; AUC, 0.84 ; 95% CI, 0.78-0.91) (Table 2). To create the risk score, we calculated the cut-off value of continuous variables from the multivariate logistic model: PROM latency period, 2.5; sensitivity, 56%; specificity, 67%, antepartum WBC, 13250; sensitivity, 62%; specificity, 73%, antepartum CRP, 1.15; sensitivity, 67%; specificity, 82%, GA at delivery, 30.5; sensitivity, 67%; specificity, 73%. We summed all component points into a total score and converted it to a probability score of FIRS (Table 3). The FIRS score ROC curve analysis produced the following results: AUC, 0.82; 95% CI, 0.76-0.89, cut-off value, 7.5; sensitivity, 89%; specificity, 63%; positive predictive value, 63%; and negative predictive value, 89% (Figure 2). We devised three categories based on the rate of FIRS; low (11%), intermediate (50%), and high risk (88%) and showed a correlation with HCA, funisitis and other characteristics (Table 4).

Discussion

The FIRS score, a combination of maternal CRP, WBC, expected delivery weeks, PROM latency period, and corticosteroid use, could predict FIRS less invasively and economically. According to the multivariate logistic regression analysis in this

retrospective study, antepartum CRP, PROM latency duration, and GA at delivery were significantly associated with FIRS. Previous studies also reported about the correlation between those factors and intrauterine infection or inflammation. Maternal CRP has previously been reported to be a predictor of infection or inflammation associated with PROM.^{17,18} To date, only one report has shown a correlation of maternal CRP with umbilical cord blood IL-6 concentration. It was reported that maternal CRP levels before, during, and after labour were significantly higher in the FIRS group.²² Maternal CRP has also been reported as a predictor of funisitis and early-onset neonatal sepsis (EONS).^{18, 23-25} Regarding chorioamnionitis and EONS, a few studies reported that chorioamnionitis occurred in 15% to 30% of patients with a long PROM latency period,²⁶ and a latency period >18 hours was reported to be a risk factor for EONS.²⁷ A few reports have shown an association between the early weeks of gestation and MIAC and FIRS^{28, 29}.

Maternal WBC was included in the FIRS score similarly to the Lencki criteria but body temperature was not. In this study, the antepartum maternal WBC was not significantly associated with FIRS according to multivariate analysis. A previous report indicated that the maternal WBC does not predict amniotic fluid bacterial infection or HCA in women with PROM.³⁰ Although the predictive power of WBC alone was also low in our study, the best multiple logistic model included WBC. Nevertheless, body temperature was not significantly different between the FIRS and non-FIRS groups. At our hospital, blood tests are performed every few days for women with PPRM, and delivery decisions are based not only on pre-parturition body temperature but also on laboratory data, labour onset, and non-reassuring foetal factors, including foetal tachycardia. Body temperature was possibly not associated with FIRS because delivery

decisions were based on laboratory findings of an inflammatory response or the onset of labour before an increase in body temperature occurred.

The strength of our study is that the score enabled the prediction of not only HCA but also umbilical cord blood IL-6 elevation by methods such as examination of blood counts, which constitute routine management of PPROM in almost every facility. If 19 patients (29%) with FIRS did not have HCA diagnosed, the prediction of chorioamnionitis would result in a missed diagnosis of FIRS. HCA is indirectly associated with neonatal prognosis, and many studies have reported that the prediction of HCA is important because it is linked to neonatal prognosis.^{31,32} However, the presence of HCA indicates placental inflammation only; it is more important in predicting fetal inflammation. Kacerovsky *et al.* (2013) reported that FIRS occurred in women with complications of both MIAC and HCA, more than in women with HCA alone, MIAC alone, or without both MIAC and HCA.⁸

Obstetricians should consider the appropriate timing for delivery at early gestational weeks with caution. fetal prematurity can also affect the prognosis of PPROM because it can lead to disorders such as cerebral palsy and developmental disabilities.³³ When an obstetrician needs to decide the timing of delivery for a patient with PPROM, the FIRS score would be one of the criteria to help determine whether the neonate will have FIRS if delivery is performed within 24 hours. We divided the score into three categories, low, intermediate, and the high risk, according to each probability for the prediction of FIRS. As mentioned, cord blood IL-6 >11 pg/mL has been associated with neonatal prognosis in several reports; this value was selected as the definition of FIRS in our study, as well^{2,7}. To avoid FIRS, delivery for women with PPROM is recommended if their risk for FIRS is intermediate or high because the cut-off value of the score to

predict FIRS was 7.5 in our study.

