ORIGINAL RESEARCH

Development, Validation and Clinical Utility of a Risk Prediction Model for Maternal and Neonatal Adverse Outcomes in Pregnant Women with Hypothyroidism

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Purpose: This study aimed to create, verify and assess the clinical utility of a prediction model for maternal and neonatal adverse outcomes in pregnant women with hypothyroidism.

Methods: A prediction model was developed, and its accuracy was tested using data from a retrospective cohort. The study focused exclusively on female patients diagnosed with hypothyroidism who were admitted to a tertiary hospital. The development and validation cohort comprised individuals who gave birth between 1 October 2020 and 31 December 2022. The primary outcome was a combination of crucial maternal and newborn problems (eg premature births, abortions and neonatal asphyxia). The prediction model was developed using logistic regression. Evaluation of the model's performance was conducted based on its ability to discriminate, calibrate and provide clinical value.

Results: In total, nine variables were chosen to develop the predictive model for adverse maternal and neonatal outcomes during pregnancy with hypothyroidism. The area under the curve of the model for predicting maternal adverse outcomes was 0.845, and that for predicting neonatal adverse outcomes was 0.685. The calibration plots showed good agreement between the nomogram predictions and the actual observations in both the training and validation cohorts. Furthermore, decision curve analysis suggested that the nomograms were clinically useful and had good discriminative power to identify high-risk mother–infant cases.

Conclusion: Two models to predict the risk probability of maternal and neonatal adverse outcomes in pregnant women with hypothyroidism were developed and verified to assist physicians in evaluating maternal and neonatal adverse outcomes throughout pregnancy with hypothyroidism and to facilitate decision-making regarding therapy.

Keywords: pregnancy with hypothyroidism, maternal and neonatal adverse outcomes, nomogram, forecasting model

Introduction

The most prevalent thyroid dysfunction observed during pregnancy is hypothyroidism, which can manifest in both overt and subclinical forms. The prevalence of thyroid dysfunction in women of reproductive age who are not pregnant has been found to be 17.2%.[1] Based on a meta-analysis of 97 studies, the estimated prevalence of hypothyroidism during pregnancy is 0.4%–13.1%, and that of subclinical hypothyroidism is 3.3%–42.9%.[2] Research has indicated that even mild hypothyroidism can result in adverse short-term outcomes for the mother and infant as well as long-term intellectual disability in the infant.[3] Hypothyroidism in pregnancy increases the risk of conditions such as preterm delivery, spontaneous abortion and gestational diabetes, and it can even result in death for both mother and child.

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Accurate identification of those at risk for maternal and neonatal adverse outcomes and early intervention among pregnant women with hypothyroidism could help improve maternal and neonatal prognosis. Unfortunately, research has shown that the diagnostic reference ranges are not necessarily the best cut-off for identifying pregnancies at high risk of adverse outcomes.[4] Moreover, the risk of maternal and neonatal adverse outcomes also depends on various factors, such as lipid differences[5] and pregnancy complications.[6] An increasing number of research works[7–9] are finding many risk factors associated with adverse maternal and neonatal outcomes, such as lipid levels, bisphenol A, retinol-binding protein 4, and first trimester thyroid stimulating hormone. However, these studies have mostly focused on individual components, and there is currently no comprehensive model available to predict the overall risk of maternal and neonatal adverse outcomes.

Therefore, the aim of this study is to explore the risk factors leading to adverse outcomes in pregnancy with hypothyroidism and thereby construct, verify and determine the clinical utility of a risk prediction model to establish a more specific percentile-based disease risk threshold. This may allow us to identify patients who are at risk of experiencing maternal and neonatal adverse outcomes due to thyroid dysfunction and could potentially benefit from treatment.

Methods
Research Objects
Pregnant women with hypothyroidism who delivered at a metropolitan tertiary teaching hospital between 1 October 2020 and 31 December 2022 were the subjects of routine collection of retrospective health data used for the development and validation of the model. A total of 713 groups of maternal and neonatal cases were collected, and 698 groups were included for analysis after screening. The study was approved by the ethics committee of Jiangnan University Affiliated Hospital, and the requirement of obtaining informed consent was exempted due to the study's retrospective nature with minimal risk (reference number: JNU20230301IRB02).

