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Original Article

Development and validation of a risk prediction model for spontaneous preterm birth

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Abstract: Objectives: To identify the factors influencing spontaneous preterm birth (SPTB) and develop a prediction model for clinical practice. Methods: This retrospective study included a total of 130 pregnant women with spontaneous preterm birth or full-term delivery at Fujian Maternity and Child Health Hospital between January 2020 and December 2023. The SPTB group consisted of 50 women with spontaneous preterm birth, while the full-term group included 70 women with full-term deliveries. Logistic regression analysis was performed to explore the factors associated with clinical prognosis, and a nomogram prediction model for SPTB risk was constructed and validated. Results: Multivariate logistic regression analysis identified multiple pregnancies (95% CI: 1.415-8.926, P=0.006), abnormal fetal position (95% CI: 1.124-2.331, P=0.008), gestational diabetes (95% CI: 4.918-19.164, P=0.002), mode of conception (95% CI: 1.765-4.285,P=0.002), lower genital tract infection (95% CI: 1.076-2.867, P=0.032), and second trimester cervical length (95% CI: 1.071-2.991, P=0.031) as independent risk factors of SPTB. Using these six variables, a nomogram was developed to predict the incidence of SPTB, with an AUC value of 0.833 (95% CI: 0.665-0.847), demonstrating acceptable agreement between predicted and observed outcomes. Decision curve analysis (DCA) showed a good positive net benefit of the model. Conclusions: Multiple pregnancies, abnormal fetal position, gestational diabetes, mode of conception, lower genital tract infection, and second-trimester cervical length are independent risk factors for the onset of SPTB. In addition, the nomogram prediction model demonstrated good predictive performance, high accuracy, and clinical applicability.

Keywords: Spontaneous preterm birth, risk prediction model, development, validation

Introduction

Spontaneous preterm birth (SPTB) refers to the occurrence of preterm labor or preterm delivery before 37 weeks of gestation, including preterm birth following premature rupture of membranes, accounting for about 70% of all preterm births [1]. Premature infants are prone to underdeveloped organ systems, leading to a higher risk of death and complications compared to full-term infants. Research shows that over one million premature infants die annually due to complications related to prematurity, making it the leading cause of death among children under 5 years of age [2-4]. Common complications of premature infants include respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, periventricular leukomalacia, epileptic seizures, intraventricular hemorrhage, cerebral palsy, infections, feeding difficulties, hypoxic-ischemic encephalopathy, and vision and hearing impairments [5-9]. Therefore, preventing premature birth is one of the most crucial issues in modern healthcare.

The pathogenesis for SPTB is complex. Research has shown that pre-pregnancy body mass index (BMI), age, and social economic status are key contributors to SPTB. Either too low or too high pre-pregnancy BMI, as well as extreme maternal age, can increase the likelihood of spontaneous preterm birth [10-14]. Pregnancies complicated by conditions such as gestational diabetes, hypertension, or intrahepatic cholestasis of pregnancy also elevate the risk of SPTB [15-17]. A history of adverse pregnancy outcomes, including spontaneous abortion [18-

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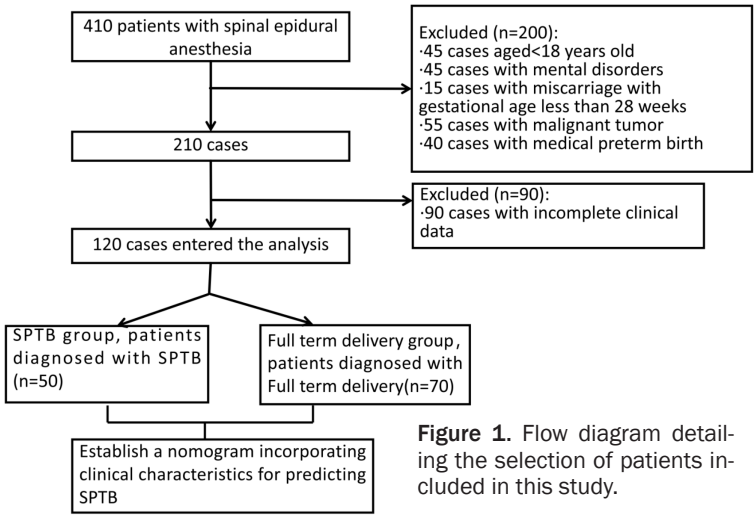

Figure 1. Flow diagram detailing the selection of patients included in this study.

