Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Risk Factors and a Predictive Nomogram for Intrapartum Fever in Parturients Receiving Combined Spinal Epidural Analgesia: A Retrospective Study

Hanzhen Zhao
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Cheng Wang
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Shuqi Xie
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Lu Shi
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Lian Tang
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Yanxia Yu
The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital
Jingjing Li
lijingno.2@163.com

The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital

Article

Keywords: Labor analgesia, Combined spinal-epidural analgesia, Intrapartum fever, Risk factors, Nomogram

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10846092/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Objective

Intrapartum fever is a notable complication of combined spinal-epidural analgesia (CSEA) associated with adverse maternal and neonatal outcomes. This study aimed to identify independent risk factors for intrapartum fever in parturients receiving CSEA and to develop a predictive nomogram for early risk stratification.

Methods

A total of 195 parturients received CSEA from Suzhou Municipal Hospital were included in this study. Seventy parturient women with intrapartum fever during analgesia were included in fever group, and 125 parturient women with normal body temperature were assigned to the control group. Maternal demographic characteristics, details of labor and delivery, anesthetic scheme, and fetal information were collected. Stepwise multivariate logistic regression was used to identify independent risk factors, which were subsequently incorporated into a nomogram. The performance of the model was assessed with receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

Results

Multivariate logistic regression analysis indicated that the number of vaginal examinations (OR 2.01, 95% CI 1.56–2.60), duration of analgesia (OR 2.39, 95% CI 1.70–3.35), and time from rupture of membranes to delivery (OR 1.19, 95% CI 1.05–1.27) were independent risk factors for intrapartum fever. The prediction model demonstrated excellent discrimination with an area under the curve (AUC) of 0.895 (95% CI 0.843–0.946). The nomogram showed good calibration and positive net benefit in DCA. A time from rupture of membranes to delivery exceeding 5.27 hours was identified as a key risk threshold.

Conclusion

The number of vaginal examinations, duration of analgesia, and time from rupture of membranes to delivery are identified as key risk factors of CSEA-induced intrapartum fever. The developed nomogram serves as a practical clinical tool for early identification of high-risk parturients, facilitating enhanced monitoring and proactive management.

Introduction

Combined spinal-epidural anesthesia (CSEA) integrates the features of rapid onset from spinal anesthesia and flexible prolongation from epidural anesthesia, and has been widely adopted for labor analgesia [1].Compared with other labor anesthesia regimens, CSEA demonstrates a faster onset, fewer

episodes of breakthrough pain, and lower drugconsumption[2].It is also associated with increased cervical dilatation, reduced motor block, and a lower risk of anesthesia failure or caesarean section [3–4]. These advantages contribute to higher maternal satisfaction scores compared with epidural analgesia alone[5].

Despite its benefits, CSEA is associated with side effects such as hypotension, pruritus and nausea, primarily due to intrathecal opioids[6].Notably, intrapartum fever has been widely observed in parturient women receiving CSEA[7], a phenomenon that contradicts the theoretical expectation of anesthetic-induced vasodilation and heat loss [8]. Maternal intrapartum fever, defined as a body temperature of 38.0°C or higher during labor, can be triggered by infectious or non-infectious causes, with neuraxial anesthesia being a major non-infectious trigger[9]. The proposed mechanisms include anesthetic-induced damage to umbilical vein endothelium and increase the production of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α[10]. Furthermore, anesthesia-induced sweating and hyperventilation also result in reduced heat dissipation[11].

The association between epidural labor analgesia and maternal fever was first demonstrated in 1989[12], and subsequently confirmed by numerous studies. As reported in a randomized clinical trial,14% of parturient women receiving CSEA experienced maternal intrapartum fever and the elevation of temperature was observed after 1 h and lasted up to 6 h of analgesia[13].A meta-analysis study evaluating the safety of various epidural analgesia regimens among parturient women, including CSEA, reported that epidural anesthesia increased the risk of fever above 38°C to more than 2 fold (RR 2.51, 95% CI 1.67–3.77)[7]. Maternal intrapartum fever is linked to significant adverse outcomes, including

neonatal brain damage, lower Apgar scores, more sepsis, and the potential for antibiotic treatment[14].

Previous retrospective studies on epidural-related fever have identified risk factors such as premature rupture of membrane (PROM), multiple vaginal examination, prolonged labor, and a long time from rupture of membrane to delivery[15]. While one randomized controlled clinical trial indicated that CSEA and epidural analgesia induce maternal fever with similar timing during labor[16], a comprehensive analyses of risk factors specific to CSEAis lacking. More importantly, a validated predictive tool to help clinicians quantify risk and identify high-risk individuals early in labor is currently unavailable.

Therefore, this study aims to identify the independent risk factors for intrapartum fever in parturients receiving CSEA and develop a practical predictive nomogram tofacilitate early risk stratification and support clinical decision-making.

Material and Methods

Study Design, Setting, and Population

This retrospective study was conducted at The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital and was approved by the hospital's medical ethics committee (K-2022-008-

K01). The requirement for individual informed consent was waived due to the retrospective nature of the investigation.

We reviewed the medical records of all parturients who received CSEA for labor analgesia between January 2021 and December 2022. Based on previously reported, incidence of intrapartum fever in parturient women receiving combined spinal epidural analgesia approximately 15%, with an allowable error of 0.05, a minimum sample size of 196 cases was estimated. Data from 579 mothers who received CSEA were initially collected. A total of 195 cases were included in the statistical analysis based on inclusion criteria, exclusion criteria and data integrity. Seventy cases with intrapartum fever (temperature ≥ 38.0°C) were assigned to the fever group (group F), while 125 cases of women with normal temperature who received CSEA in the same period were collected as the control group (group C) (Figure.1).

Inclusion and Exclusion Criteria

Inclusion criteria were: (1)normal baseline temperature (< 38.0°C) before CSEA administration; (2)age < 35 years; (3)American Society of Anesthesiologists (ASA) classification Ⅰ–Ⅱ; (4)singleton, full-term pregnancy with normal fetal head position; (5)normal placental function and amniotic fluid; (6)documented use of oxytocin for labor augmentation or induction; (7)no food and drug allergies; (8)no history of alcoholism, smoking and drug abuse. The age criterion (< 35 years) was established to create a more homogeneous study population and minimize confounding from Advanced Maternal Age, which is an independent risk factor for numerous obstetric complications[17].

