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Establishment and validation of a nomogram for predicting preterm birth in intrahepatic cholestasis during pregnancy: a retrospective study

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Abstract

Objective This study aimed to develop and evaluate a nomogram for predicting preterm birth in patients with intrahepatic cholestasis of pregnancy (ICP), with a view to assisting clinical management and intervention.

Methods This retrospective observational study included 257 pregnant women with ICP from Sichuan Provincial People's Hospital between January 1, 2022 and July 30, 2024. The routine clinical and laboratory information of these patients were also collected. We used the least absolute shrinkage and selection operator (LASSO) and multivariable logistic regression analysis to investigate the association between clinical and laboratory data and preterm birth in ICP patients. A nomogram was developed to predict the likelihood of preterm birth in ICP patients. The prediction accuracy of the model was evaluated by consistency index (C-index), receiver operating characteristic (ROC) curve, area under the curve (AUC), and calibration curve. Decision curve analysis (DCA) was used to evaluate its applicability in clinical practice.

Results Among the 257 ICP patients, 56 (21.79%) were diagnosed with preterm birth. Cases were randomly divided into a training set (154 cases) and a test set (103 cases). A nomogram was developed to predict preterm birth in ICP patients based on height, twin pregnancy (TP), gestational age at diagnosis (GA at diagnosis), and total bile acid level (TBA) at diagnosis. The calibration curve of the training set was close to the diagonal (C-index = 0.864), and the calibration curve of the test set was also close to the diagonal (C-index = 0.835). These results indicate that the model has a good consistency. The AUC of the training group and the test group were 0.864 and 0.836, respectively, indicating the good accuracy of the model. The DCA reveals that this nomogram could be applied to clinical practice.

Conclusion The combination of TBA level, TP, height and GA at diagnosis is an effective model for identifying preterm birth in ICP patients. These results will help guide the clinical management and treatment of patients with ICP, thereby reducing maternal and infant safety issues caused by preterm birth.

Keywords Intrahepatic cholestasis of pregnancy, Nomogram, Preterm birth, Predictive model, Validation

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder exclusively associated with pregnancy, characterized by pruritus and increased bile acid levels, with fasting serum total bile acids (TBA) exceeding 10 μmol/L. Typically, maternal symptoms manifest in the mid to late phases of pregnancy and subside swiftly postpartum [1]. ICP severity is categorized based on TBA concentrations: very severe (≥ 100 μmol/L in pregnant women), severe (40–99 μmol/L), and mild (10–39 μmol/L) [2]. The incidence and prevalence of ICP differ notably across races and geographic regions, ranging from less than 1% to as high as 27.6% [3]. ICP is associated with notable perinatal risks, including preterm birth, stillbirth, meconium-stained amniotic fluid, and fetal distress, both therapeutic and spontaneous [4]. Importantly, women with ICP are at a 15-fold increased risk of preterm birth compared to those without the condition, potentially due to bile acid accumulation in the myometrium, which may enhance uterine activity [5, 6].

Babies born before the 37th week of pregnancy are classified as preterm. These infants face an increased risk of death in their first 28 days and throughout their first year when compared to those born at full term, with the risk escalating inversely with gestational age or birth weight [7]. This vulnerability largely stems from the underdevelopment of organ systems in preterm infants, which are ill-prepared for extrauterine life. Complications encountered include necrotizing enterocolitis, intraventricular hemorrhage, and respiratory distress syndrome. Moreover, children born before term often struggle with lasting health concerns, ranging from cerebral palsy and mental development issues to sensory disabilities and chronic illnesses including cardiac failure and hypertension [8, 9].

Consequently, early identification of ICP patients at risk for preterm birth is imperative. Enhancing monitoring protocols and implementing timely and effective interventions, such as administering dexamethasone to advance fetal lung maturity, are crucial for improving outcomes. Although various studies have investigated the risk factors for preterm birth in ICP patients, including twin pregnancy and total bile acid levels [10, 11], traditional prediction methods predominantly rely on clinical judgment and basic laboratory tests, which may not provide precise risk assessments. To date, no comprehensive, clinically applicable tool has been developed to predict the risk of preterm birth in ICP patients.

A nomogram is a graphical tool that facilitates individualized risk assessments by integrating multiple risk factors into a statistical model, thereby offering more accurate predictions than conventional clinical methods. This tool has gained widespread acceptance in clinical settings [12–14]. This study introduces the first nomogram for predicting preterm birth in ICP patients, setting it apart from previous study that solely conducted multivariate analyses without developing a comprehensive predictive model for preterm birth risk [15]. In addition, Existing studies have predominantly focused on the relationship between single factor (such as twin pregnancy) and adverse pregnancy outcomes (such as stillbirth or preterm birth) in ICP [16–18]. In contrast, our study constructs a multivariable regression model that integrates multiple clinical indicators, offering a more in-depth analysis of the association between each variable and the risk of preterm birth. This comprehensive approach provides a more holistic perspective on preterm birth prediction.

The nomogram developed in this study encompasses various variables, including twin pregnancy, maternal height, gestational age at diagnosis, and TBA levels at diagnosis. The primary goal of this study is not only to devise a prediction model but also to validate its clinical utility through rigorous statistical evaluations, including calibration curves and decision curve analysis (DCA). This study aims to demonstrate that the proposed nomogram can effectively guide clinicians in assessing the risk of preterm birth in ICP patients, thereby enhancing clinical decision-making, optimizing management, and ultimately mitigating the maternal and neonatal safety risks associated with preterm birth.

Materials and methods

Data collection

This study received approval from the Ethics Committee of Sichuan Provincial People's Hospital (Approval No.: Ethics Review 2024 No. 634) and was conducted in strict adherence to the relevant guidelines and regulations. Participants included in this study were drawn from the patient population of Sichuan Provincial People's Hospital and had undergone treatment with ursodeoxycholic acid (UDCA) following their diagnosis. The criteria for inclusion in this study were: (1) a fasting TBA concentration exceeding 10 μmol/L accompanied by pruritus manifesting in the second or third trimester of pregnancy (≥ 13 weeks); (2) maternal age ranging from 18 to 45 years; and (3) initiation of antenatal care at our institution from the second trimester (≥ 13 weeks) with continued care through to delivery. Exclusion criteria were: (1) presence of skin diseases, allergic reactions, autoimmune conditions, gallstones, persistent viral infections impacting the liver (including hepatitis A, B, and C, cytomegalovirus, or herpes simplex virus), or chronic liver disease; and (2) termination of pregnancy due to fetal structural abnormalities.