20] or preterm birth [21, 22], further raises this risk. Therefore, identifying relevant risk factors for SPTB as early and correctly as possible is crucial for implementing effective preventive interventions.

Current studies have developed predictive models for SPTB. Alfirevic Z et al. [23] constructed a predictive model for preterm birth in women following cervical cerclage, incorporating three influencing factors: cervical length, history of cervical conization, and history of cervical cerclage. The area under the ROC curve (AUC) of the model was 0.907. Tranidou A et al. [24] developed a model tailored for high-risk pregnancies, with factors including fetal fibronectin (fFN), cervical length, and history of preterm birth/premature rupture of membranes, yielding an AUC ranging from 0.77 to 0.99. Although these models demonstrate relatively good predictive performance, they do not include Asian populations in their development or validation. Since the factors contributing to SPTB may vary across different racial groups, the applicability of these models is limited. Additionally, the small sample size and single-source samples raise concerns about overfitting, and none of these models have undergone external clinical validation. Therefore, their practical use in clinical settings remains uncertain, and further verification is needed.

Given this, there is still a gap in the availability of an effective and clinically feasible predictive model for SPTB. Thus, more research is required to develop a model that can meet clinical needs. The aim of this study is to identify the relevant factors influencing SPTB and construct a prediction model suitable for clinical practice, providing a useful tool for obstetric healthcare professionals in their assessments.

Methods

Study patients

We retrospectively collected and analyzed the medical records of 130 pregnant women with SPTB or full-term delivery at Fujian Maternity and Child Health Hospital between January 2020 and December 2023. The study included 50 women diagnosed with spontaneous preterm birth, comprising the SPTB group, and 70 women who had full-term deliveries, comprising the full-term group. The patient selection process is shown in **Figure 1**. This study was approved by the Ethics Review Board of Fujian Maternity and Child Health Hospital.

Inclusion criteria for SPTB subjects: Those who received antenatal check-ups at Fujian Maternity and Child Health Hospital during pregnancy, with regular and standardized antenatal care; Those diagnosed with SPTB [25]: gestational age between 28 and 37 weeks, with neonatal birth weight ≥1000 g; Patients aged ≥18 years.

Inclusion criteria for full-term delivery subjects: Those who received antenatal check-ups at Fujian Maternity and Child Health Hospital during pregnancy, with regular and standardized antenatal care; Those diagnosed with full-term delivery [26]: gestational age ≥37 weeks; Patients aged ≥18 years.

Exclusion criteria: Pregnant women without regular antenatal check-ups during pregnancy; Pregnancies complicated with malignant tumors; Miscarriage before 28 weeks of gestation; Medically indicated preterm birth due to safety considerations such as placental implantation, threatened uterine rupture, chorioamnionitis, gestational hypertension disorders, placental abruption, fetal distress, or fetal growth

retardation, where clinical advice recommends early termination of the pregnancy; Pregnancies involving cervical insufficiency or a history of cervical conization or cerclage performed either during or before pregnancy.

Data collection

Two researchers collected demographic data from the patients' medical records, including age, comorbidities and laboratory results.

The primary outcome was the performance of the predictive model, which was evaluated using the concordance index (c-index), calibration curve, decision curve analysis (DCA), and the area under the receiver operating characteristic (ROC) curve (AUC). The secondary outcome focused on clinical data, including age, pre-pregnancy BMI, history of pre-pregnancy disease, weight change during pregnancy, ethnicity, parity, conception method, history of tobacco and alcohol exposure during pregnancy, nutrient supplementation, physical activity during pregnancy, and pregnancy complications.

Statistical analysis

All statistical analyses were conducted using SPSS V26.0 (SPSS Inc.) and R software v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The sample size was calculated using power analysis and corrected for attrition, leading to a final sample size of approximately 130 participants. Categorical variables were expressed as percentage, while continuous variables were expressed as mean ± standard deviation. For comparisons of categorical data between groups, chi-square or Fisher's exact tests were used as appropriate. For continuous data, if normally distributed, t-tests or analysis of variance (ANOVA) were applied; for non-normally distributed data, the Kruskal-Wallis test was used. A multivariate logistic regression model was used to analyze factors associated with SPTB and to identify risk factors. The nomogram was constructed based on the results of the multivariate logistic regression analysis to calculate the predicted probability of SPTB for each patient. The prognostic performance of the nomogram was measured using the concordance index (c-index), calibration curve, DCA, and AUC. $P<0.05$ was considered statistically significant.