Exclusion criteria included: (1)temperature ≥ 38.0℃ before CSEA administration; (2) analgesia failure; (3) pregnancy comorbidities (e.g. gestational hypertension, gestational diabetes mellitus, gestational cholestasis and pre-eclampsia, etc.); (4)contraindications to analgesia for labor (e.g. maternal refusal, coagulation dysfunction, uncontrolled local and systemic infections, primary or secondary uterine inertia, increased intracranial pressure, pulmonary hypertension, upper respiratory tract oedema, etc.); (5) infectious diseases or metabolic diseases; (6)emergency labor.

Data Collection and Definitions

The following data were collected: (1)Demographics: Age, height, weight, body mass index (BMI), gestational age; (2)Physiological and pathological state: Parity, baseline temperature, amniotic fluid contamination, PROM, positive bacterial and Group B Streptococcus culture, hematological indicators; (3)Anesthesia and delivery information: Artificial rupture of membrane, number of vaginal examinations, duration of analgesia, time from rupture of membrane to delivery, duration of labor, the amount of bleeding, use of oxytocin, cervical ripening balloon for labor induction, use of prostaglandin for cervical ripening, urinary catheterization; (4)Medication use: Prenatal corticosteroid, prenatal pethidine, use of antibiotics during labor. Use of antibiotics during labor was defined as the administration of any

antibiotic agent during the intrapartum period, regardless of whether the indication was for prophylaxis (e.g., for GBS or PROM) or for treatment; (5)Fetal information: Fetal weight, Apgar score.

Anesthesia Protocol

CSEA was administered when cervical dilation reached 2 cm. Following successful epidural space identification in the L2–3 or L3–4 interspace, a spinal needle was advanced through the epidural needle into the subarachnoid space, and 2–3 mg of 0.125% ropivacaine was injected. The epidural catheter was then placed cephalad; left the catheter in the body for 3–5cm. Maternal vital signs were continuously monitored throughout the puncture procedure. After 20 min of epidural anesthesia, injected 3ml of saline containing 1:200,000 adrenaline through the epidural catheter before connecting with a pump in the epidural. The response of total spinal anesthesia was observed for 3–5 min and excluded the epidural catheter placement in the blood vessel; labor analgesia management was implemented (observing the vital signs, visual simulation of the pain scores and Bromage scores); routinely observed the uterine contractions, the fetal heartbeat, and the management of the labor process; The patient-controlled epidural analgesia (PCEA) pump, containing 0.005% sufentanil and 0.125% ropivacaine, maintenance volume 6–10ml, self-control volume 6–10ml, locking time 15–20 min, was adopted in the maintenance phase of analgesia. Observed and resolved abnormalities, recorded the sheet of labor analgesia. After delivery, parturients were observed for 2 h and returned to the ward without any abnormality.

Temperature Monitoring

Maternal temperature was monitored using a single, standardized model of a clinical-grade cochlear (tympanic) thermometer. This non-invasive method is a standard proxy for core body temperature in obstetric settings[18]. Monitoring began 30 minutes after CSEA administration and continued hourly until delivery. Standardized technique, including proper positioning and ear canal straightening, was used to ensure accuracy. Intrapartum fever was defined as a maternal temperature ≥ 38.0°C during the monitoring period. Parturients who diagnosed as intrapartum fever during the monitoring period were designated as group F, whereas those who did not were designated as group C.

Clinical Procedures and Protocols

Intrapartum Antibiotic Prophylaxis: The hospital's protocol for intrapartum antibiotic prophylaxis (IAP) aligns with ACOG guidelines[19]. IAP was administered for positive Group B Streptococcus (GBS) screens or for patients with unknown GBS status who developed risk factors, such as rupture of membranes ≥ 18 hours or an intrapartum temperature ≥ 38.0°C.

Labor Monitoring and Dystocia Diagnosis: Labor progress was monitored using a partograph for all parturients, a standard tool for this purpose[20]. Labor dystocia was defined according to contemporary ACOG criteria[21]. Active phase arrest was diagnosed at ≥ 6 cm cervical dilation with ruptured

membranes and no cervical change despite ≥ 4 hours of adequate contractions or ≥ 6 hours of inadequate contractions with oxytocin augmentation[21].

Vaginal Examinations Hygiene: All vaginal examinations were performed using a standardized aseptic technique, which included hand washing, the use of sterile gloves, and application of a sterile lubricant, in accordance with institutional infection control policies[22].

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 and R software version 3.1.2 with the *rms* statistical packages. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) and categorical variables were presented as counts (percentages). The t-test, rank sum test and chi-square test were used in univariable analysis. Variables with a P-value < 0.05 in the univariable analyses were entered into a stepwise multivariate logistic regression model to identify independent risk factors for intrapartum fever. Receiver operating characteristic (ROC) curves were constructed, area under the curve (AUC), the optimal cut-off value and the Youden's index (Youden's index = sensitivity + specificity-1) were calculated. Internal validation was performed using leave-one-out cross validation, 10-fold cross validation and bootstrap validation method. A nomogram was developed based on the final multivariate model and evaluated using calibration curves and decision curve analysis (DCA). P < 0.05 was considered statistically significant.

Results

Baseline Characteristics and Univariable Analysis

A total of 195 parturients received CSEA were included, with 70(36%) in Group F and 125 (64%) in Group C. Baseline characteristics and univariable analysis were presented in Table 1. Compared to the control group, patients in the fever group had a significantly higher number of vaginal examinations, longer duration of analgesia, longer duration of labor, and a greater time from rupture of membranes to delivery (all P < 0.05). The use of oxytocin, urinary catheterization, and artificial rupture of membranes were also significantly more common in the fever group (all *P* < 0.05). Notably, the incidence of PROM was significantly lower in the fever group compared to the control group (8.6% vs. 26.4%, *P* = 0.005). Figure 2 provides a visual representation of the distribution of key continuous variables between the two groups in the form of boxplots.