This retrospective study encompassed a cohort of 257 pregnant women diagnosed with ICP at Sichuan Provincial People's Hospital between January 1, 2022, and

July 30, 2024. We collected comprehensive clinical and laboratory data from these patients. All clinical measurements, with the exception of pre-delivery weight (PDW), were obtained at the time of diagnosis. Clinical data encompassed age, height, pre-pregnancy weight (PPW), pre-pregnancy body mass index (BMI), weight gain (calculated as pre-pregnancy weight minus pre-delivery weight, WG), and educational level (coded as ≤ middle school = 0, high school = 1, college and above = 2, EDU). We also documented the presence of complications such as hyperthyroidism (HT), kidney disease (KI), infections, cardiovascular disease (CI), anemia (AN), thrombocytopenia (TCP), hypoproteinemia (HPT), gestational hypertension (GH), gestational diabetes (GDM), hypothyroidism, polyhydramnios, oligohydramnios, and fetal growth restriction (FGR). Additionally, obstetric history data were recorded, including primiparity, adverse pregnancy history (APH), a history of ICP (HICP), in vitro fertilization and embryo transfer (IVF-ET), twin pregnancy (TP), previous childbirth history (G, excluding the current pregnancy), and gestational age (GA) at diagnosis (coded as ≥ 13 weeks and ≤ 33 weeks = 0, > 33 weeks and ≤ 36 weeks = 1, > 36 weeks = 2). Further obstetric details included placental abnormalities (such as placenta previa [PP] and placental shape abnormalities [PS]), history of uterine surgery (e.g., myomectomy, polypectomy, cesarean section), and history of cesarean scar uterus (SU). The serum biomarkers at diagnosis comprised levels of direct bilirubin (DBil), alkaline phosphatase (ALP), total bilirubin (TBil), total bile acids (TBA), alanine transaminase (ALT), and aspartate transaminase (AST).

Statistical methods

Data analysis was performed using R software, version 4.4.1. The first step involved assessing the normality of all continuous variables with the Kolmogorov-Smirnov test. For those variables not adhering to a normal distribution, appropriate transformations, including logarithmic, square root, and Box-Cox transformations, were employed to meet the analytical prerequisites.

Clinical characteristics were compared using chi-square tests (for categorical variables) and T-tests (for continuous variables). We used univariate analysis to screen for variables that are notably correlated with dependent variables. Then, to ensure that the number of events (EPV) for each variable had at least 10 observations [19], we used LASSO regression to further select the best predictor from the variables identified in the univariate analysis. In LASSO regression, the optimal λ value was selected through 10-fold cross-validation, and the variables that contributed the most to the model was identified. These selected variables were then used to construct a multivariate logistic regression model.

In the multivariate logistic regression analysis, to ensure the stability and validity of the model, we carried out strict collinearity tests on the variables. The variance inflation factor (VIF) was used to identify and remove highly collinearity variables to avoid overfitting. The final multivariate logistic regression model was constructed using LASSO regression and the variables selected by VIF. In addition, a stepwise regression analysis was performed to optimize the model. We further screened variables and determined the best combination of variables through bidirectional stepwise regression, which combines both forward selection and backward elimination methods, to enhance the explanatory and predictive power of the model.

We randomly divided the dataset into a training set (60%) and a test set (40%) for assessing the model's generalizability. The seed was set to 1 to ensure result consistency. The chi-square test was applied when the sample size exceeded 30 and each category's expected frequency was ≥ 5; Fisher's exact test was utilized for smaller samples or when expected frequencies were lower than 5. For continuous variables, normality was assessed initially; if confirmed, the t-test was used for comparisons. If not, comparisons were conducted using the Mann-Whitney U test. Model performance was evaluated using calibration curves (Hosmer-Lemeshow test for goodness of fit), ROC curves (assessing discriminatory ability through AUC), and DCA to determine the clinical utility and benefits of the model. A *P*-value of less than 0.05 was deemed to indicate statistical significance.

Results

Participant characteristics

In this study, we included a total of 257 patients diagnosed with ICP. Of these, 56 (21.79%) experienced preterm births, whereas 201 (78.20%) did not. We applied transformations to continuous variables that deviated from a normal distribution. Specifically, the variables age, ALT, AST, TBil, DBil, height, PPW, and PDW underwent logarithmic transformation (denoted as Age_log, ALT_log, AST_log, TBil_log, DBil_log, Height_log, PPW_log, and PDW_log, respectively). WG and BMI were square root transformed (represented as WG_sqrt and BMI_sqrt, respectively). For TBA, neither logarithmic nor square root transformation resulted in normality; hence, we employed a Box-Cox transformation (denoted as TBA_bc) for further normalization. All transformed variables successfully passed the Kolmogorov-Smirnov normality test, as illustrated in Fig. 1. Univariate analysis was conducted to identify predictors of preterm birth among ICP patients. The log-transformed age values showed no significant difference between the groups (3.39 vs. 3.39, $P = 0.807$). The prevalence of TP was notably higher in the preterm birth group compared to those without

