Nomogram for Perinatal Prediction of Intrapartum Fever: A Case-control Study

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Research Article

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Abstract

Objective: To explore the risk factors of intrapartum fever and develop a nomogram to predict the incidence of intrapartum fever.

Methods: The general demographic characteristics and perinatal factors of 696 parturient who underwent vaginal delivery in the Affiliated Hospital of Xuzhou Medical University from May 2019 to April 2020 were retrospectively analyzed. 487 patients collected from May 2019 to October 2019 were formed into a training cohort. A multivariate logistic regression model was used to identify the independent risk factors associated with intrapartum fever during vaginal delivery, then a nomogram was developed to predict the occurrence. 209 cases collected from January 2020 to April 2020 were formed into a validation cohort to verify the nomogram.

Results: Intrapartum fever was found in 72 of 487 parturient (14.78%) in the training cohort, and the incidence of intrapartum fever in the validation cohort was 14.83% (31/209). Multivariate logistic regression analysis showed that primiparas (Odds Ratio [OR]2.433; 95% confidence interval [CI]1.149-5.150), epidural labor analgesia (OR2.890; 95%CI 1.225-6.818), premature rupture of membranes (OR2.366; 95%CI 1.130-4.954), second stage of labor ≥120min (OR4.363; 95%CI 1.419-13.410), amniotic fluid pollution ≥ degree (OR10.391; 95%CI 3.299-32.729), fetal weight ≥4000g (OR7.492; 95%CI 2.115-26.542) were significantly related to intrapartum fever. According to clinical experience and previous studies, the duration of epidural labor analgesia also seemed to be a meaningful factor for intrapartum fever, so these 7 variables were incorporated to develop a nomogram, which achieved good area under ROC curve of 0.855 in the training cohort and 0.808 in the validation cohort, and it had a well-fitted calibration curve, which showed an excellent diagnostic performance.

Conclusion: We constructed a model to predict the occurrence of fever during childbirth and developed an accessible nomogram. The nomogram can help doctors assess the risk of fever during childbirth, so as to lead to reasonable treatment measures.

Clinical Trial Registration: (www.chictr.org.cn ChiCTR2000035593)

Introduction

Intrapartum fever, which defined as the phenomenon that maternal body temperature higher than 38°C during delivery. The prevalence of intrapartum fever ranges from 1.6–14.6%. A widely accepted theory in the past was that intrapartum fever was an infectious inflammation, but the preventive application of antibiotics cefonicid to the parturient found that it could not reduce the occurrence of intrapartum fever. This was likely to indicate that intrapartum fever couldn’t be completely attributed to maternal infection. Current researches believed that most part of intrapartum fever is secondary to non-inflammatory infection.
A few studies have shown that intrapartum fever had serious adverse consequences on maternal safety and newborn growth and development.\(^2\)–\(^4\) Women with maternal fever are more likely to receive antibiotics and undergo cesarean section. Meanwhile, it may cause low Apgar scores, respiratory distress, hypotonia and neonatal seizures. What is more worrying is that intrapartum fever is related to neonatal encephalopathy. The long-term prognosis of children with neonatal encephalopathy depends on its severity, even causing cerebral palsy and mental retardation.\(^5\),\(^6\) Nevertheless, the current research on the risk factors of intrapartum fever have been studied, but they were all limited by small sample sizes or much missing data.\(^7\) In addition, previous research didn't distinguish between low-risk and high-risk mothers. If the risk and incidence of fever during delivery can be early and quickly predicted, it may help obstetricians to give intervention measures in advance, and better manage the stage of labor.

Owing to the lack of a specific and practical predictive method, development of a prediction model that incorporates factors associated with intrapartum fever based on perinatal clinical data becomes desirable. Of all available models, nomograms can provide a personalized, evidence-based, and highly accurate risk estimation.\(^8\) The nomogram is easy to use and can guide the relevant clinical management. However, as far as we know, no such model has been established to help identify patients at high risk of intrapartum fever in time.

Therefore, the objective of this study was to conduct a comprehensive and systematic review of antenatal and perinatal factors related to intrapartum fever in order to distinguish independent risk factors for perinatal fever. At the same time, a risk prediction model was established and a nomogram was developed to facilitate obstetricians to identify clinically high-risk patients, and to optimize their management in the early stages of delivery to reduce the risk for mothers and babies.