Table 1
Comparison of general information and risk factors in group F and group C.

Variables	**Group F (n = 70)**	**Group C (n = 125)**	***P***
Age (years)	28(26,30)	27(25,29)	0.080
Gestational age (weeks)	40.1(39.6,40.7)	39.7(39.0,40.3)	0.001*
Body mass index (kg/m^2)	26.5(25.2,28.1)	26.6(24.2,28.3)	0.289
Nulliparous women (n,%)	65(92.9%)	119(95.2%)	0.528
Baseline Temperature (℃)	36.5 ± 0.2	36.4 ± 0.2	0.053
Fetal weight (g)	3425 (3200.5,3650)	3350 (3100,3650)	0.221
Number of vaginal examinations (n)	8(4,10)	4(3,5)	< 0.001*
Duration of analgesia (h)	3.96(2.67,5.81)	2.25(1.50,3.00)	< 0.001*
Duration of labor (h)	13.4(10.3,23.7)	9.5(7.4,15.0)	< 0.001*
The time from rupture of membrane to delivery(h)	9.58(6.65,15.70)	7.77(1.28,16.40)	0.028*
The amount of bleeding (mL)	250(200,254)	200(200,250)	< 0.001*
Artificial rupture of membrane (n,%)	36(51.4%)	29(23.3%)	< 0.001*
Amniotic fluid contamination (n,%)	17(24.3%)	15(12.0%)	0.043*
PROM (n,%)	6(8.57%)	33(26.4%)	0.005*
Positive vaginal bacterial culture (n,%)	12(17.1%)	34(27.2%)	0.158
Group B streptococcus positive (n,%)	4(5.7%)	4(3.2%)	0.461
Use of antibiotics during labor (n,%)	8(11.4%)	9(7.2%)	0.460
Oxytocin (n,%)	64(91.4%)	96(76.8%)	0.018*
Pethidine (n,%)	9(12.9%)	12(9.6%)	0.643
Cervical ripening balloon (n,%)	9(12.2%)	2(1.6%)	0.005*
Use of prostaglandin for cervical ripening (n,%)	2(2.86%)	6(4.80%)	0.714
Prenatal corticosteroid (n,%)	1(1.43%)	1(0.80%)	1.000

Variables	Group F (n = 70)	Group C (n = 125)	*P*
Urinary catheterization (n,%)	28(40.0%)	15(12.0%)	< 0.001*
White blood cell (10^9/L)	10.5(8.3,13.7)	10.5(8.8,12.6)	0.824
Neutrophil (10^9/L)	7.88(6.25,11.20)	7.87(6.38,9.70)	0.797
Lymphocyte (10^9/L)	1.75(1.45,2.11)	1.74(1.40,2.05)	0.963
Monocyte (10^9/L)	0.61(0.47,0.78)	0.57(0.45,0.71)	0.149
Hemoglobin (g/L)	118(110,126)	115(109.120)	0.107

Logistic Regression and Prediction Model Development

The results of the multivariate logistic regression analysis are shown in Table 2. The final prediction model included three significant independent risk factors: number of vaginal examinations (OR 2.01, 95%CI 1.56–2.60; $P < 0.001$), duration of analgesia (OR 2.39, 95%CI 1.70–3.35; $P < 0.001$), and time from rupture of membranes to delivery (OR 1.19, 95%CI 1.05–1.27; $P = 0.004$).

Table 2
Logistic regression analysis of risk factors for intrapartum fever: group F vs. group C.

Variables	**Univariable Logistic OR (95%CI ,*P*)**	**Multivariable Logistic OR (95%CI ,*P*)**
Age (years)	1.08 (0.98–1.20, p = 0.118)	
Gestational age (weeks)	1.69 (1.22–2.32, p = 0.001*)	
Body mass index (kg/m^2)	1.05 (0.94–1.16, p = 0.389)	
Nulliparous women (n,%)	0.66 (0.19–2.23, p = 0.499)	
Baseline temperature (℃)	4.75 (0.88–25.71, p=.071)	
Number of vaginal examinations (n)	1.68 (1.42–1.99, p < 0.001*)	2.01(1.56–2.60, p < 0.001*)
Duration of analgesia (h)	2.28 (1.75–2.97, p < 0.001*)	2.39(1.70–3.35, p < 0.001*)
Duration of labor (h)	1.07 (1.03–1.11, p < 0.001*)	
The time from rupture of membrane to delivery(h)	1.02 (1.01–1.04, p = 0.033*)	1.19(1.05–1.27, p = 0.004*)
The amount of bleeding (mL)	1.00 (1.00-1.01, p = 0.203)	
Artificial rupture of membrane (n,%)	3.51 (1.87–6.56, p < 0.001*)	
Amniotic fluid contamination (n,%)	2.35 (1.09–5.07, p = 0.029*)	
PROM (n,%)	0.26 (0.10–0.66, p = 0.004*)	
Positive vaginal bacterial culture (n,%)	0.55 (0.27–1.16, p = 0.116)	
Group B Streptococcus positive (n,%)	1.83 (0.44–7.57, p = 0.402)	
Use of antibiotics during labor (n,%)	1.66 (0.61–4.53, p = 0.319)	
OR, odds ratio; CI, confidence interval		

Variables	Univariable Logistic OR (95%CI ,*P*)	Multivariable Logistic OR (95%CI ,*P*)
Oxytocin (n,%)	3.22 (1.27–8.20, p = 0.014*)	
Pethidine (n,%)	1.39 (0.55–3.48, p = 0.483)	
Cervical ripening balloon (n,%)	7.94 (1.64–38.5, p = 0.010*)	
Use of prostaglandin for cervical ripening (n,%)	0.58 (0.11–2.97, p = 0.516)	
Prenatal corticosteroid (n,%)	1.80 (0.11–29.18, p = 0.680)	
Urinary catheterization (n,%)	4.89 (2.38–10.05, p<.001*)	
White blood cell (10^9/L)	1.01 (0.93–1.10, p=.803)	
Neutrophil (10^9/L)	1.01 (0.93–1.10, p=.859)	
Lymphocyte (10^9/L)	0.97 (0.55–1.72, p=.915)	
Monocyte (10^9/L)	2.26 (0.74–6.97, p=.154)	
Hemoglobin (g/L)	1.01 (0.99–1.04, p=.370)	
OR, odds ratio; CI, confidence interval		