Results

Comparison of clinical characteristics between the two groups

The characteristics of the two group, including age, pre-pregnancy weight, preconception BMI, parity, and regular physical activity, were comparable (all $P>0.05$). However, significant differences were observed between the two groups in terms of weight gain, mode of conception, nutritional supplementation during pregnancy, and alcohol/tobacco exposure during pregnancy (all $P<0.05$) (**Table 1**).

Comparison of pregnancy complications between the two groups

As shown in **Table 2**, compared with full-term delivery group, the SPTB group had significantly higher rates of multiple pregnancies, gestational diabetes, abnormal fetal position, abnormal umbilical cord, history of abnormal fetal heart monitoring, and lower genital tract infections (all $P<0.05$). In contrast, there were no statistically significant differences between the two groups regarding other medical and surgical diseases, abnormal amniotic fluid, placental abnormalities, uterine myoma, history of threatened abortion, thyroid dysfunction, or uterine malformation (all $P>0.05$).

Comparison of pregnancy-related laboratory tests between the two groups

As shown in **Table 3**, significant differences were observed between the two groups in terms of reproductive tract infections, second-trimester cervical length, white blood cell count, and neutrophil percentage (all $P<0.05$). However, no significant difference was noted in hemoglobin levels ($P>0.05$).

Multivariate logistic regression analysis

The results of multivariate logistic regression analysis identified multiple pregnancies (95% CI: 1.415-8.926, P=0.006), abnormal fetal position (95% CI: 1.124-2.331, P=0.008), gestational diabetes (95% CI: 4.918-19.164, P=0.002), mode of conception (95% CI: 1.765-

Table 1. Comparison of clinical characteristics between the two groups

	Spontaneous preterm birth group (n=50)	Full term delivery group (n=70)	t/χ^2	P
Age			0.247	0.619
<35	38 (76.00%)	48 (68.57%)		
≥35	12 (24.00%)	22 (31.43%)		
Pre-pregnancy weight (Kg)	56.78±7.12	57.23±9.45	1.658	0.278
Weight gain during pregnancy (Kg)	11.78±3.39	13.53±4.56	7.607	0.036
Preconception BMI	22.26±2.84	21.83±3.49	2.199	0.132
Mode of conception			6.628	0.028
Spontaneous conception	45 (90.00%)	68 (97.14%)		
Assisted reproduction	5 (10.00%)	2 (2.86%)		
Parity			0.022	0.997
Primipara	39 (78.00%)	56 (80.00%)		
Multipara	11 (22.00%)	14 (20.00%)		
Nutrient supplementation during pregnancy			10.01	0.007
Folic acid in early pregnancy	39 (78.00%)	51 (72.86%)		
Multivitamin in second trimester	40 (80.00%)	54 (77.14%)		
No supplementation	4 (8.00%)	4 (5.71%)		
Alcohol and tobacco exposure during pregnancy			6.68	0.021
Yes	4 (8.00%)	5 (7.14%)		
No	46 (92%)	65 (92.86%)		
Regular physical activity			0.87	0.476
Yes	8 (16.00%)	11 (15.71%)		
No	42 (84%)	59 (84.3%)		

Note: BMI, body mass index

Table 2. Comparison of pregnancy complications between the two groups

	Spontaneous preterm birth group (n=50)	Full term delivery group (n=70)	χ^2	P
Multiple pregnancy	8 (16.00%)	4 (5.71%)	10.681	<0.001
Gestational diabetes	9 (18.00%)	4 (5.71%)	5.681	<0.001
Uterine myoma	1 (2.00%)	1 (1.43%)	-0.233	0.816
History of threatened abortion	8 (16.00%)	12 (17.14%)	0.317	0.752
Combined with thyroid dysfunction	5 (10.00%)	4 (5.71%)	-0.062	0.951
Uterine malformation	1 (2.00%)	1 (1.43%)	-0.264	0.792
Placental abnormality	3 (6.00%)	4 (5.71%)	-1.422	0.158
Abnormal amniotic fluid	4 (8.00%)	5 (7.14%)	1.677	0.097
Abnormal fetal position	6 (12.00%)	4 (5.71%)	6.979	<0.001
Abnormal umbilical cord	11 (22.00%)	8 (11.43%)	12.182	<0.001
History of abnormal fetal heart monitoring	11 (22.00%)	9 (12.86%)	14.362	<0.001
Pregnancy with other medical/surgical diseases	1 (2.00%)	1 (1.43%)	-0.758	0.451
Lower genital tract infection	6 (12.00%)	2 (2.86%)	10.681	<0.001