**Methods**

This retrospective case-control study has been registered in the Chinese Clinical Trial Center (ChiCTR2000035593), and approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2020-KL135-01). Informed consent was obtained from all mothers for their data to be used for research. From May 2019 to April 2020, data on women who gave birth via vaginal in the Affiliated Hospital of Xuzhou Medical University were abstracted. The inclusion criteria were: (1) singleton pregnancy, cephalic presentation; (2) term births (37–41 weeks of gestation) via vaginal, and the exclusion criteria were as follows: (1) patients whose basal body temperature \(\geq 37.5^\circ C\); (2) women who had other known infections; (3) transferred to caesarean delivery for non-febrile reasons. Parturient gave premature birth or stillbirth and missed electronic medical record were eliminated.

All mothers and infants received standard obstetric and neonatal care. If the patient chose to use epidural anesthesia, the epidural analgesia pump regimen remained the same (PCEA: loading dose:10 ml 0.1% ropivacaine + 0.5ug/ml sufentanil; maintenance: 0.1% ropivacaine + 0.5ug/ml sufentanil at 8 ml/h; bolus
It is up to the obstetricians whether to use antibiotics or antipyretic therapy during delivery.

Referred to relevant literature and expert opinions,\textsuperscript{9,10} the following factors were collected from the electronic medical record system as observation indicators: general demographic characteristics include maternal age, BMI, gestational age, parity, and fetal weight; perinatal factors: body temperature on admission, white blood cell count on admission, hemoglobin on admission, pregnancy complications (including gestational diabetes, hypertension during pregnancy, abnormal thyroid function), method of membrane rupture, premature rupture of membranes, time from rupture of membranes to delivery, duration of the first and second stage of labor, epidural labor analgesia, analgesia time, amniotic fluid statement, oxytocin usage, and number of vaginal examinations.

**Statistical Analysis**

Using IBM SPSS 23.0 software for statistical analysis: numeric variables were analyzed for a normal distribution by the Shapiro-Wilk test. Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD) and were compared using the independent-sample \( t \)-test. Continuous variables with a non-normal distribution are expressed by the median (interquartile range) and comparisons between groups are presented by Mann-Whitney \( U \)-test; Categorical data are presented by number (%), using \( \chi^2 \) test or Fisher's exact probability test, the missing data uses the mean interpolation method. The significance of each variable in the training cohort was assessed by univariate analysis for investigating the independent factors of intrapartum fever. All variables associated with intrapartum fever at a significant level were candidates for stepwise multivariate logistic regression analysis using stepwise variable selection method. All potential predictors were included. The standard for entering multivariate analysis was \( p < 0.2 \), and the retention in the logistic regression model requires \( p < 0.05 \), the results are expressed in odds ratio (OR) and 95% CI.

R4.0.3 software was used to develop a predictive model and draw a nomogram to predict the occurrence. \textsuperscript{11} Use discrimination and the calibration to verify the predictive ability of the model. Discrimination is expressed by the area under the receiver operating characteristic curve, and the Youden index (sensitivity + specificity - 1) is used to find the best critical value (Cut-off value), the accuracy of the best cut-off value is evaluated by sensitivity, specificity, predictive value and likelihood ratios. Calibration is demonstrated by the Hosmer-Lemeshow goodness-of-fit test, which compares the difference between the predicted probability and the actual probability, apart from these, a calibration plot will be drawn. \( P > 0.05 \) indicates that the difference between the predicted value and the actual probability of the outcome is not statistically significant, which represents goodness of fit.

**Results**

From May 2019 to April 2020, there were 1762 pregnant women planning a vaginal delivery in the Affiliated Hospital of Xuzhou Medical University. After exclusions and eliminations, 696 patients were
included in the study. Of these, 487 patients collected from May 2019 to December 2019 were formed into a training cohort to assess the risk factors of intrapartum fever and develop a nomogram. According to whether intrapartum body temperature exceeds 38°C, they were divided into afebrile group (n = 415) and febrile group (n = 72). The remaining 209 cases abstracted from January 2020 to April 2020 were formed into a validation cohort to test the nomogram. The patient recruitment flowchart is shown in Fig. 1.