Inclusion and Exclusion Criteria
Regarding thyroid disorders during the pregnancy and postpartum periods, we referred to the Guidelines for the Diagnosis and Treatment of Thyroid Diseases during Pregnancy and Postpartum (Second Edition).[10] Clinical hypothyroidism during pregnancy is classified according to the following diagnostic criteria: as pregnancy approaches, serum TSH exceeds the upper limit of the pregnancy-specific reference range, while serum free thyroxine (FT4) falls below the lower limit. If the specific reference range of TSH during pregnancy cannot be obtained, the cut-off value of the upper limit of TSH in early pregnancy can be obtained by the following two methods: the upper limit of the TSH reference range in the general population decreases by 22% or 4.0 mU/L.

The diagnostic criteria for subchorionic hematoma during pregnancy are a serum TSH level that exceeds the upper limit of the pregnancy-specific reference range and a serum FT4 level that remains within the pregnancy-specific reference range.

In this study, the maternal inclusion criteria were as follows: (1) individuals aged 18 to 45 years; (2) individuals who were diagnosed with hypothyroidism during pregnancy or had hypothyroidism before pregnancy; and (3) complete case data. The exclusion criteria were as follows: (1) significant organ malfunction; (2) other autoimmune diseases aside from autoimmune thyroiditis; and (3) severe uterine or vaginal malformations.

Candidate Predictors
We selected candidate predictors through relevant research.[5,11–15] The following predictors were assessed for potential inclusion in the model.

General maternal information encompassed many factors, such as age, pre-pregnancy body mass index, gestational age, number of pregnancies, number of live births, method of conception, cholesterol levels, platelet count and haemoglobin levels. Patient medical history included previous conditions, such as thyroid dysfunction, hypertension, diabetes mellitus, anaemia and group B streptococcal infection (GBS; *Streptococcus agalactiae*). Family medical history included thyroid dysfunction, diabetes mellitus, hypertension and anaemia. Current medical history included gestational diabetes, gestational hypertension, eclampsia/preeclampsia, pregnancy complicated with GBS, and perinatal anaemia. Thyroid function and therapy during pregnancy encompassed factors such as gestational age, levels of TSH and FT4 at

diagnosis, frequency of TSH monitoring during pregnancy, medication usage, treatment administration, and attainment of standard TSH levels as well as the duration it took to achieve the standard. Delivery methods encompassed spontaneous delivery, lateral episiotomy, forceps delivery, emergency caesarean section, spontaneous delivery to caesarean section and planned caesarean section. Newborn information, such as gender and weight, was also included.

Outcomes

The primary outcome was a composite of maternal and neonatal adverse outcomes.

Several maternal complications and adverse outcomes were associated with preterm delivery, foetal distress, intrauterine foetal growth restriction, threatened abortion/preterm delivery, abortion/stillbirth, premature rupture of membranes, placental abruption, placental dysfunction, polyhydramnios, oligohydramnios/oligohydramnios, foetal malformation and intrauterine growth restriction.

Neonatal adverse outcomes included low birth weight, macrosomia, low Apgar score (≤7 points at 1–5 min after birth), transfer to neonatal intensive care unit (NICU), neonatal thyroid dysfunction, neonatal asphyxia, neonatal hyperbilirubinemia, neonatal pneumonia/infection and neonatal anaemia.

Sample Size

The sample size of this case–cohort study was calculated based on Maraka's study.[16] The sample size was calculated to be 570, and considering 20% sample loss, the total sample size was 713.