The ROC curve for the prediction model demonstrated excellent discrimination, with an AUC of 0.895 (95% CI 0.843–0.946) (Figure.3A). Leave-one-out cross validation, bootstrap validation and 10-fold cross validation were used to internal validation with the accuracy of 0.862, 0.843, 0.862 respectively, as shown in Table 3. Optimal cut-off values from the ROC analysis indicated that a number of vaginal examinations ≥ 7, an analgesia duration > 3.35 hours, and a time from rupture of membranes to delivery > 5.27 hours were associated with a heightened risk of fever (Table 4).

Table 3
Area under the curve and internal validation

Prediction Model	AUC	95% CI
	0.895	**0.843-0946**
Leave-One-Out Cross Validation	0.848	
Bootstrap Validation	0.843	
10-fold Cross Validation	0.862	
AUC, area under curve; CI, confidence interval		

Table 4
Optimal cut-off values for risk factors

Variables	≥	Sensitivity	Specificity	Youden Index
Number of vaginal examinations (n)	7.0	0.629	0.944	0.573
Duration of analgesia (h)	3.35	0.614	0.816	0.430
The time from rupture of membrane to delivery (h)	5.27	0.800	0.416	0.216
The optimal cut-off value of number of vaginal examinations was 6.5, which was rounded to the nearest integer for clinical application.				

Nomogram Development and Predictive Performance

A predictive nomogram was developed based on the three independent risk factors (Figure.3B). The calibration plot showed good agreement between the nomogram-predicted probabilities and the observed frequencies of fever (Figure. 3C). DCA indicated that the nomogram provided a net clinical benefit across a wide range of threshold probabilities (Figure. 3D).

Discussion

This study is, to our knowledge, the first to develop and validate a predictive nomogram specifically for intrapartum fever in parturients receiving CSEA. Our principal finding is that the number of vaginal examinations, duration of analgesia and the time from rupture of membranes to delivery are significant, independent risk factors. These factors were integrated into a high-performing nomogram that can assist clinicians in early risk stratification.

The mechanism of anesthesia-induced fever is difficult to elucidate. Some investigators have proposed that it is secondary to a decrease in hyperventilation following pain relief, a decrease in sweating due to sympathetic blockade, and a bias in the information from the temperature control center, which all combine to result in a decrease in body heat loss[23].Even more, the temperature of the labor room, which is traditionally raised to avoid hypothermia of newborn, can also have an effect on intrapartum

fever[24]. In regard to CSEA, the mental stress of labor and the surgical trauma of epidural catheter insertion induce inflammatory mediator and cytokine release, which inevitably lead to aseptic inflammation[25]. Our study identified risk factors are not merely independent triggers of fever but are more likely clinical markers of an underlying, unifying condition: labor dystocia. A prolonged and difficult labor necessitates more frequent vaginal examinations to assess progress and a longer duration of analgesia to manage pain. Therefore, these variables are proxies for a stalled or protracted labor course. This reframing provides a more clinically coherent explanation for our observations. Labor dystocia itself may induce a subclinical inflammatory state in the mother[26]. The subsequent administration of CSEA, while necessary for pain relief, may act as a "second hit" that perturbs thermoregulatory pathways in these already susceptible individuals, precipitating a febrile response. This aligns with the non-infectious inflammatory hypothesis of neuraxial-associated fever[25].

This perspective also clarifies why oxytocin, a significant factor in the univariable analysis, did not remain in the final multivariate model. Oxytocin use is highly collinear with labor dystocia; it is the primary treatment for arrested or protracted labor, not an independent cause of fever in this context. Furthermore, labor dystocia is a leading indication for cesarean and instrumental delivery[27]. Although delivery mode was not an outcome in our study, the combination of risk factors we identified—prolonged labor requiring extended analgesia and frequent examinations—is characteristic of the very population that ultimately requires operative intervention.

Frequent vaginal examinations have been identified as a risk factor for fever during epidural anesthesia in previous studies[15, 28, 29]. Our findings confirm this association in a Chinese population receiving CSEA ($P < 0.05$). The frequency of vaginal examinations was 8 (5,10) and 4 (3,5) times respectively in the fever and normal temperature group with significant difference. Maternal aseptic inflammation of placenta and reproductive tract induced by anesthesia increases the incidence of infection during vaginal examination[30, 31]. This aligns with findings that a high number of examinations is associated with an increased risk of adverse outcomes such as leukocytosis or fetal tachycardia[32]. While aseptic technique is standard, the mechanical stimulation of repeated examinations in the context of a prolonged, inflammatory labor state may exacerbate local inflammatory responses.

Our study found that when the duration of analgesia was longer than 3.35h, there will be greater influence on intrapartum fever. However, limiting analgesia duration to under 3.35 hours is clinically unrealistic, as analgesia duration is a consequence of labor length, not an independently modifiable variable. In our study, the local anesthetics combination for CSEA is 0.125% ropivacaine and 0.005% sufentanil. A meta-analysis reported that the combination of bupivacaine and sufentanil was effective in a shorter duration of analgesia and the length of labor compared to ropivacaine combined with sufentanil and levobupivacaine combined with sufentanil [33]. In studies on epidural analgesia, the duration of high concentration and continuous analgesics is associated with intrapartum fever. However, a logistic regression based on analgesic pump delivery of 0.08% ropivacaine and 0.4ug/ml sufentanil found that prolonged analgesia was not a risk factor for intrapartum fever[15]. This suggests that the

concentration and selection of local anesthetics for sustained analgesia may have a greater impact on postpartum fever, warranting further investigation.