Table 1 presents the general demographic characteristics and perinatal factors of the training cohort and the validation cohort. No statistically significant difference was found between two groups.
Table 1
Comparison of demographic characteristics and perinatal factors between training cohort and validation cohort

| Variable                                      | Training cohort | Validation cohort (n = 197) | P     |
|-----------------------------------------------|-----------------|----------------------------|-------|
|                                               | (n = 487)       |                            |       |
| Age [M (IQR)]                                 | 28(4)           | 29(5)                      | 0.081 |
| BMI [M (IQR)]                                 | 26.67(3.89)     | 26.40(4.72)                | 0.565 |
| Gestational age [M (IQR)]                    | 275(11)         | 274(10)                    | 0.402 |
| Accompany disease (%)                         |                 |                            |       |
| GDM                                           | 62(12.7%)       | 24(11.5%)                  | 0.647 |
| Abnormal thyroid function                     |                 |                            |       |
| Hypertension during pregnancy                 |                 |                            |       |
| Parity (%)                                    |                 |                            |       |
| Primipara                                     | 294(60.4%)      | 123(58.9%)                 | 0.708 |
| Multipara                                     | 193(39.6%)      | 86(41.1%)                  |       |
| Body temperature on admission [M (IQR)]       | 36.5(0.2)       | 36.5(0.2)                  | 0.232 |
| WBC counts on admission [M (IQR)]             | 8.3(2.7)        | 8.7(3.0)                   | 0.168 |
| HB on admission [M (IQR)]                     | 12.1(2)         | 12(2)                      | 0.508 |
| Premature rupture of membranes (%)            |                 |                            |       |
| Yes                                           | 72(14.8%)       | 25(12%)                    | 0.324 |
| No                                            | 415(85.2%)      | 184(88%)                   |       |
| Time from rupture of membranes to delivery [M (IQR)] | 188(434) | 234(480)                  | 0.836 |
| Method of membrane rupture (%)                |                 |                            |       |
| Spontaneous                                   | 224(46.0%)      | 89(42.6%)                  | 0.407 |
| Surgical                                      | 263(54%)        | 120(57.4%)                 |       |

Abbreviations:

BMI, body mass index; GDM, gestational diabetes; WBC, white blood cell; HB, Hemoglobin; IQR, interquartile range
| Variable                                | Training cohort (n = 487) | Validation cohort(n = 209) | \( P \) |
|-----------------------------------------|---------------------------|----------------------------|--------|
| Oxytocin usage (%)                      |                           |                            | 0.325  |
| Yes                                     | 276(56.7%)                | 110(52.6%)                 |        |
| No                                      | 211(43.3%)                | 99(47.4%)                  |        |
| Fetal weight [M (IQR)]                  | 3340(490)                 | 3350(580)                  | 0.749  |
| Amniotic fluid pollution (%)            |                           |                            | 0.686  |
| Yes                                     | 20(4.1%)                  | 11(5.3%)                   |        |
| No                                      | 467(95.9%)                | 198(94.7%)                 |        |
| Duration of the first stage of labor [M (IQR)] | 470(450)                 | 420(438)                   | 0.203  |
| Duration of the second stage of labor [M (IQR)] | 31(46)                   | 28(48)                     | 0.120  |
| Number of vaginal examinations [M (IQR)]   | 2(1)                     | 2(2)                       | 0.803  |
| Epidural labor analgesia (%)            |                           |                            | 0.933  |
| Yes                                     | 139(28.5%)                | 59(28.2%)                  |        |
| No                                      | 348(71.5%)                | 150(71.8%)                 |        |
| Analgesia time [M (IQR)]                | 0(160)                    | 0(133)                     | 0.834  |

Abbreviations:

BMI, body mass index; GDM, gestational diabetes; WBC, white blood cell; HB, Hemoglobin; IQR, interquartile range