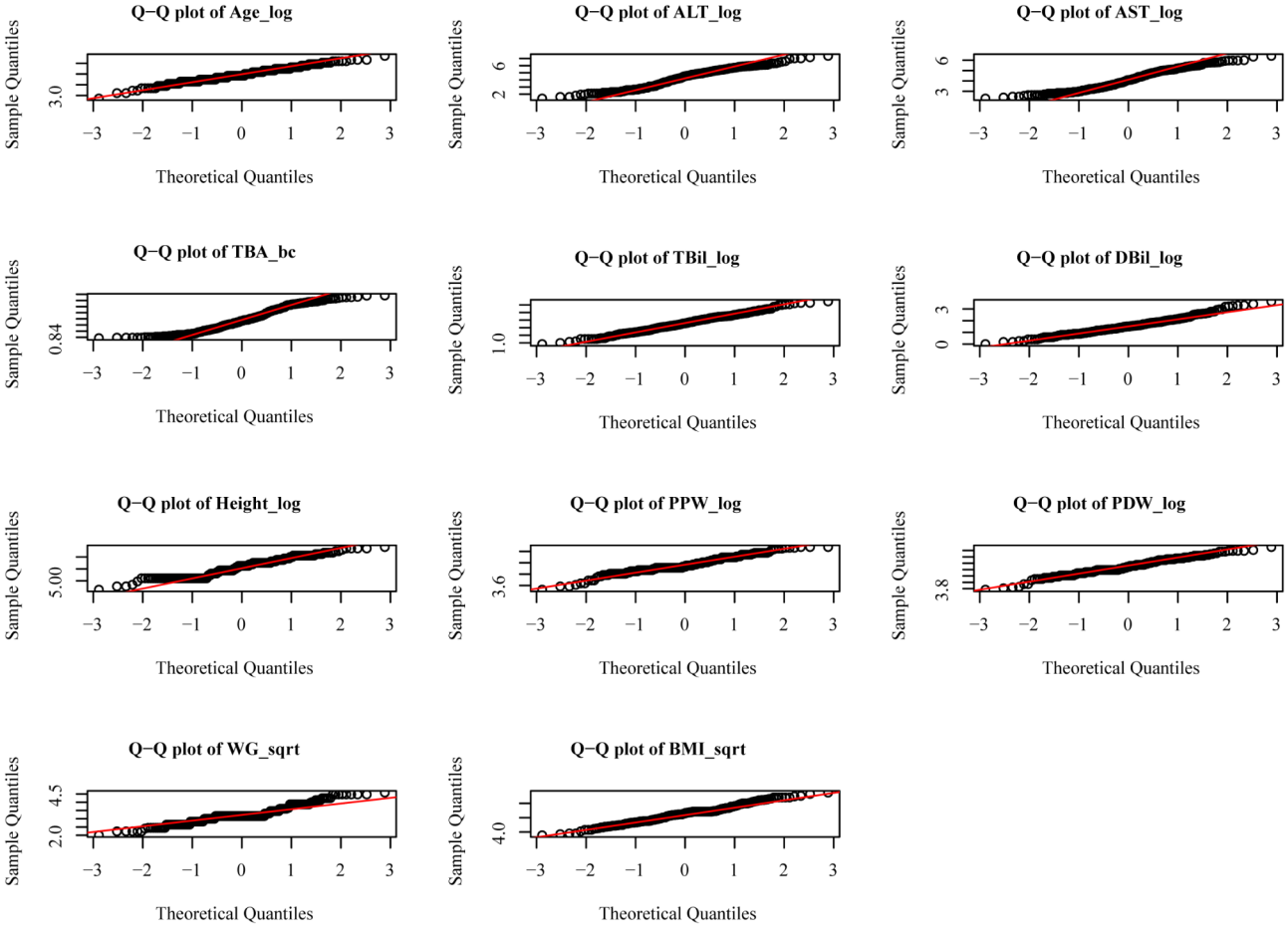

Fig. 1 Q-Q Plots of Continuous Variables After Normality Transformation. This figure presents the Q-Q plots of continuous variables after a normality assessment using the KS test. Each subplot displays the Q-Q plot for a specific variable, where the x-axis represents the theoretical quantiles and the y-axis shows the sample quantiles. The red line indicates the theoretical reference line for a normal distribution, and the black dots illustrate the observed data distribution. The plots suggest that the distributions of the transformed variables approximate normality, meeting the prerequisites for further analysis

preterm births (21.4% vs. 3.0%, $P<0.001$). Additionally, GA at diagnosis was notably earlier in the preterm group (0: 58.9% vs. 24.4%, 1: 39.3% vs. 36.3%, 2: 1.8% vs. 39.3%, $P<0.001$). Following the Box-Cox transformation, the levels of TBA_bc were notably elevated in the preterm group compared to the non-preterm group (0.88 vs. 0.87, $P<0.001$), as detailed in Table 1.

Feature selection

In the initial univariate analysis, variables such as TP, FGR, GA at diagnosis, ALT_log, AST_log, DBil_log, Height_log, and TBA_bc demonstrated significant associations and were thus included in the LASSO regression analysis. Additionally, GH, with a near-significant *P*-value of 0.052, was also considered in the LASSO regression to ensure a comprehensive variable selection. As depicted in Fig. 2A, with increasing values of the penalty parameter λ (Lambda) in the LASSO regression, the regression coefficients of the included variables progressively approached zero. The optimal λ, determined via cross-validation, was found to be 0.007. At this λ value, the LASSO model retained the following variables with non-zero regression coefficients: TP (1.98), FGR (0.83), GA at diagnosis (-1.50), AST_log (1.05), DBil_log (0.07), Height_log (-1.62), TBA_bc (2.61), and GH (0.78). The cross-validation curve, shown in Fig. 2B, illustrates the binomial deviance of the model across different λ values, with the optimal λ corresponding to the minimum binomial deviance. This indicates an optimal balance between model complexity and predictive performance.

Following the LASSO regression analysis, the variables selected for further analysis included TP, FGR, GA at diagnosis, AST_log, Height_log, and TBA_bc. A new dataset incorporating these variables was constructed for multivariable logistic regression analysis. Preliminary results from this analysis indicated that TP (Odds Ratio [OR] = 8.89, $P=0.001$), GA at diagnosis (OR = 0.18, $P<0.001$), Height_log (OR = 1.22, $P=0.030$), and TBA_bc (OR = 5.44, $P<0.001$) were significant predictors of preterm birth in ICP patients. In the multivariable regression

Table 1 Preliminary screening of risk factors for preterm birth in ICP patients

Variables	Non-preterm (*n* = 201)	Preterm (*n* = 56)	*P*
GDM = Yes (%)	49 (24.4)	12 (21.0)	0.941
GH = Yes (%)	11 (5.5)	8 (14.3)	0.052
Hypothyroidism = Yes (%)	29 (14.4)	9 (16.1)	0.925
Primipara = Yes (%)	149 (74.1)	44 (78.6)	0.613
APH = Yes (%)	9 (4.5)	2 (3.6)	1
HICP = Yes (%)	4 (2.0)	0 (0.0)	0.65
ART = Yes (%)	15 (7.5)	6 (10.7)	0.61
TP = Yes (%)	6 (3.0)	12 (21.4)	**< 0.001**
Polyhydramnios = Yes (%)	1 (0.5)	0 (0.0)	1
Oligohydramnios = Yes (%)	6 (3.0)	0 (0.0)	0.419
FGR = Yes (%)	8 (4.0)	7 (12.5)	**0.037**
PP = Yes (%)	5 (2.5)	0 (0.0)	0.519
PS = Yes (%)	20 (10.0)	5 (8.9)	1
EDU (%)			0.378
0	71 (35.3)	24 (42.9)	
1	57 (28.4)	11 (19.6)	
2	73 (36.3)	21 (37.5)	
Uterine.Surgery = Yes (%)	34 (16.9)	7 (12.5)	0.554
SU = Yes (%)	29 (14.4)	5 (8.9)	0.395
HT = Yes (%)	1 (0.5)	2 (3.6)	0.234
KI = Yes (%)	6 (3.0)	4 (7.1)	0.302
Infection = Yes (%)	9 (4.5)	6 (10.7)	0.15
CI = Yes (%)	10 (5.0)	3 (5.4)	1
AN = Yes (%)	56 (27.9)	15 (26.8)	1
TCP = Yes (%)	19 (9.5)	1 (1.8)	0.107
HPT = Yes (%)	18 (9.0)	8 (14.3)	0.358
G (%)			0.173
0	149 (74.1)	45 (80.4)	
1	47 (23.4)	9 (16.0)	
2	5 (2.5)	1 (1.8)	
3	0 (0.0)	1 (1.8)	
GA.at.diagnosis (%)			**< 0.001**
0	49 (24.4)	33 (58.9)	
1	73 (36.3)	22 (39.3)	
2	79 (39.3)	1 (1.8)	
ALP (mean (SD))	187.15 (92.93)	166.00 (76.90)	0.12
Age_log (mean (SD))	3.39 (0.13)	3.39 (0.13)	0.807
ALT_log (mean (SD))	4.17 (1.30)	4.70 (1.43)	**0.009**
AST_log (mean (SD))	4.03 (0.93)	4.43 (1.09)	**0.007**
TBil_log (mean (SD))	2.26 (0.54)	2.41 (0.63)	0.073
DBil_log (mean (SD))	1.49 (0.61)	1.75 (0.77)	**0.009**
Height_log (mean (SD))	5.06 (0.04)	5.05 (0.04)	**0.032**
PPW_log (mean (SD))	3.97 (0.14)	3.95 (0.13)	0.328
PDW_log (mean (SD))	4.16 (0.12)	4.13 (0.11)	0.174
WG_sqrt (mean (SD))	3.25 (0.51)	3.18 (0.43)	0.382
BMI_sqrt (mean (SD))	4.63 (0.30)	4.63 (0.25)	0.888
TBA_bc (mean (SD))	0.87 (0.02)	0.88 (0.02)	**< 0.001**