Similarly, the time from rupture of membranes to delivery was identified as a significant predictor ($P < 0.05$). It has been reported in epidural analgesia [12, 15]. Our ROC analysis quantified this risk, establishing a threshold of > 5.27 hours as being associated with a heightened risk of fever. This finding is consistent with previous literature linking prolonged rupture of membranes to an increased risk of infection, especially chorioamnionitis[34].Premature artificial rupture of membrane leaves the fetus unprotected and increase the incidence of microbiological infection[35]. A longer duration between membrane rupture and delivery extends the period during which ascending microorganisms can colonize the uterine cavity, thereby increasing the inflammatory burden that may culminate in fever, especially when compounded by the thermoregulatory effects of CSEA. Our study also found that urinary catheterization was more frequent in the fever group in the univariable analysis. Catheterization is a known risk factor for urinary tract infections[36]. However, it did not remain an independent predictor in our multivariate model. This suggests that, similar to the number of vaginal examinations, catheterization is likely another marker of a prolonged and complex labor course (i.e., dystocia) rather than a direct cause of the systemic febrile response observed. Its effect is likely captured by the stronger, more direct predictors like duration of analgesia.

A particularly interesting finding was the lower incidence of PROM in the fever group. This paradoxical result can be explained by our hospital's adherence to ACOG-guided antibiotic prophylaxis protocols[19]. Parturients with PROM, especially with prolonged rupture, are routinely administered prophylactic antibiotics. This intervention likely prevents the development of infection-related fever, thereby causing these patients to be classified into the non-febrile control group. This finding does not suggest PROM is protective but rather highlights the effectiveness of prophylactic antibiotic strategies and reveals a selection bias inherent in this type of retrospective analysis.

Explicit preventive measures of intrapartum fever are urgently needed to reduce risk factors and to evade the adverse outcomes. Oxytocin use is considered a risk factor of intrapartum fever in epidural analgesia[28], but it has not been confirmed in our analysis of CSEA. Interestingly, another study revealed that high-dose oxytocin reduced the risk of fever and the duration of labor[37, 38], which maybe due to the effect of different doses of oxytocin on labor duration, rather than the independent risk factor during anesthesia.

The primary strength of this study is the development of a novel, practical nomogram for specific clinical scenario. The nomogram can help clinicians identify parturients at high risk for developing fever at the outset and during the course of labor. This allows for heightened vigilance, closer temperature monitoring, and a lower threshold for investigating potential causes of fever in this subgroup, thereby facilitating more proactive and personalized care.

However, we must acknowledge its limitations. First, the retrospective, single-center design limits the generalizability of our findings. External validation in diverse populations is required. Second, our dataset

lacked several key potential confounders. We were unable to account for specific oxytocin dosage and timing protocols, baseline maternal inflammatory markers (e.g., IL-6), or formally diagnosed labor dystocia.Most significantly, the inability to distinguish between prophylactic and therapeutic antibiotic use is the likely source of our paradoxical PROM finding. Future prospective studies should aim to collect these variables to build a more comprehensive model.

Conclusion

Our study successfully identified the number of vaginal examinations, the duration of analgesia, and the time from rupture of membrane to delivery as key independent risk factors for intrapartum fever in parturients receiving CSEA. The primary contribution of this work is the development and internal validation of a clinically applicable predictive nomogram that integrates these factors, Which enable clinicians to perform early risk stratification, facilitate targeted interventions to reduce the risk of CSEA-related fever and improve maternal and neonatal outcomes. Future prospective, multi-center studies are warranted to externally validate this model and explore the underlying pathophysiological mechanisms.

Abbreviations

AUC, area under curve; BMI, body mass index; CI, confidence interval; CSEA, combined spinal-epidural analgesia; DCA, decision curve analysis; OR, odds ratio; ROC, receiver operating characteristic; SE, standard deviation.

Declarations

Ethics approval and consent to participate

All experimental protocols were approved by the medical ethics committee of The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital(K-2022-008-K01). All procedures were performed according to the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Data Availability

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

Competing interests

All authors declare no competing interests or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Funding

This work was supported by Jiangsu Pharmaceutical Association. Hospital Pharmacy Research Project (H202121). Funders had no influence on the design of the study, the data collection and analysis, and the manuscript writing.

Author Contributions

JJL, LT and YXY designed the study; CW, HZZ, SQX and LS collected the data; HZZ, LT, and JJL analyzed the data; HZZ, LS and LT drafted the manuscript; LT, YXY and JJL revised the manuscript and approved the final version. HZZ and CW are co-first authors. LT, YXY, and JJL are co-corresponding authors. All authors reviewed the manuscript.

Authors' information

a Department of Pharmacy, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, Jiangsu 215002, China

b Department of Anesthesiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, Jiangsu 215002, China

c Gusu School, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, Jiangsu 215002, China

References

1. Cook, T. M. Combined spinal-epidural techniques: CSE techniques. *Anaesthesia* **55**, 42–64 (2000).
2. Guasch, E., Brogly, N. & Gilsanz, F. Combined spinal epidural for labour analgesia and caesarean section: indications and recommendations. *Curr. Opin. Anaesthesiol.* **33**, 284–290 (2020).
3. Landau, R. Combined spinal-epidural analgesia for labor: Breakthrough or unjustified invasion? *Semin. Perinatol.* **26**, 109–121 (2002).
4. Klimek, M. et al. Combined spinal-epidural vs. spinal anaesthesia for caesarean section: meta-analysis and trial-sequential analysis. *Anaesthesia* **73**, 875–888 (2018).