The data of 487 parturient in the training cohort were analyzed to examine the influencing factors of intrapartum fever. The univariate analysis results of the influencing factors related to intrapartum fever were shown in Table 2. The results showed: nulliparity, premature rupture of membranes, time from rupture of membranes to delivery, fetal weight, method of membrane rupture, oxytocin usage, amniotic fluid state, duration of the first stage of labor, duration of the second stage of labor, number of vaginal examinations, epidural labor analgesia and analgesia time were related to intrapartum fever (\( P < 0.2 \)).
|                                      | Febrile (n = 72) | Afebrile (n = 415) | P    |
|--------------------------------------|------------------|--------------------|------|
| Age [M (IQR)]                        | 28(4)            | 28(4)              | 0.760|
| BMI [M (IQR)]                        | 26.29(3.79)      | 26.77(3.85)        | 0.756|
| Gestational age [M (IQR)]            | 275.5(11)        | 275(11)            | 0.466|
| Accompany disease (%)                |                  |                    |      |
| GDM                                  | 10(13.9%)        | 52(12.5%)          | 0.749|
| Abnormal thyroid function            | 3(4.2%)          | 14(3.5%)           | 0.667|
| Hypertension during pregnancy        |                  |                    |      |
| Parity (%)                           | 59(81.9%)        | 235(56.6%)         | < 0.001|
| Primipara                            | 13(18.1%)        | 180(43.4%)         |      |
| Multipara                            |                  |                    |      |
| Premature rupture of membranes (%)   | 20(27.8%)        | 52(12.5%)          | 0.001|
| Yes                                  | 52(72.2%)        | 363(87.5%)         |      |
| No                                   |                  |                    |      |
| Body temperature on admission [M (IQR)] | 36.5(0.2)       | 36.5(0.2)          | 0.414|
| WBC counts on admission [M (IQR)]    | 7.95(3.2)        | 8.4(2.5)           | 0.360|
| HB on admission [M (IQR)]            | 12.05 ± 1.24     | 12.07 ± 1.1        | 0.995|
| Time from rupture of membranes to delivery [M (IQR)] | 318.5(671) | 168(406) | 0.009|
| Method of membrane rupture (%)       | 40(55.6%)        | 184(44.3%)         | 0.078|
| Spontaneous                          | 32(44.4%)        | 231(55.7%)         |      |
| Surgical                             |                  |                    |      |
| Oxytocin usage (%)                   | 52(72.2%)        | 224(54%)           | 0.004|
| Yes                                  | 20(27.8%)        | 191(46%)           |      |
| No                                   |                  |                    |      |
| Fetal weight [M (IQR)]               | 3410(508)        | 3320(480)          | 0.175|

Abbreviations: BMI, body mass index; GDM, gestational diabetes; WBC, white blood cell; HB, Hemoglobin; IQR, interquartile range
|                                   | Febrile  | Afebrile |   |
|-----------------------------------|----------|----------|---|
| Amniotic fluid pollution (%)      | 12(16.6%)| 8(1.9%)  | <0.001|
| Yes                               | 60(83.4%)| 407(98.1%)|   |
| No                                |          |          |   |
| Duration of the first stage [M (IQR)] | 695.9(192.3) | 417.5(443.1)  | <0.001|
| Duration of the second stage [M (IQR)] | 83.8(48.5)  | 28(38)             | <0.001|
| Number of vaginal examinations [M (IQR)] | 3(2)      | 2(2)            | <0.001|
| Epidural labor analgesia (%)      | 50(69.4%)| 89(21.4%)| <0.001|
| Yes                               | 22(30.6%)| 326(78.6%)|   |
| No                                |          |          |   |
| Analgesia time [M (IQR)]         | 330(433) | 0(100)   | <0.001|

Abbreviations: BMI, body mass index; GDM, gestational diabetes; WBC, white blood cell; HB, Hemoglobin; IQR, interquartile range