Bold indicates $P < 0.05$, thus indicating statistical significance

model, the VIF values for all included variables were below 5, suggesting negligible multicollinearity concerns. Subsequent stepwise regression analysis maintained an AIC value of 193.83, indicating no further variables required optimization, thus confirming the appropriateness of the selected variables. The final multivariable logistic regression model, which included TP, GA at diagnosis, Height_log, and TBA_bc, exhibited a residual deviance of 179.83 and an AIC of 193.83. These metrics suggest that the model was well-fitted and demonstrated robust predictive performance, as detailed in Table 2.

Nomogram development and validation

This study utilized data from 154 ICP patients, featuring a preterm birth rate of 21%, to form the training set. Additionally, data from 103 ICP patients with a preterm birth rate of 22% constituted the test set, as illustrated in the flowchart (Fig. 3). We evaluated the consistency of feature distributions between the training and test sets by comparing both categorical and continuous variables. For categorical variables, the analysis revealed no statistically significant differences in the distributions of most variables between the sets (P-values > 0.05). This similarity suggests that the categorical variables were consistently distributed across both sets. For continuous variables, most showed no significant differences (P-values > 0.05), certain variables such as the logarithmic transformation of age (Age_log) exhibited differences ($P = 0.03$). Thus, the overall feature distributions between the training and test sets were sufficiently similar, providing a stable and consistent foundation for further model development (Table 3). We incorporated four key risk factors—TP, GA at diagnosis, TBA_bc, and Height_log—into R Studio to construct a nomogram. This nomogram established a predictive model for assessing the risk of preterm birth among ICP patients (Fig. 4). The model's predictive capability was evaluated using AUC. For the training set, the model achieved an AUC of 0.864 with a 95% confidence interval ranging from 0.784 to 0.945, indicating robust discriminative ability and a high level of accuracy in predicting preterm birth risk. For the test set, the model achieved an AUC of 0.836, with a 95% confidence interval ranging from 0.745 to 0.926. This score indicates strong generalization performance on unseen data and consistent predictive accuracy across different datasets. These results suggest that the model is highly accurate and demonstrates robust generalization capabilities, effectively identifying the risk of preterm birth in ICP patients (Fig. 5). We also evaluated the model's predictive performance using calibration curves (Fig. 6). The calibration curve for the training set closely aligns with the diagonal, achieving a C-index of 0.864, which indicates good agreement between predicted values and actual outcomes. Similarly, the calibration curve for

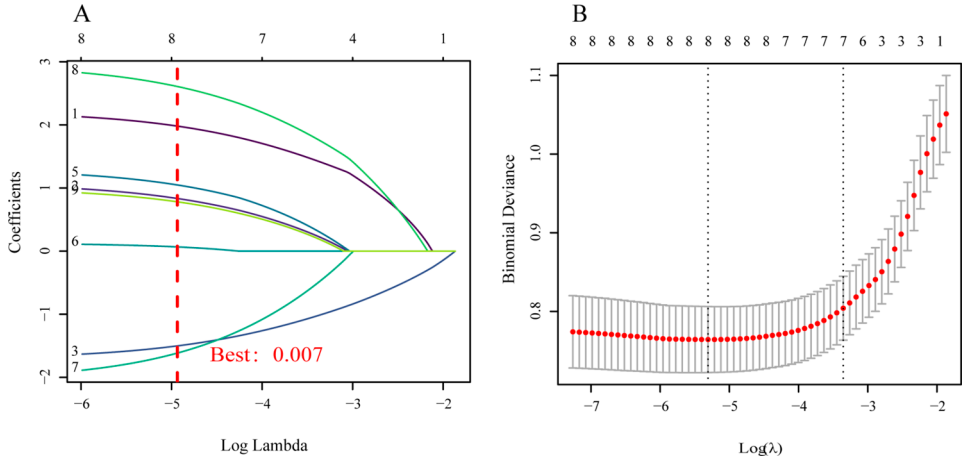

Fig. 2 LASSO Regression Analysis. (**A**) The optimal penalty parameter λ (0.007) retained eight variables with non-zero coefficients: TP (1.98), FGR (0.83), GA at diagnosis (-1.50), AST_log (1.05), DBil_log (0.07), Height_log (-1.62), TBA_bc (2.61), and GH (0.78). (**B**) The cross-validation curve indicates that the optimal λ corresponds to the minimum binomial deviance, striking a balance between model complexity and predictive performance

Table 2 Multivariate logistic regression analysis of risk factors for preterm birth in ICP patients

Variables	OR (multivariable)	95% CI	*P*
TP	8.89	(2.33, 31.50)	**0.001**
FGR	3.61	(0.94, 13.74)	0.100
GA.at.diagnosis	0.18	(0.03, 0.52)	**< 0.001**
AST_log	1.37	(0.89, 2.54)	0.098
Height_log	1.22	(1.04, 2.91)	**0.030**
TBA_bc	5.44	(2.52, 44.75)	**< 0.001**