4.285, P=0.002), lower genital tract infection (95% CI: 1.076-2.867, P=0.032), and second-trimester cervical length (95% CI: 1.071-2.991, P=0.031) as independent risk factors for SPTB (**Table 4**).

Development and validation of the nomogram

Based on the multivariate logistic regression analysis results, we constructed a nomogram incorporating the independent risk factors

Table 3. Comparison of pregnancy-related laboratory indices between the two groups

	Spontaneous preterm birth group (n=50)	Full term delivery group (n=70)	t/χ^2	P
Reproductive tract infection	12 (24.00%)	10 (14.29%)	5.681	<0.001
Second trimester cervical length (cm)	24.89±3.12	32.98±4.88	9.070	<0.001
Hemoglobin level (g/L)	113.94±11.87	117.23±11.89	1.664	0.089
White blood cell count (×10^9/L)	11.98±2.45	9.34±2.12	11.482	<0.001
Neutrophil percentage (%)	0.78±0.03	0.87±0.03	9.023	<0.001

Table 4. Multivariate logistic regression analysis

Factors	Bate	SE	Wald	OR	95% CI	P
Multiple pregnancy	1.224	0.429	7.425	3.521	1.415-8.926	0.006
Abnormal fetal position	0.536	0.128	6.633	1.538	1.124-2.331	0.008
Gestational diabetes	2.218	0.617	45.812	9.816	4.918-19.164	0.002
Mode of conception	0.954	0.258	15.852	2.856	1.765-4.285	0.002
Lower genital tract infection	0.666	0.266	4.966	1.755	1.076-2.867	0.032
Second trimester cervical length	0.451	0.251	4.581	1.741	1.071-2.991	0.031

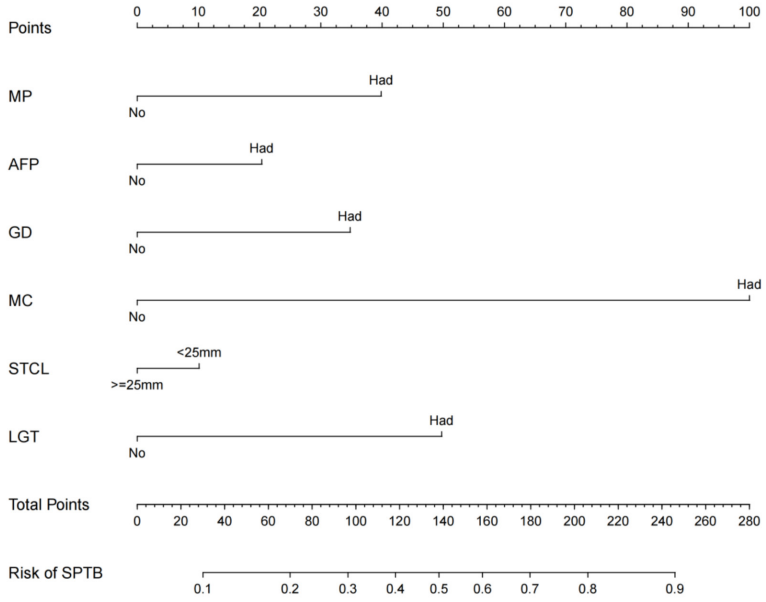

Figure 2. The nomogram for predicting the risk of SPTB. MP: Multiple pregnancies; AFP: Abnormal fetal position; GD: Gestational diabetes; MC: Mode of conception; STCL: Second trimester cervical length; LGT: Lower genital tract infection.

(**Figure 2**). The regression equation was based on these factors:

logit(P) = -2.120 + 0.521 * multiple pregnancies + 0.538 * abnormal fetal position + 0.816 * gestational diabetes + 0.856 * mode of conception + 0.755 * lower genital tract infection + 0.741 * second-trimester cervical length. To use this nomogram, the corresponding position on each variable axis was located first according to patient's manifestation. Then, a line was drawn vertically to the points axis above to obtain the respective points. Finally, the points from all six variables were added up, and a line was drawn from the total points axis to the predicted probability axis to estimate the likelihood of SPTB.