The above 12 factors with significant univariate analysis results were assigned, and then included in the multivariate logistic regression analysis, using forward stepwise regression. The results were shown in Table 3.
Table 3
Multivariate analysis of related factors of intrapartum fever

| Risk factor                              | B     | SE    | Wald  | P    | OR    | 95% CI        |
|------------------------------------------|-------|-------|-------|------|-------|---------------|
| Primipara                                | 0.889 | 0.383 | 5.400 | 0.02 | 2.433 | 1.149–5.150   |
| Premature rupture of membranes           | 0.861 | 0.377 | 5.213 | 0.022| 2.366 | 1.130–4.954   |
| Epidural labor analgesia                 | 1.061 | 0.438 | 5.872 | 0.015| 2.890 | 1.225–6.818   |
| Amniotic fluid pollution ≥ degree         | 2.341 | 0.585 | 15.991| 0.000| 10.391| 3.299–32.729  |
| The second stage of the labor ≥ 120 min   | 1.473 | 0.573 | 6.612 | 0.010| 4.363 | 1.419–13.410  |
| Fetal weight                             | 2.014 | 0.645 | 9.738 | 0.002| 7.492 | 2.115–26.542  |
| Analgesia time < 4 h                     |       |       |       |      |       | 11.823        |
| Analgesia time (4–6 h)                   | -0.815| 0.555 | 2.513 | 0.142| 0.443 | 0.149–1.315   |
| Analgesia time > 6 h                     | 0.798 | 0.519 | 2.364 | 0.124| 2.220 | 0.803–6.135   |
| Constant                                 | -2.941| 0.670 | 19.274| 0.000| 0.053 |               |

Abbreviations: OR, odds ratio; CI, confidence interval

On multivariate logistic regression analysis, with results reported as OR [odds ratio] (95% CI), nulliparity (2.433[1.149–5.150]), epidural labor analgesia (2.890[1.225–6.818]), premature rupture of membranes (2.366[1.130–4.954]), second stage of labor ≥ 120 min (4.363[1.419–13.410]), amniotic fluid pollution ≥ degree (10.391[3.299–32.729]), fetal weight ≥ 4000 g (7.492[2.115–26.542]) were significantly related to intrapartum fever. According to clinical experience and previous studies, the duration of epidural analgesia also played a significant role in intrapartum fever. Although in our study, this variable did not show any significance, we still incorporated it into nomogram development.

Figure 2 shows the nomogram formed to predict the risk of intrapartum fever based on these selected parameters. By drawing a vertical line to the first row, the observed value of each parameter is designated as a certain point. Then calculate the total score, which corresponds to the individual’s risk of intrapartum fever.

Nomogram to estimate the risk of intrapartum fever. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total points axis to determine the fever probabilities at the lower line of the nomogram.
The nomogram demonstrated good accuracy in estimating the risk of intrapartum fever, with an AUC of 0.855 (95% CI 0.810–0.899). In addition, Hosmer-Lemeshow goodness-of-fit test ($X^2 = 4.585, P = 0.801$) and calibration plots graphically indicated good agreement between the predicted value of the model and the actual observed value, all of these showed good agreement on the presence of intrapartum fever.

In the testing cohort, the nomogram displayed an AUC of 0.808 (95% CI 0.727–0.889), and the risk estimate also had a good calibration curve. The ROC curve and calibration diagram of the training cohort and the verification cohort were shown in Fig. 3.

The best cut-off value for the total score of the nomogram was determined to be 167. The sensitivity, specificity, positive predictive value, and negative predictive value used to distinguish the occurrence of intrapartum fever were 88.6%, 66.7%, 97.6%, and 27.8% in the training cohort, and 88.5%, 52.9%, 95.5% and 29.0% in the validation cohort, respectively. (Table 4).

| Variable                          | Value(95%CI)                              |
|-----------------------------------|-------------------------------------------|
|                                  | Training Cohort Validation Cohort         |
| Area under ROC curve,             | 0.855(0.810–0.899)                        |
| Concordance index                 | 0.808(0.727–0.889)                        |
| Cutoff score                      | 167                                       |
| Sensitivity, %                    | 88.6(85.3–91.3)                           |
|                                  | 88.5(83.0–92.5)                           |
| Specificity, %                    | 66.7(47.1–82.1)                           |
|                                  | 52.9(28.5–76.1)                           |
| Positive predictive value, %      | 97.6(95.5–98.8)                           |
|                                  | 95.5(91.0–97.9)                           |
| Negative predictive value, %      | 27.8(18.2–39.8)                           |
|                                  | 29.0(14.9–48.2)                           |
| Positive likelihood ratio         | 2.659(1.601–4.415)                        |
|                                  | 1.882(1.134–3.123)                        |
| Negative likelihood ratio         | 0.171(0.128–0.228)                        |
|                                  | 0.216(0.132–0.355)                        |