Bold indicates $P < 0.05$, thus indicating statistical significance

the test set closely follows the diagonal, with a C-index of 0.835, demonstrating consistent predictive accuracy on unseen data. The mean absolute error for the training set is 0.036, with a mean squared error of 0.002, and the 90th percentile of absolute error is 0.075, indicating relatively small prediction errors in the training set. For the test set, the mean absolute error is 0.032, with a mean squared error of 0.002, and the 90th percentile of absolute error is 0.071, further confirming the model's accuracy and stability on unseen data. These findings affirm the model's strong predictive ability and consistency, highlighting its effectiveness in predicting preterm birth risks in ICP patients. The clinical utility of the model is illustrated in Fig. 7. DCA shows that the model provides significant net benefits, especially within the high-risk threshold range of 0 to 0.4. Within this range, the curves for both the training and test sets closely overlap, indicating the model's stability and consistency across datasets. This robustness makes the model suitable for clinical decision-making in identifying high-risk patients. When the risk threshold exceeds 0.4, the net benefit curve for the test set gradually plateaus and approaches a horizontal line, suggesting that the model's net benefit stabilizes and its predictive capacity becomes comparable to random decision-making at higher thresholds. In contrast, the net benefit curve for the training set remains slightly higher in this range, likely due to the larger sample size of the training set, which could lead to relatively higher net benefits in the high-threshold region.

Discussion

The rate of preterm birth among patients with ICP is notably higher than in women with normal pregnancies. Specifically, preterm birth rates for pregnant women with serum TBA levels of 10–39, 40–99, and ≥ 100 μmol/L are 16.5% (373/2,264), 19.1% (261/1,368), and 30.5% (157/514) respectively [5]. Preterm birth associated with ICP is notably more detrimental than typical preterm births. Firstly, elevated TBA levels in ICP patients can cross the placenta, exposing the fetus to bile acids which possess neurotoxic and cytotoxic effects. These effects may compromise fetal cardiac function, potentially leading to fetal distress, bradycardia, and even intrauterine death [20]. Such outcomes are less frequent in general preterm births. Secondly, ICP may impair placental function, leading to inadequate fetal nutrition and increasing the risk of FGR [21]. Additionally, the rapid progression of ICP during pregnancy can cause a sudden escalation in bile acid levels, notably heightening the risk of fetal distress and mortality [22]. Consequently, preterm births in ICP cases often occur abruptly, unlike some general preterm births where interventions such as medications can delay delivery to enhance fetal lung maturity [23]. Lastly, ICP affects not only the liver but also the absorption of vitamin K in pregnant women, potentially increasing prothrombin time and the risk of postpartum hemorrhage. To mitigate these risks, some experts recommend administering 10 mg of vitamin K to reduce maternal complications during and after delivery [24].

The timing for terminating a pregnancy in ICP patients is a subject of ongoing debate. According to guidelines

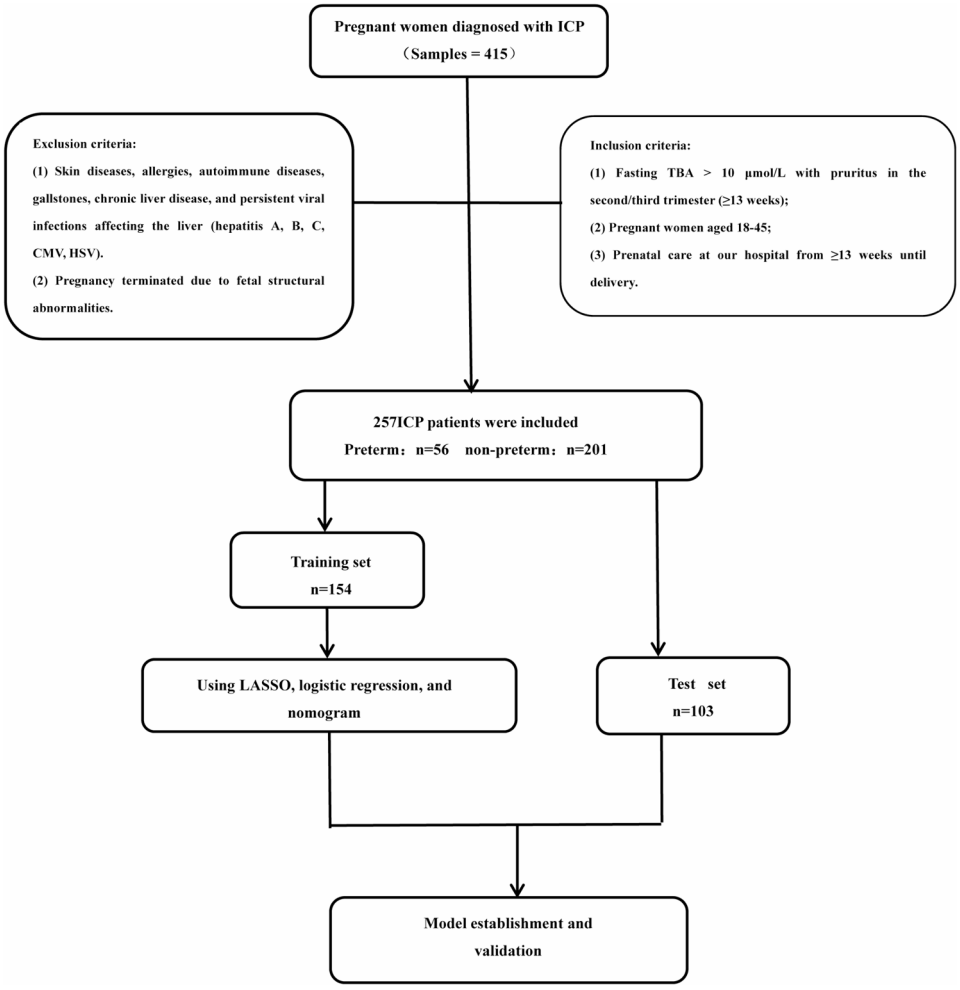

Fig. 3 Flowchart of this study. A total of 257 patients with ICP were included in this study based on the inclusion criteria. We used LASSO logistic regression and multivariate analysis to identify significant predictive factors and establish a nomogram. The training dataset ($n = 154$) was utilized to estimate the predictive model for preterm birth in ICP patients, while the test dataset comprised 103 patients. We evaluated the nomogram using the AUC, C-index, calibration curves, and DCA

from the Royal College of Obstetricians and Gynaecologists (RCOG), it is suggested that patients with mild ICP plan for delivery at 40 weeks of gestation, while those with severe ICP should consider ending the pregnancy before 39 weeks. This recommendation takes into account factors such as the patient's history of ICP, fetal death, or other pregnancy-related complications and comorbidities. If needed, pregnancy termination may occur between 36 and 38 weeks [22]. Therefore, assessing the risk factors for preterm birth in ICP patients is essential, helping clinicians to predict preterm birth risks individually and determine the most appropriate timing for pregnancy termination with sufficient preparation.