The calibration curve (**Figure 3**) for the training set showed that predicted and actual risks of SPTB are closely aligned, indicating the model's high prediction accuracy. The AUC was 0.833, demonstrating good predictive performance (**Figure 4**).

Clinical utility evaluation and validation

The DCA curve showed that the nomogram provided a high clinical utility (**Figure 5**). The decision curve indicates that when the threshold probability of SPTB is between 40% and 80%, using this nomogram would provide a clear net benefit.

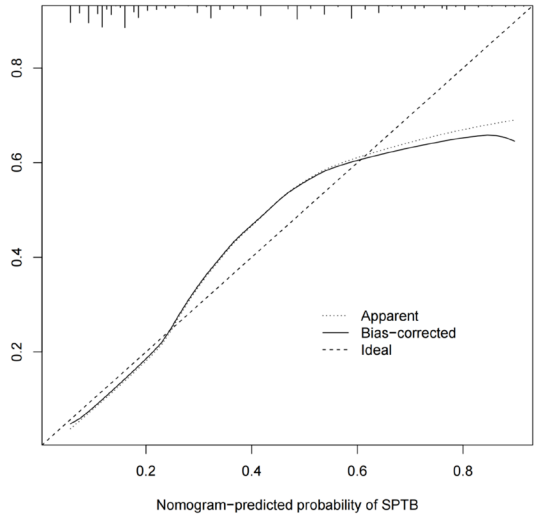

Figure 3. Calibration curve of the nomogram.

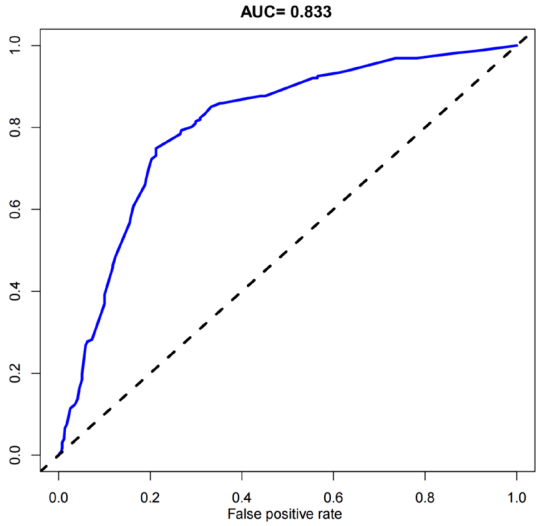

Figure 4. ROC curve analysis of the predictive performance of the nomogram, with an AUC of 0.833 (95% CI: 0.665-0.847).

Discussion

In this retrospectively study of 130 pregnant women who experienced either spontaneous preterm birth (SPTB) or full-term delivery, we first analyzed the general clinical data and various clinical indicators of the patients, to identify the independent risk factors for SPTB. The results showed that multiple pregnancies, abnormal fetal position, gestational diabetes, mode of conception, lower genital tract infection, and second-trimester cervical length were independent risk factors for SPTB. Using these six identified risk factors, a risk prediction

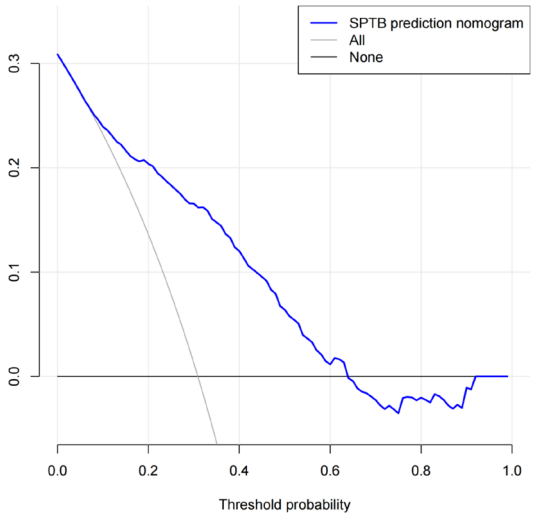

Figure 5. Decision curve analysis of the nomogram model.

model for SPTB was successfully constructed, which was subsequently evaluated and validated.