5. Collis, R. E., Davies, D. W. L. & Aveling, W. Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* **345**, 1413–1416 (1995).
6. Grangier, L. et al. Adverse side effects and route of administration of opioids in combined spinal-epidural analgesia for labour: a meta-analysis of randomised trials. *Int. J. Obstet. Anesth.* **41**, 83–103 (2020).
7. Anim-Somuah, M. et al. Epidural versus non-epidural or no analgesia for pain management in labour. *Cochrane Database of Systematic Reviews*. ;2018. (2018). 10.1002/14651858.CD000331.pub4
8. Hall, G. M. BODY TEMPERATURE AND ANAESTHESIA. *Br. J. Anaesth.* **50**, 39–44 (1978).
9. Goetzl, L. Maternal fever in labor: etiologies, consequences, and clinical management. *Am. J. Obstet. Gynecol.* **228**, S1274–S1282 (2023).
10. Goetzl, L. et al. Elevated maternal and fetal serum interleukin-6 levels are associated with epidural fever. *Am. J. Obstet. Gynecol.* **187**, 834–838 (2002).
11. Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India et al. Epidural Fever: Hiding in the Shadows. *Turk J Anaesthesiol Reanim*. ;48:350–5. (2020).
12. Fusi, L. et al. MATERNAL PYREXIA ASSOCIATED WITH THE USE OF EPIDURAL ANALGESIA IN LABOUR. *Lancet* **333**, 1250–1252 (1989).
13. De Orange, F. A. et al. Combined spinal and epidural anaesthesia and maternal intrapartum temperature during vaginal delivery: a randomized clinical trial. *Br. J. Anaesth.* **107**, 762–768 (2011).
14. Patel, S. et al. Epidural-related maternal fever: incidence, pathophysiology, outcomes, and management. *American Journal of Obstetrics and Gynecology*. ;228:S1283-S1304.e1. (2023).
15. Ren, J. et al. Risk Factors and Safety Analyses for Intrapartum Fever in Pregnant Women Receiving Epidural Analgesia During Labor. *Med. Sci. Monit.* **27** 10.12659/MSM.929283 (2021).
16. Chu, Q. et al. Combined spinal-epidural analgesia and epidural analgesia induced maternal fever with a similar timing during labor-A randomized controlled clinical trial. *Front. Med. (Lausanne)*. **9**, 927346 (2022).
17. Odibo, A. O., Nelson, D., Stamilio, D. M., Sehdev, H. M. & Macones, G. A. Advanced maternal age is an independent risk factor for intrauterine growth restriction. *Am. J. Perinatol.* **23** (5), 325–328 (2006).
18. Konopad, E., Kerr, J. R., Noseworthy, T. & Grace, M. A comparison of oral, axillary, rectal and tympanic-membrane temperatures of intensive care patients with and without an oral endotracheal tube. *J. Adv. Nurs.* **20** (1), 77–84 (1994).
19. Hoover, L. E., Group, B. & Streptococcus Disease AAP Updates Guidelines for the Management of At-Risk Infants. *Am. Fam Physician*. **101** (6), 378–380 (2020).
20. Médecins Sans Frontières. Essential obstetric and newborn care.2019 Edition. https://medicalguidelines.msf.org/en/viewport/ONC/english/5-2-monitoring-labour-and-delivery-51416957.html

21. First and Second Stage Labor Management. ACOG Clinical Practice Guideline No. *Obstet. Gynecol.* **143** (1), 144–162 (2024). 8.
22. Merck Manual Professional Version. Video: The Vaginal Exam in Labor [EB/OL]. [2025-09-22]. https://www.merckmanuals.com/professional/multimedia/video/the-vaginal-exam-in-labor
23. Glosten, B. et al. Epidural anesthesia and the thermoregulatory responses to hyperthermia - preliminary observations in volunteer subjects. *Acta Anaesthesiol. Scand.* **42**, 442–446 (1998).
24. Banerjee, S. & Steer, P. J. The rise in maternal temperature associated with regional analgesia in labour is harmful and should be treated. *Int. J. Obstet. Anesth.* **12**, 280–284 (2003).
25. Igarashi, T. et al. The Fiberscopic Findings of the Epidural Space in Pregnant Women. *Anesthesiology* **92**, 1631–1636 (2000).
26. Ashwal, E. et al. Intrapartum fever and the risk for perinatal complications - the effect of fever duration and positive cultures. *J. Matern Fetal Neonatal Med.* **31** (11), 1418–1425 (2018).
27. LeFevre, N. M., Krumm, E. & Cobb, W. J. Labor Dystocia in Nulliparous Women. *Am. Fam Physician*. **103** (2), 90–96 (2021).
28. Yuan, J. et al. Maternal intrapartum fever during epidural labour analgesia: Incidence and influencing factors. *Int J. Nurs. Practice* ;e13188. (2023).
29. Curtin, W. M. et al. Intrapartum fever, epidural analgesia and histologic chorioamnionitis. *J. Perinatol.* **35**, 396–400 (2015).
30. Newton, E. R., Piper, J. & Peairs, W. Bacterial vaginosis and intraamniotic infection. *Am. J. Obstet. Gynecol.* **176**, 672–677 (1997).
31. Jia, L. et al. Evaluation of Epidural Analgesia Use During Labor and Infection in Full-term Neonates Delivered Vaginally. *JAMA Netw. Open.* **4** (9), e2123757 (2021).
32. Gomez Slagle, H. B. et al. Incremental risk of clinical chorioamnionitis associated with cervical examination. *Am. J. Obstet. Gynecol. MFM*. **4**, 100524 (2022).
33. Lv, B. et al. Efficacy and safety of local anesthetics bupivacaine, ropivacaine and levobupivacaine in combination with sufentanil in epidural anesthesia for labor and delivery: a meta-analysis. *Curr. Med. Res. Opin.* **30**, 2279–2289 (2014).
34. Batts, J. A. & Chorioamnionitis *J. Reprod. Med.* ;**17**:296–298. (1976).
35. Gibson, K. S. & Brackney, K. Periviable Premature Rupture of Membranes. *Obstet. Gynecol. Clin. N. Am.* **47**, 633–651 (2020).
36. Kranz, J. et al. Catheter-Associated Urinary Tract Infections in Adult Patients. *Dtsch. Arztebl Int.* **117** (6), 83–88 (2020).
37. Son, M. et al. High-Dose Compared With Standard-Dose Oxytocin Regimens to Augment Labor in Nulliparous Women: A Randomized Controlled Trial. *Obstet. Gynecol.* **137**, 991–998 (2021).
38. Zeng, Y. et al. Side-effects of oxytocin in postpartum hemorrhage: a systematic review and meta-analysis. *Am. J. Transl Res.* **14**, 1934–1951 (2022).