Several studies have identified risk factors for preterm birth in ICP patients, with TBA levels being a primary factor. A comprehensive study in Sweden demonstrated that in pregnancies where fasting TBA levels exceeded 40 μmol/L, each 1 μmol/L increase in TBA was associated with a 1–2% increase in fetal complications such as spontaneous preterm birth and meconium-stained amniotic fluid [25]. Another large cohort study confirmed a significant correlation between elevated TBA levels and the risk of spontaneous preterm birth, noting a dose-response relationship above the 20 μmol/L threshold. When TBA levels surpassed 40 μmol/L, the relative risk of iatrogenic preterm birth was greater than 1.0 [26]. These findings align with our own, which show a significant association between preterm birth and TBA levels at diagnosis ($P < 0.001$). This may be due to the vasoconstrictive effects of abnormally elevated bile acids at the maternal-fetal interface, leading to placental hypoperfusion and chronic hypoxia. Such conditions can result in malnutrition, neonatal asphyxia, or even stillbirth, thus highlighting TBA levels as a key determinant of iatrogenic preterm birth [27]. Moreover, bile acids can activate oxytocin receptors, thereby intensifying myometrial contractions, which is a

Table 3 Comparison of feature distributions between training and test sets

Variable	Training Set	Test Set	*P*
Diagnosis = Yes(%)	21%	22%	0.99
GDM = Yes(%)	21%	28%	0.23
GH = Yes(%)	8%	7%	0.96
Hypothyroidism = Yes(%)	16%	14%	0.79
Primipara = Yes(%)	75%	75%	1.00
APH = Yes(%)	4%	5%	0.95
HICP = Yes(%)	1%	3%	0.31
ART = Yes(%)	8%	9%	0.97
TP = Yes(%)	7%	7%	1.00
Polyhydramnios = Yes(%)	0%	1%	0.40
Oligohydramnios = Yes(%)	1%	4%	0.22
FGR = Yes(%)	7%	4%	0.42
PP = Yes(%)	3%	1%	0.65
PS = Yes(%)	6%	16%	0.02
EDU	0 = 34%; 1 = 27%; 2 = 39%	0 = 41%; 1 = 26%; 2 = 33%	0.53
Uterine.Surgery = Yes(%)	15%	17%	0.71
SU = Yes(%)	13%	14%	1.00
HT = Yes(%)	1%	1%	1.00
KI = Yes(%)	3%	6%	0.21
Infection = Yes(%)	5%	7%	0.79
CI = Yes(%)	5%	6%	0.87
AN = Yes(%)	27%	28%	0.99
TCP = Yes(%)	8%	7%	0.81
HPT = Yes(%)	9%	12%	0.65
G	0 = 77%; 1 = 21%; 2 = 1%; 3 = 1%	0 = 74%; 1 = 22%; 2 = 4%; 3 = 0%	0.54
GA.at.diagnosis	1 = 34%; 2 = 38%; 3 = 28%	1 = 28%; 2 = 36%; 3 = 36%	0.24
ALP	177.01 (89.02)	190.82 (91.17)	0.20
Age_log	3.37 (0.13)	3.41 (0.13)	0.03
ALT_log	4.25 (1.4)	4.34 (1.26)	0.59
AST_log	4.09 (1.02)	4.16 (0.93)	0.50
TBil_log	2.3 (0.57)	2.29 (0.56)	0.98
DBil_log	1.54 (0.64)	1.56 (0.68)	0.93
Height_log	5.06 (0.04)	5.06 (0.04)	0.90
PPW_log	3.97 (0.14)	3.96 (0.12)	0.57
PDW_log	4.15 (0.12)	4.14 (0.11)	0.59
WG_sqrt	3.23 (0.53)	3.25 (0.43)	0.54
BMI_sqrt	4.64 (0.3)	4.61 (0.27)	0.49
TBA_bc	0.87 (0.02)	0.87 (0.02)	0.65

The *P*-values for most variables are greater than 0.05, indicating no significant differences in the distributions of variables between the two sets. Therefore, the feature distributions of the training and test sets are generally consistent

potential mechanism behind spontaneous preterm birth [20, 28].

Patients with TP exhibit higher estrogen levels compared to women with singleton pregnancies. The metabolites of estrogen impair the function of the bile salt export pump, thereby increasing susceptibility to bile acid accumulation and heightening the risk of preterm birth [29, 30]. Our research identified a significant association between preterm birth and twin pregnancies in patients with ICP ($P = 0.001$). A large meta-analysis supported these findings, indicating that most multiple pregnancies lead to preterm birth [26]. Regarding the GA at diagnosis, many researchers agree that 28 weeks of gestation marks the critical threshold distinguishing early-onset ICP from late-onset ICP [31]. Compared to late-onset ICP, early-onset ICP is associated with more severe clinical symptoms and higher levels of serum biochemical markers, such as TBA and TBil, increasing the likelihood of preterm birth [30, 32]. This increased risk is partially due to the tendency to induce labor earlier in gestation in early-onset ICP to prevent adverse fetal outcomes. Additionally, as gestational age progresses, estrogen levels rise, leading to increased bile acid concentrations and further raising the risk of preterm birth [33, 34]. Our study corroborated these findings, demonstrating a significant correlation between preterm birth and gestational age at diagnosis in ICP patients ($P<0.001$). Furthermore, we found a significant association between maternal height (logged) and the risk of preterm birth in ICP patients ($P = 0.03$). Shorter maternal height may reflect several physiological factors that influence the risk of preterm birth, such as smaller uterine volume, a narrower pelvis, and other physiological characteristics, potentially increasing the risk of fetal restriction or preterm birth during pregnancy. Additionally, logged maternal height may be indicative of maternal nutrition, weight, and other factors, all of which are crucial for fetal growth and development during pregnancy [35–37].