In this study, multiple pregnancies was identified as independent risk factors for SPTB, which is consistent with the findings of Murray et al. [27]. In multiple pregnancies, there is an increased demand for nutrients and oxygen to support the growth and development of multiple fetuses. This may lead to an imbalance or insufficiency in the supply, potentially affecting the normal development and stability of the pregnancy, thus increasing the risk of miscarriage [28]. Additionally, the uterine environment in multiple pregnancies is more crowded, leading to greater competition and interaction among fetuses. This can result in complications such as improper implantation or placental abnormalities, which are important contributors to spontaneous abortions [29]. Therefore, pregnant women with multiple pregnancies should be more vigilant about the risk of SPTB and take precautions in advance.

Abnormal fetal position was another independent risk factor for SPTB. An abnormal fetal position may cause changes in the intrauterine environment and increase fetal stress. When the fetus is not in the proper position, it may lead to uneven pressure distribution within the uterus, affecting the stability and function of the placenta and amniotic fluid, which in turn increases the risk of preterm contractions and

early rupture of membranes [30]. In addition, an abnormal fetal position may complicate labor, making it more difficult for the fetus to adapt to the process. This can lead to labor complications, more intense uterine contractions, and fetal distress, all of which can contribute to the occurrence of premature birth [31]. In general, an abnormal fetal position can disrupt the normal physiological state of the uterus and fetus through various mechanisms, increasing the likelihood of SPTB.

Gestational diabetes was identified as another independent risk factor for SPTB. Gestational diabetes may cause abnormal glucose metabolism, which may impair placental function. If the placenta does not function properly, it may fail to deliver sufficient oxygen and nutrients to the fetus, potentially triggering preterm contractions and leading to preterm birth [32]. Elevated maternal blood sugar levels can also affect fetal growth, causing fetal overgrowth or other complications that increase the risk of preterm birth [33]. Moreover, gestational diabetes mellitus is associated with increased inflammation, which can contribute to instability in the uterine environment and promote preterm birth [34].

Mode of conception was identified as an independent risk factor for SPTB, particularly in cases involving assisted reproductive technology (ART). The processes involved in ART, including invasive procedures and hormonal interventions, can disrupt the normal physiological state of the uterus and embryo [34]. Hormonal imbalances or fluctuations caused by these procedures may negatively affect the stability and progression of the pregnancy [35]. Additionally, ART involves culturing and manipulating embryos in vitro, which may bring some uncertainties and potential damage [36]. These artificial processes can impact the quality and adaptability of embryos, increasing the risk of complications during implantation and subsequent development [37]. Furthermore, women undergoing ART often have underlying fertility issues or other health conditions, which themselves may increase pregnancy risks [38]. These pre-existing factors, in combination with the ART procedures, contribute to a higher likelihood of spontaneous abortion.

Lower genital tract infection can cause an inflammatory response, releasing inflammatory mediators and cytokines that adversely affect the uterine environment and fetal membranes [39]. This inflammatory response may lead to premature activation and weakening of the fetal membrane, increasing uterine contractions and the risk of preterm birth [40]. Certain pathogens can also directly invade the amniotic cavity and placenta, causing damage and dysfunction, further contributing to preterm birth [41]. Moreover, persistent or severe infections can disrupt the normal physiological and immune function in the reproductive tract, heightening the risk of SPTB. Therefore, pregnant women diagnosed with lower genital tract infection should take preventive measures to reduce the risk of SPTB.

During the second trimester, an insufficient cervical length may be less capable of withstanding the increasing pressure and mechanical stress within the uterus as pregnancy progresses [42]. This can make the cervix more prone to premature dilation and weakening, increasing the risk of preterm birth. Additionally, issues related to the connective tissue and collagen composition of the cervix may affect its stability and ability to remain closed [43].

In conclusion, based on the identified risk factors for SPTB, this study constructed a nomogram prediction model with good predictive performance, high accuracy, and clinical applicability. The model is straightforward and user-friendly in clinical practice, providing a safe and non-invasive screening method that is easily accepted by both doctors and patients. This model aids in the early identification of high-risk populations for SPTB, improving the detection rate while reducing complications associated with excessive invasive examinations. By offering a cost-effective approach for SPTB screening in clinical practice, it is of great medical and social significance.

Disclosure of conflict of interest

None.

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