Data Pre-Processing

Variables were eliminated when the proportion of missing values exceeded 20%. This study did not include subjects with more than 20% of missing items. If missing items were not included in the study (less than 20%), continuous variables were attributed with missing values, such as the mean or median. Categorical variables were assigned as "No" and "Uncertain". The logistic regression analysis converted the continuous variables of gestational age, number of hospitalisations, gravidity and parity to binary classification. The study included term births (gestational age: 37–41 weeks) and preterm births (gestational age: 37 weeks) but did not include post-term births (gestational age: ≥42 weeks). The study also considered numerous hospitalisations and multiple pregnancies as well as single and multiple deliveries. Forceps delivery and episiotomy were combined in cases where just one parturient was undergoing forceps delivery.

Statistical Analysis

A random ratio of 7:3 was utilised to divide the 698 pregnant women and their newborns into a training set and a validation set. The model was established using the training set and assessed for accuracy via the validation set. The training set contained 488 cases, while the validation set comprised 210 cases. Simultaneously, the 698 pregnant women and 698 newborns were divided into two groups according to the presence or absence of adverse outcomes. The presence of any one of the maternal/neonatal adverse outcomes was considered an adverse pregnancy outcome.

Descriptive statistics were presented as the median (IQR) for continuous variables and as the frequency for categorical variables. Wilcoxon rank-sum and χ^2 tests were used for between-group comparisons. A logistic regression model was established using a single-factor analysis. Based on the Akaike information criterion minimum, stepwise regression was used to select variables for inclusion in the nomogram.[17] Model evaluation measures included the area under the curve (AUC), sensitivity, specificity and Brier score. The cut-off referred to the prediction probability p according to the model: if $p \geq$ Cut-off, the prediction was positive; otherwise, it was negative. Discriminatory power was assessed using the AUC of the receiver operating characteristic (ROC) curve. The calibration curve was used to evaluate the calibration proficiency. The calibration plot illustrated the predicted and actual probabilities for each patient in the nomogram, with a line that closely aligned with the ideal 45° angle indicating a good correlation. The clinical value of the nomograms was assessed using decision curve analysis (DCA).

All p-values were two-tailed, where $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the R programming language and environment.

Results

Characteristics of Patients and Disease

A total of 713 groups of maternal and neonatal cases were collected, and 698 groups were included for analysis after screening. Specifically, 488 groups of maternal/neonatal cases were included in the development cohort, and 210 maternal/neonatal cases were included in the validation cohort (Figure 1).

Table 1 depicts the general clinical data for the entire population. The median maternal age was 29 (IQR: 6), and the median gestational age at delivery was 39 (IQR: 2). Moreover, the median number of hospitalisations was 1 (IQR: 1), and the median gestational age at diagnosis of hypothyroidism was 24 (IQR: 21). Finally, the median number of TSH monitoring instances during pregnancy was 4 (IQR: 3). Overall, 14.5% of the pregnant women had been diagnosed with thyroid dysfunction before this pregnancy. More than 58.4% of the pregnant women had other diseases at the same time, such as gestational diabetes mellitus (20.8%) and perinatal anaemia (23.8%). Additionally, 86.7% of the pregnant women took the levothyroxine sodium tablet 21 (IQR: 26) days after diagnosis, and TSH returned to normal More than half of all deliveries were by caesarean section or other vaginal delivery methods (52.4%).

Finally, most mothers (70.5%) experienced negative consequences of pregnancy with hypothyroidism, with the most prevalent being premature rupture of membranes (21.6%), followed by foetal distress in utero (14.8%) and postpartum thyroid dysfunction (14.6%). Of the 22.9% of newborns who experienced adverse results, 14.2% were sent for neonatal or NICU treatment; 8.0% were infected bacteria; 5.9% had hyperbilirubinemia; and 5.9% had thyroid dysfunction. Moreover, the families of 5.6% of those newborns declined to transfer the neonate in those cases.