In addition, we also paid attention to the perinatal outcomes of mothers and infants in the febrile group and the afebrile group. The results confirmed that maternal fever during delivery increased the rate of cesarean delivery, the rate of bleeding during delivery, and increased the chance of antibiotic use. Because only Apgar scores records in the obstetrical records, so we just analyzed the Apgar score < 7 at 1 minute and 5 minutes, and found that the febrile group had lower Apgar scores of newborns. (Table 5)
Table 5
Comparison of maternal and infant perinatal outcomes between febrile group and afebrile group

|                                | Febrile (n = 104) | Afebrile (n = 593) | P    |
|--------------------------------|-------------------|--------------------|------|
| Transferred to cesarean delivery | 27(26%)           | 0(0%)              | < 0.001 |
| Bleeding during delivery       | 250(100)          | 300(200)           | < 0.001 |
| Antibiotic                     |                   |                    |      |
| Yes                            | 65(90.3%)         | 106(25.5%)         | < 0.001 |
| No                             | 7(9.7%)           | 309(74.5%)         |      |
| Apgar score < 7 at 1 minute    | 9(8.7%)           | 8(1.3%)            | < 0.001 |
| Apgar score < 7 at 5 minutes   | 6(5.8%)           | 4(0.7%)            | 0.001 |

Discussion

In this study, we systematically analyzed the risk factors of intrapartum fever, and we established a predictive model which incorporated the following 7 factors: primipara, premature rupture of membranes, fetal weight, epidural analgesia during delivery, and the duration of the second stage of labor ≥ 120 min, amniotic fluid pollution degree and the duration of epidural analgesia. The predictive model was represented by a nomogram. As far as we know, this is the first nomogram that used to distinguish the high risk puerpera who may experience intrapartum fever.

Intrapartum fever is a common complication during delivery. The incidence of intrapartum fever in our study is 14.78%, which is similar to previous studies. The mechanism may be the endogenous heat generated by the contractions of the uterus and skeletal muscle, or infectious inflammation after the rupture of the amniotic membrane, or epidural analgesia. It has a close relationship with the adverse outcomes of mothers and newborns. Therefore, we collected maternal-related perinatal data, and confirmed the independent risk factors for intrapartum fever through multivariate logistic regression, including primipara, premature rupture of membranes, fetal weight, epidural analgesia during delivery, and the duration of the second stage of labor ≥ 120 min and amniotic fluid pollution degree. Risk factors above for intrapartum fever we identified have been noted in prior studies. Interestingly, Buegess found that high BMI, longer premature rupture of membranes, and more frequent vaginal examinations were also independent risk factors for fever during labor. These were not found in our study. Similarly, several other factors we analyzed, including gestational age, body temperature on admission, WBC on admission, HB on admission etc., couldn't predict intrapartum fever, we thought the reason may be that puerpera of different regions may have different physiological characteristics and for example, the timing of vaginal examinations was different among different centers.
It is well-known that pregnancy is similar to the immune response of sterile inflammation in many aspects and has been confirmed that it is well-accompanied with increased inflammation,\textsuperscript{20–21} which is also considered to be likely to be the pathophysiological basis of the occurrence of intrapartum fever, and is supported in the Riley’s study,\textsuperscript{22} regardless of whether the intrapartum fever occurs or not, as if the parturient receives epidural analgesia during delivery, levels of IL-6 and IL-8 were significantly higher than those at admission, and this phenomenon has nothing to do with infection. Besides, Riley et al. also pointed out that intrapartum fever is more likely to occur in women who have higher levels of IL-6 and IL-8 before receiving epidural analgesia. However, Dominique collected blood samples at 9.7, 17.9, 26, and 35.1 weeks of pregnancy to check the levels of inflammatory factors during pregnancy, the results showed that the occurrence of intrapartum fever is not significantly related to the level of any inflammatory factors at any time point of pregnancy,\textsuperscript{23} which means the level of inflammation before delivery couldn't predict the occurrence of intrapartum fever, which is in keeping with our findings. It could be understood that the onset of intrapartum fever is not depend on prenatal inflammatory levels, but is more likely to be triggered by events during labor that enhance maternal inflammatory responses such as epidural labor analgesia. However, our hospital didn't routinely measure the level of inflammation during childbirth, so further studies are needed to explore the relationship between maternal fever and the level of inflammation and the origin of inflammation levels.