Figures

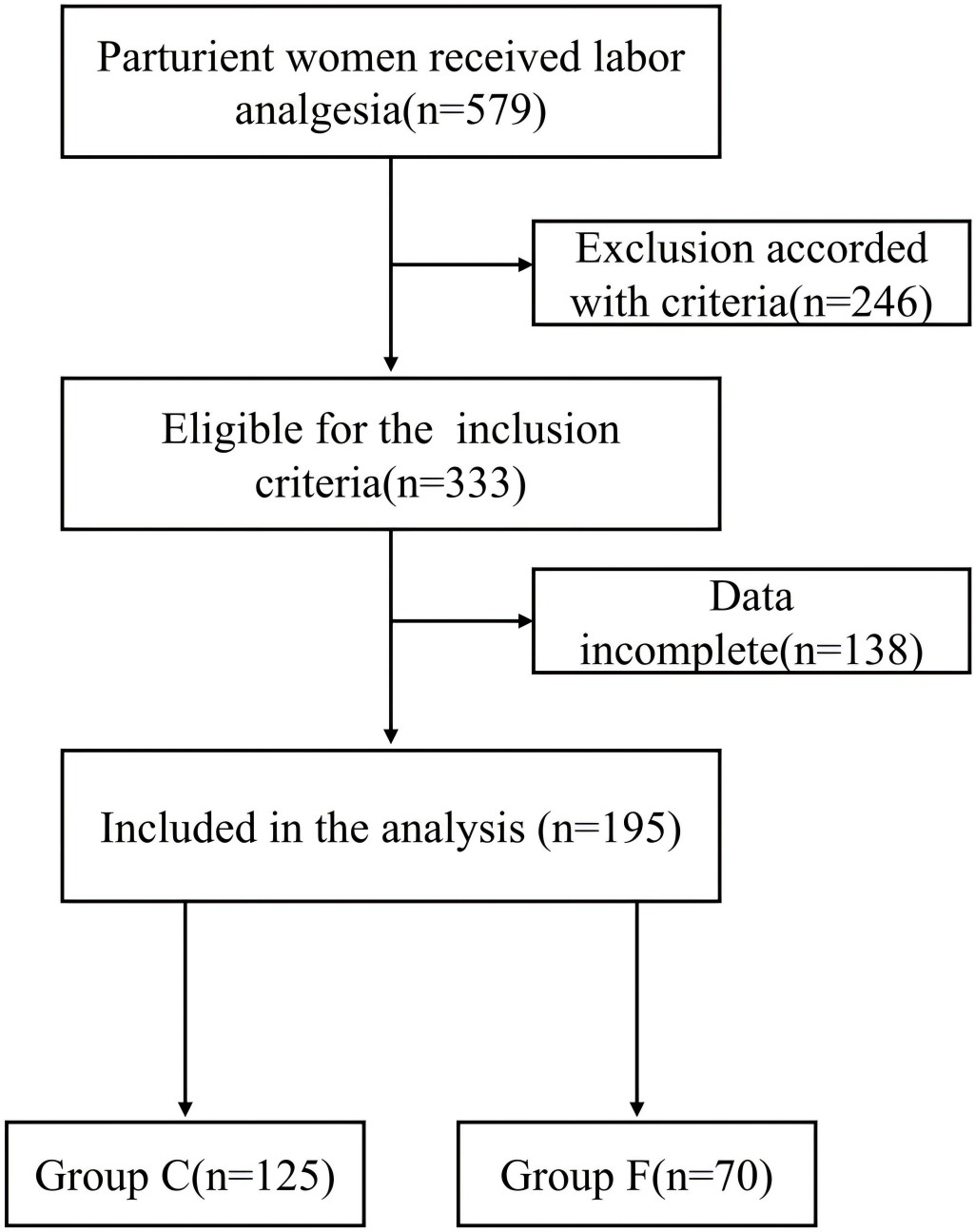

Figure 1

Flow chart of exclusion and inclusion.