The present study had some limitations. First, by being retrospective, confounding factors cannot be completely adjusted. In addition, neonatal prognosis has not been examined sufficiently in this study which was conducted in a single-centre due to the small number of event occurrences. Future validation studies will be conducted in a multi-centre setting to examine the relationship between FIRS score and neonatal prognosis. Second, there is no clear evidence about whether we can interpret IL-6 values from the umbilical vein the same as those obtained from the umbilical artery. Inflammation of the umbilical cord is thought to begin in the umbilical vein, and the stage of fetal inflammatory response is reported to be different between umbilical arteritis and phlebitis.³⁴

In conclusion, we could predict FIRS less invasively by using the FIRS score. Innovative methods, which can be evaluated objectively by any physician to improve neonatal prognosis in women with PPROM, to diagnose FIRS before delivery are crucial.

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Disclosure statement

The authors report no conflict of interest.

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Figure legends

Figure 1. Flow diagram of patient selection for inclusion in the study

Figure 2. Receiver-operator curve showing FIRS score

Figure 1.

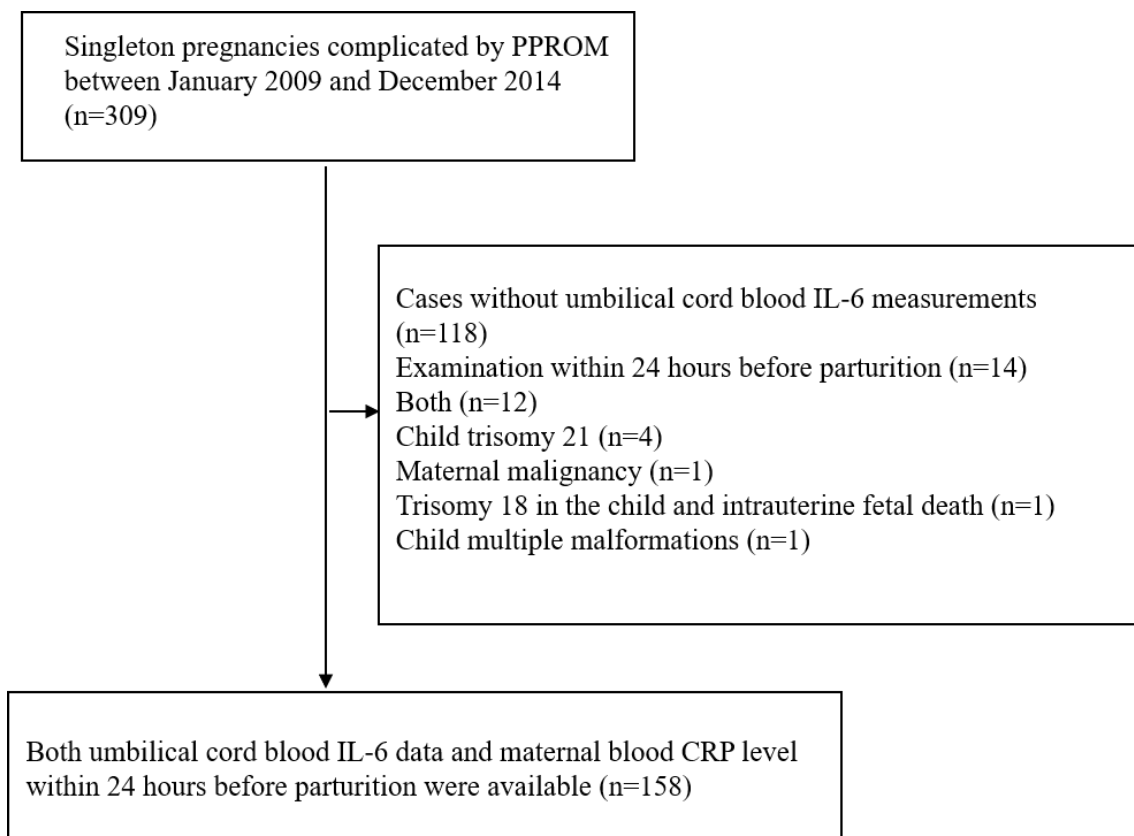
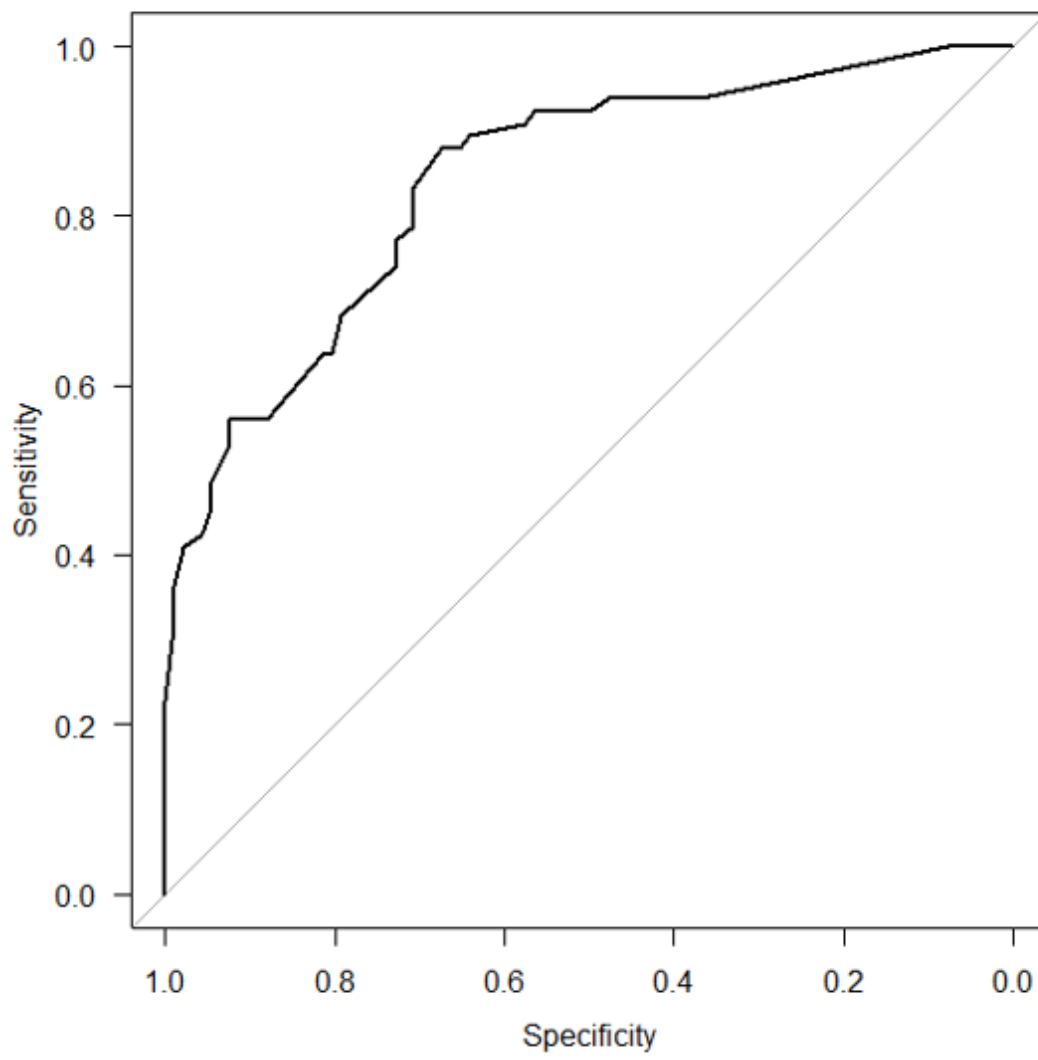


Figure 2.