Epidural labor analgesia has been proved to be an independent risk factor for intrapartum fever since 1994,\textsuperscript{24} its prevalence ranges from 1.6–46.3%, with an average of about 20%. Studies have shown that ERMF accounts for 90.4% of fever in full-term pregnancies, the rate of cesarean section and device-assisted delivery was also significantly higher than that of non-analgesia women.\textsuperscript{25} At present, the most concerned mechanism of ERMF is the aseptic inflammatory mechanism.\textsuperscript{26–30} The current difficulties with ERMF continued to be its identification with infectious fever and the maternal and neonatal outcomes caused by epidural analgesia. It has been reported the time of fever is mainly concentrated in 4–6 hours after epidural analgesia, and most of fever recovered within 24 hours\textsuperscript{31,32} while a few studies found different results. Wang randomized 12,793 nulliparous women to early epidural or delayed epidural analgesia in order to ensure the optimal timing of epidural analgesia, and found that incidence of fever was not significant different\textsuperscript{33}, which showed the body temperature changes caused by anesthetics were not dose-dependent, the results above were controversial. Although the duration of epidural analgesia did not show significant difference in the multivariate analysis, we still included it as a risk factor in the nomogram.

Nomogram\textsuperscript{34,35} in estimating the risk of occurring intrapartum fever is a new concept. The nomogram we established in this study included 7 variables that are easily available during labor, performed well with the AUC was 0.855 and 0.808 respectively in the training and verification cohorts, and the calibration plots showed well agreement between the prediction and actual observation. For the clinical application of this model, we summarized the sensitivity, specificity, negative predictive value, and positive predictive value of using 167 as the cutoff value in estimating the intrapartum fever (Table 5). Patients with a score of 167 or more are high-risk patients with intrapartum fever. Based on this preoperative prediction, the
nomogram can be used as a tool for randomized clinical trials to select patients to evaluate the efficacy of diagnosis for women with fever at different risks.

There were several limitations in this study. First of all, this was a retrospective study involving a small number of patients. There were some inherent shortcomings of retrospective research. Firstly, doctors and nurses did not record maternal and fetal information well, leading to lack of information; secondly, this analysis is limited to the data of a single institution, and it is necessary to verify the results in other research centers; finally, although the nomogram obtained good predictive accuracy, prospective studies are needed to further confirm the reliability of the nomogram.

Conclusion

In this retrospective study, we established a mathematical prediction model that included 7 risk factors for intrapartum fever, and developed a nomogram that can be used to score the risk of fever for each patient, which can help obstetricians predict the possibility of intrapartum fever in advance and prevent in advance, finally improve the delivery process and outcome. Of course, although the nomogram has certain predictive value, it still needs comprehensively analysis and dynamically monitor in order for maternal and neonatal safety.

Abbreviations

GDM: Gestational Diabetes Mellitus; BMI, body mass index; WBC, white blood cell; HB, Hemoglobin; IQR, interquartile range; OR: Odds Ratio; CI: Confidence Interval; ROC: Receiver Operating Characteristic

Declarations

- Ethics approval and consent to participate:

This study was performed in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2020-KL135-01), Informed consent was obtained from all mothers for their data to be used for research.

- Consent for publication:

Not applicable.

- Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

- Competing interests:
The authors declare that they have no competing interests.

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• **Authors’ contributions:**

JZF and TC conceived the study design; JZF and ZHB drafted the manuscript; NCY and WXH were responsible for the acquisition; HXY made contributions to the interpretation of data, the manuscript was reviewed and approved by DLY and LS. All authors read and approved the final manuscript.

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Figure 1

The Patient Recruitment Flowchart
Figure 2

Nomogram for estimation of the intrapartum fever
Figure 3

ROC curves and calibration plots for training cohort and testing cohort. Abbreviations: ROC, receiver operating characteristic; AUC, area under ROC curve.