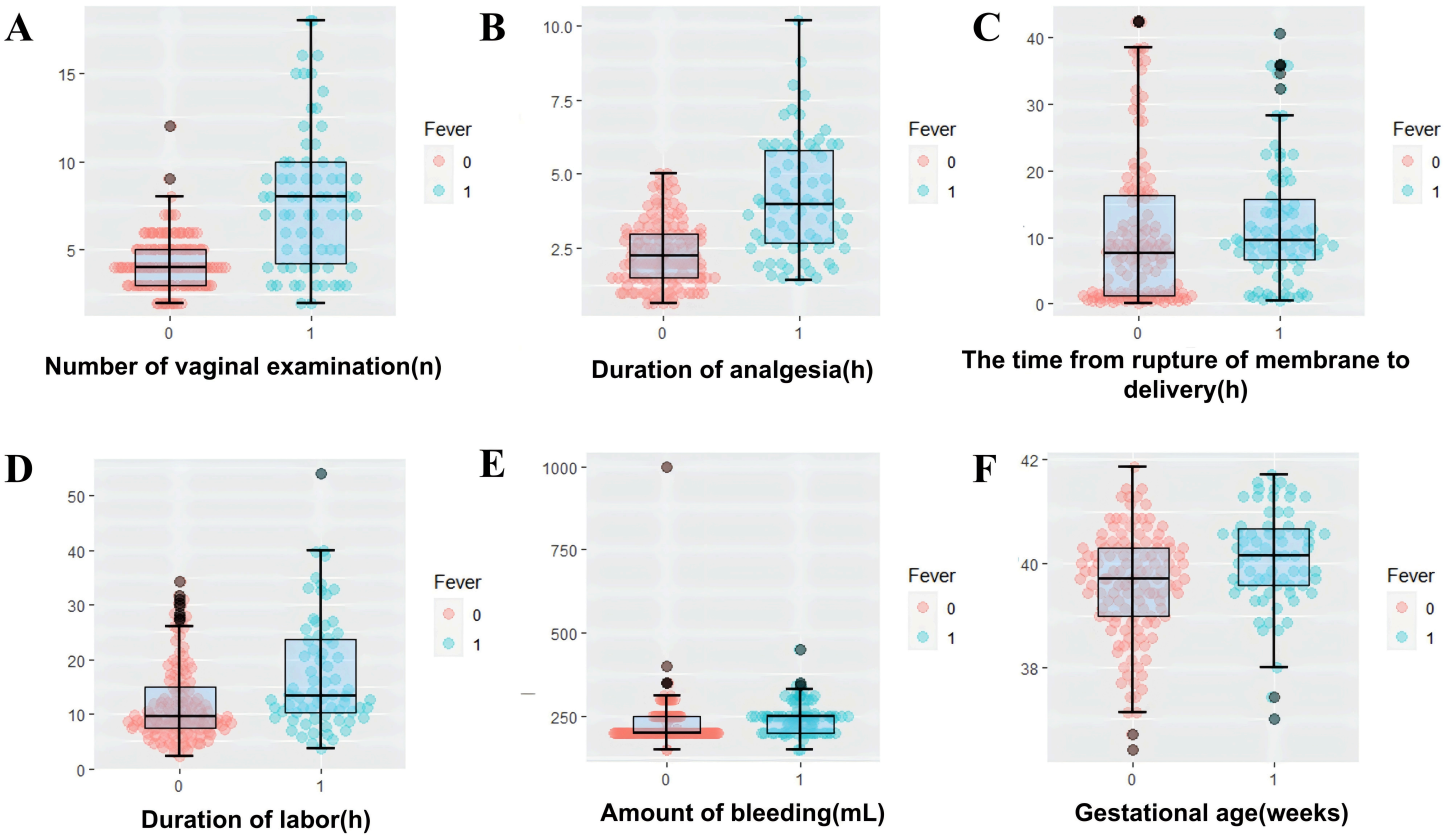

Figure 2

Comparison of risk factors between the fever group and the control group.

2A: Number of vaginal examination(n),2B: Duration of analgesia(h),2C: The time from rupture of membrane to delivery(h),2D: Duration of labor(h),2E: The amount of bleeding(mL),2F: Gestational age(week). The red spots represent patients in the normal group, the green spots represent patients in the fever group.

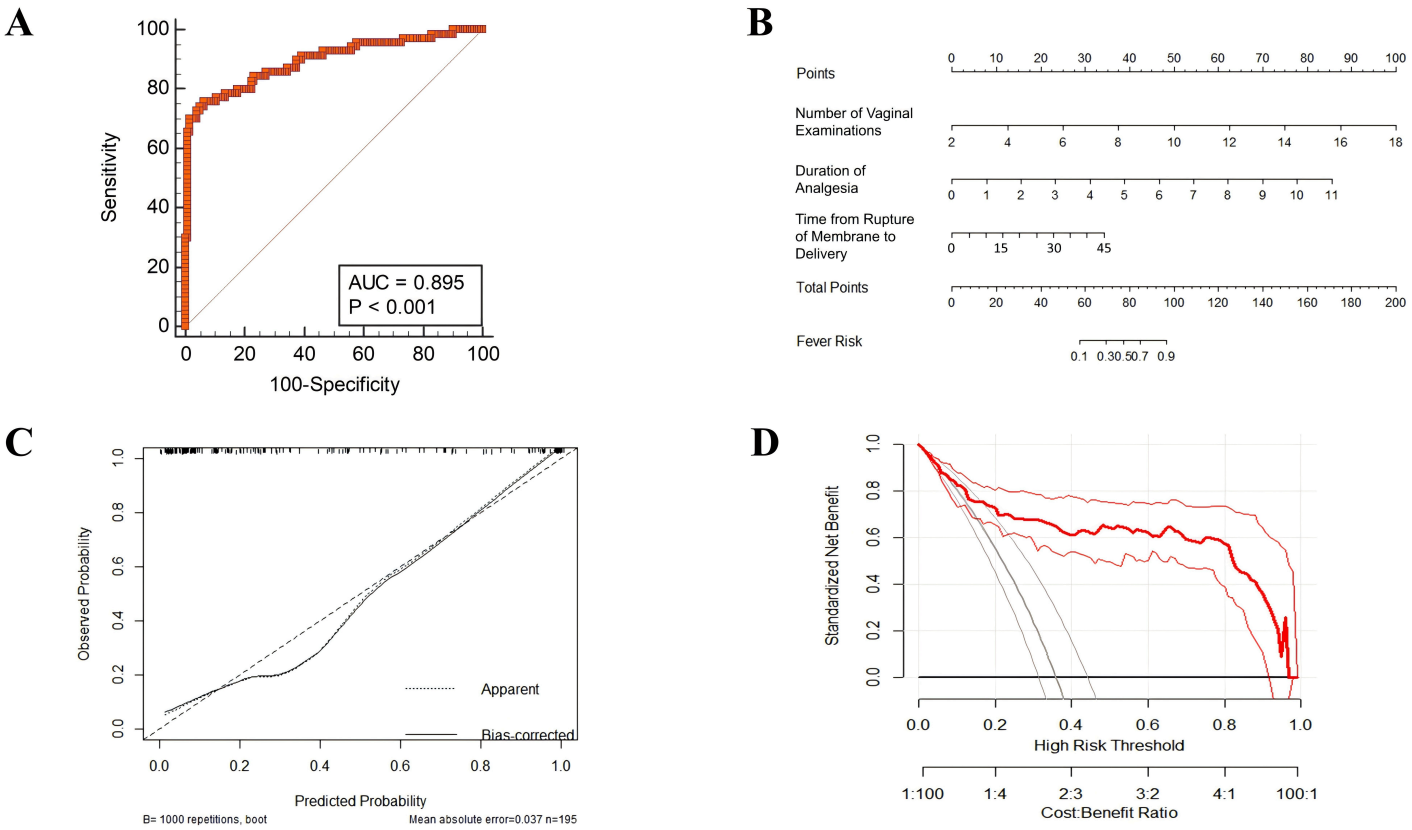

Figure 3

Predictive performance of prediction model and nomogram.

3A: ROC curve of prediction model, 3B: A nomogram of prediction model, 3C: Calibration curve of the nomogram prediction, 3D: Decision curve analysis of the nomogram prediciton