Tables

Table 1. Characteristics of pregnancies (n=158) with and without FIRS

	Non-FIRS (n=92)	FIRS (n=66)	P-values
Maternal age (years)	33 (29-36)	33 (30-35)	0.64
Nulliparous	47 (51.1)	28 (42.4)	0.33
Pre-pregnancy BMI (kg/m ²)	20.7 (18.8-23.1)	21.1 (19.3-23.0)	0.74
Smoking	4 (4.7)	7 (11.5)	0.20
Cervical length at admission (mm)	23.5 (14.5-32.2)	29.2 (19.6-40.7)	0.03
GA at PROM (weeks)	32 (30-34)	28 (25-31)	<0.001
PROM latency period (days)	1 (0-5)	4 (0-11)	0.011
GA at delivery (weeks)	33 (30-34)	29 (27-32)	<0.001
Corticosteroid therapy	32 (34.8)	32 (48.5)	0.33
Tocolytic therapy	59 (64.8)	45 (68.2)	0.73
Antibiotic therapy	75 (81.5)	53 (80.3)	0.84
Body temperature (°C)	37.0 (36.7-37.3)	37.1 (36.8-37.5)	0.14
Antepartum WBC (/μL)	11300 (8900-13625)	14,300 (10375-17475)	<0.001
Antepartum CRP (mg/dL)	0.41 (0.20-1.02)	1.87 (0.78-3.28)	<0.001
Caesarean delivery	35 (38.0)	41 (62.1)	<0.01
Placenta weight (g)	445 (384-523)	390 (340-455)	<0.001
Birth weight (g)	1807 (1507-2179)	1300 (915-1701)	<0.001
HCA (%)	10 (10.9)	47 (72.3)	<0.001
Funisitis (%)	2 (2.2)	33 (50)	<0.001
5-minute Apgar score	9 (8-9)	8 (8-9)	0.001
Umbilical artery blood pH	7.37 (7.32-7.40)	7.36 (7.31-7.39)	0.32
Male (%)	59 (64.1)	31 (47.0)	0.04

Values are presented as numbers (%) or medians (interquartile range). BMI, body mass index; CRP, C-reactive protein; GA, gestational age; HCA, histological chorioamnionitis; PROM, premature rupture of membrane; WBC, white blood cell count.

Table 2. Logistic regression analysis for prediction of FIRS (n=158)

	OR[†]	95% CI	P-value	Adjusted OR[‡]	95% CI	Adjusted P-value
PROM latency period	1.04	1.00-1.08	0.035	1.05	1.01-1.09	0.012
Antepartum WBC	1.15	1.06-1.24	<0.0001	1.03	0.92-1.14	0.65
Antepartum CRP	1.97	1.45-2.67	<0.0001	1.77	1.23-2.56	0.002
GA at delivery	0.72	0.64-0.82	<0.0001	0.76	0.65-0.88	<0.001
corticosteroid use	1.76	0.93-3.37	0.085	0.84	0.34-2.06	0.70

†univariate;‡multivariate

FIRS, foetal inflammatory response syndrome; CRP, C-reactive protein; GA, gestational age; PROM, premature rupture of membrane;

WBC, white blood cell count.

OR, Odds ratio, CI, Confidence Interval

Table 3. The point scoring system of FIRS score

Maternal factors	Cut-off value	point
Expected delivery weeks	≤ 30 weeks	6
Maternal CRP	≥ 1.2 mg/dl	7
Maternal WBC	$\geq 13000/\mu\text{l}$	3
Corticosteroid use	none	1
PROM latency period	≥ 3 days	5

CRP, C-reactive protein; PROM, premature rupture of membrane; WBC, white blood cell count.

Table 4. Correlation between FIRS score (the total point score) and other characteristics (n=158)

Category	FIRS score	n	FIRS (%)	Umbilical Cord blood IL-6 (pg/ml)	HCA (%)	Funisitis (%)	Maternal CRP (mg/ml)	Maternal WBC (/ μ l)
Low	0-7	65	7 (11)	3.3 (1.7, 5.9)	7 (11)	4 (6)	0.35 (0.22, 0.71)	9800 (8500, 11400)
Intermediate	8-15	60	30 (50)	10.7 (4.0, 39.8)	26 (43)	13 (22)	0.98 (0.23, 2.24)	13650 (10675, 16675)
High	16-22	33	29 (88)	72 (27, 269)	24 (75)	18 (55)	2.29 (1.79, 4.04)	16400 (14200,18500)

Values are presented as numbers (%) or medians (interquartile range). CRP, C-reactive protein;

FIRS, foetal inflammatory response syndrome; HCA, histological chorioamnionitis; IL-6,

interleukin-6; PROM, premature rupture of membrane; WBC, white blood cell count.