For patients at high risk of preterm birth, regular monitoring of TBA levels, liver function, and fetal health is crucial. Patients with mild ICP should have their TBA levels rechecked every two weeks, whereas those with severe or extremely severe ICP should be rechecked weekly [2]. Early intervention becomes particularly important if TBA levels continue to rise, if the diagnosis occurs early in gestation, or in cases of TP. Patients with ICP can begin taking UDCA from the time of diagnosis, as it is the first-choice treatment for this condition. UDCA helps to improve bile flow and reduce bile acid levels, thus alleviating symptoms. It also helps in reducing the risk of preterm birth associated with ICP and decreases the chances of fetal distress and death [38, 39]. Additionally, the glutathione precursor S-adenosylmethionine (SAMe) can be considered for treating ICP. SAMe functions by affecting the composition and fluidity of the hepatocyte plasma membrane, thereby enhancing the methylation of hormone metabolites and promoting bile excretion [40]. Moreover, the use of tocolytics, such as nifedipine, can prolong pregnancy, particularly in patients who are at high risk of preterm birth before 32 weeks [41]. Finally, lifestyle and dietary interventions are essential. Patients with ICP are advised to maintain

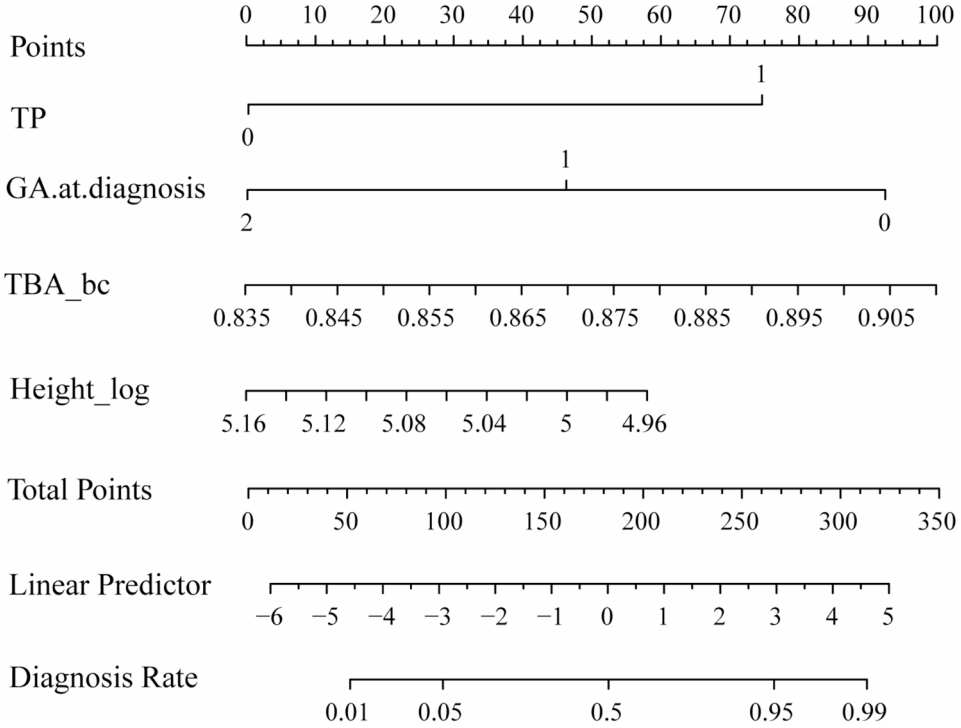

Fig. 4 Nomogram for estimating preterm birth in ICP patients. At the top, points represent the contribution score of each variable to the predicted outcome, ranging from 0 to 100. TP is a binary variable with values of 0 or 1, each value corresponding to a specific score, indicating its impact on the prediction. GA at diagnosis is divided into three ranges: ≥13 weeks and ≤ 33 weeks is set as 0, >33 weeks and ≤ 36 weeks as 1, and >36 weeks as 2, with each range contributing a specific score to the prediction. TBA_bc and Height_log are continuous variables, where Height_log = ln(Height Value) and $TBA\_bc = TBA^{\lambda}\text{-}1/\lambda$ (with the optimal parameter $\lambda = -1.0972$). By summing the scores of all variables, the Total Points can be calculated, ranging from 0 to 350. These total points are then used to determine the Linear Predictor value, which ranges from −6 to 5, and subsequently, the Diagnosis Rate, which represents the probability of the event occurring, ranging from 0.01 (1%) to 0.99 (99%)

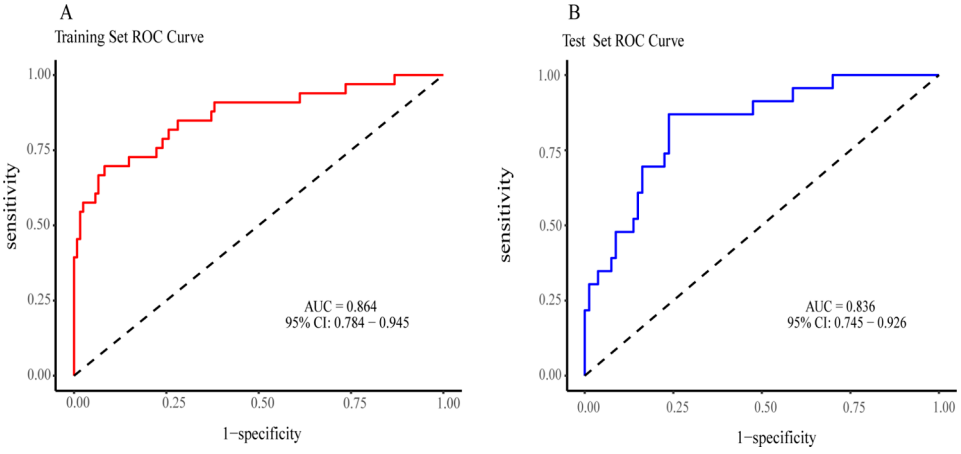

Fig. 5 ROC curves for the training and test sets. (**A**) AUC for the training set. (**B**) AUC for the test set. The model demonstrates strong discriminative ability and robust generalization, effectively predicting the risk of preterm birth in ICP patients

a low-fat diet to lessen the burden on the liver. Additionally, they should avoid drugs and toxins that may exacerbate liver stress, as well as refrain from smoking and drinking to protect liver function and alleviate ICP symptoms [42].

In pregnant women at high risk of preterm birth, administering dexamethasone to promote fetal lung maturation is recommended before 37 weeks to lower the risk of neonatal respiratory distress syndrome (RDS) [2]. However, continuous fetal monitoring has not been shown to reduce the incidence of stillbirth and is therefore not recommended unless indicated by decreased fetal movement, abnormal electronic fetal heart rate monitoring, or other pregnancy complications. If

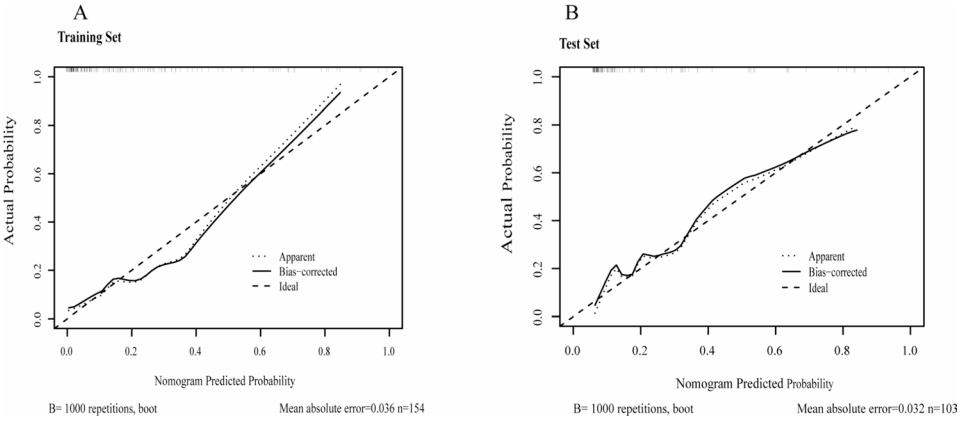

Fig. 6 Calibration curves for the training and test sets. (**A**) Calibration curve for the training set. (**B**) Calibration curve for the test set. These curves demonstrate good agreement between the predicted and actual outcomes, with low prediction errors, indicating the model's accuracy and stability in predicting the risk of preterm birth in patients with ICP

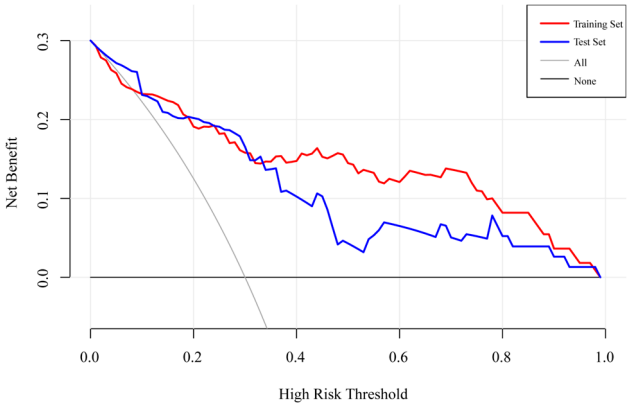

Fig. 7 Analysis of DCA for the training and test sets. The blue line represents the net benefit for ICP patients not deemed to be at risk of preterm birth in the training set; the red line represents the net benefit for ICP patients not deemed to be at risk of preterm birth in the test set. The gray diagonal line represents the net benefit of treating all patients as if they were at risk of preterm birth. The further the blue and red lines are from the gray line, the greater the benefit that the model provides in accurately predicting preterm birth

pharmacological treatments are ineffective, particularly when bile acid levels exceed 40 μmol/L or fetal distress is noted, timely delivery may decrease the risk of adverse pregnancy outcomes [2, 22, 24, 43]. ICP alone does not necessitate a cesarean section. Induced labor should be considered when the gestational age is suitable for delivery, unless there are specific indications for a cesarean section, such as cephalopelvic disproportion [44]. During vaginal delivery for severe or extremely severe ICP, close fetal monitoring is essential. If additional risk factors are present, such as severe pregnancy complications, meconium-stained amniotic fluid, or abnormal fetal heart rate monitoring, continuous electronic fetal heart rate monitoring may be warranted. Persisting abnormalities may lower the threshold for opting for a cesarean section [45]. Obstetricians must be proactive in preparing for preterm births; consulting neonatologists is necessary to ensure the safety of both mother and baby [46].

Our research introduces several innovations compared to prior studies. To begin with, no existing nomogram that employs clinical data has been developed to predict the risk of preterm birth among patients with ICP [15]. Our study is the first to validate the combined effect of TBA, TP, GA, and patient height at the time of diagnosis in forecasting this risk. This model not only allows clinicians to better evaluate the risk of preterm birth but also facilitates the creation of tailored management plans. By integrating straightforward clinical data with laboratory results, the nomogram provides an economical and highly practical tool for clinical use. Additionally, our study considered multiple factors linked to preterm birth, unlike most previous studies that focused solely on traditional indicators such as TBA levels [14, 47–50]. By incorporating various clinical features, our model enhances the accuracy of predicting preterm birth risk. This multifactorial approach delivers a more robust basis for clinical decision-making, potentially leading to more precise risk evaluations. Furthermore, the variables in our nomogram are derived from data collected at the initial diagnosis. This allows clinicians to diagnose early, manage risks effectively, and better protect the health of both mother and child.

However, our study does have limitations. Firstly, the sample size is relatively small, particularly for TP, with only 12 cases of preterm birth and 6 cases of non-preterm birth. Although TP is included in the nomogram, its specific influence requires further investigation. Future studies should increase the sample size and examine the interplay between TP and other risk factors, such as bile acids and estrogen. Secondly, the GA at diagnosis was not categorized based on a 28-week threshold but rather according to the overall data distribution. Subsequent research should employ more precise categorization

methods. Additionally, TBA_log levels were not classified; such categorization demands more experimental and data support to establish appropriate thresholds. Future studies should not only expand sample sizes but also consider dynamic monitoring of TBA in their predictive models. Lastly, our analysis did not sufficiently explore the interactions between different factors. Future research should delve deeper into these interactions to enhance the accuracy of predictive models.

Conclusion

Through analyzing basic pregnancy records, we identified four independent risk factors for preterm birth in ICP patients: height, TP, GA at diagnosis, and TBA levels at diagnosis. A nomogram can assist in the early clinical management of such patients, including initiating aggressive drug treatments. For pregnant women at high risk of preterm birth, administration of dexamethasone before 37 weeks is recommended to enhance fetal lung maturity. Should drug treatments prove ineffective, especially when bile acid levels exceed 40 μmol/L or if signs of fetal distress are evident, timely delivery may mitigate adverse pregnancy outcomes.

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Author contributions
WX and LJ participated in all parts of the study, design, data acquisition, analysis, interpretation, and drafting of the paper.DL, LY, QL, LK and QH was involved in review and assisted in revising the manuscript. JM supervised data collection and critically reviewed the manuscript. All authors approved the final version submitted.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, the data are not publicly available.

Declarations

Ethical approval and consent to Participate
This study was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of Sichuan Provincial People's Hospital (Approval No.: Ethics Review 2024 No. 634). As a retrospective study utilizing existing data that did not contain any personally identifiable information, the Ethics Committee of Sichuan Provincial People's Hospital approved the waiver of informed consent based on the retrospective nature of the study.

Consent for publication
This retrospective study did not require informed consent as it involved the analysis of existing data that did not include personally identifiable information.

Competing interests
The authors declare no competing interests.

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