Nomogram Variable Selection

The whole population was divided into two groups based on the occurrence or absence of adverse maternal outcomes. In univariate regression analysis, nine variables (ie age, gravidity, parity, haemoglobin, current history of eclampsia/
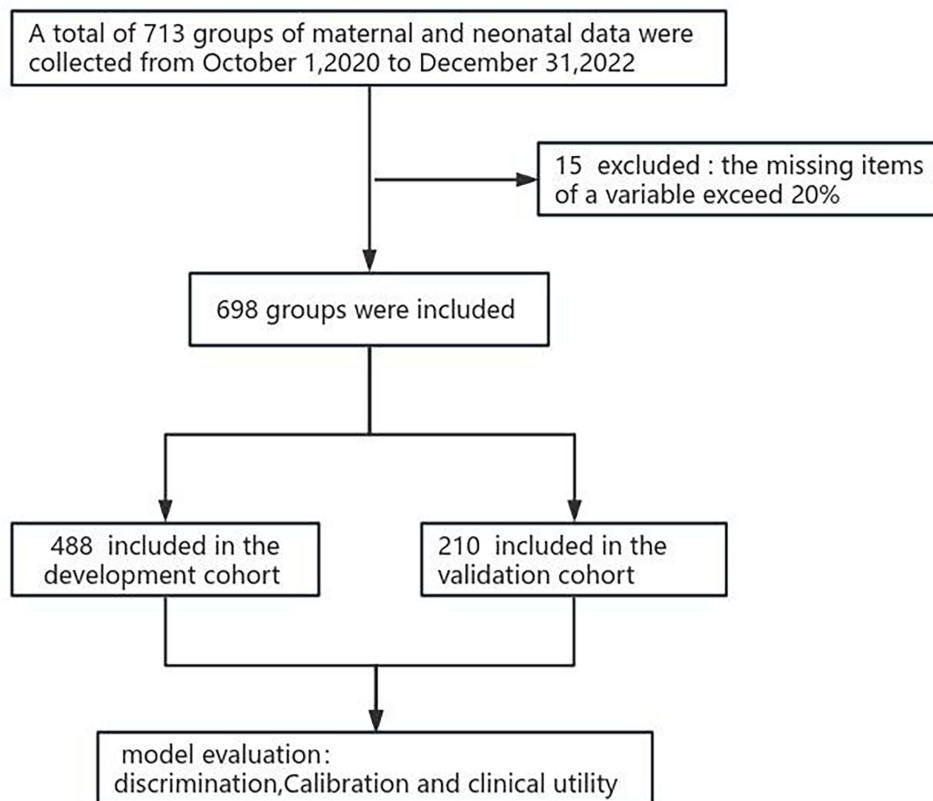

Figure 1 Flowchart of patient selection.

Table 1 Comparison of General Clinical Data of the Mother and Neonatal During a Pregnancy Complicated by Hypothyroidism

Data Classification	Variable	Median (IQR)/Number (%)
General information on maternity*	Age (years)	29 (6)
	Height (cm)	161 (7)
	Weight (kg)	70 (11)
	Gestational week of delivery	39 (2)
	Gravidity	1 (1)
	Parity	1 (1)
	Cholesterol (mmol/L)	6.58 (1.57)
	Platelet (×10⁹/L)	200.5 (70)
	Hemoglobin (g/L)	120 (13)
	Number of hospitalizations	1 (1)
Thyroid function and treatment during pregnancy*	Gestational week at diagnosis	24 (21)
	TSH level at diagnosis Gestational age (mU/L)	4.39 (1.28)
	FT4 level at diagnosis Gestational age (mU/L)	0.77 (0.19)
	Number of TSH monitoring during pregnancy	4 (3)
	Time to TSH target if medication (days)	21 (26)
Newborn*	Neonatal Weight (g)	3300 (573)
Maternal BMI#		
	Obesity (≥23)	435 (62.3)
	Emaciation (<18.5)	6 (0.9)
	Normal (18.5–22.9)	257 (36.8)
Mode of conception#		
	Natural conception	653 (93.6)
	Assisted reproduction	45 (6.4)
Past medical history (pre-pregnancy) #		
	Diagnosis of thyroid dysfunction	101 (14.5)
	Thyroid dysfunction medication	92 (13.2)
	Diagnosed with diabetes	2 (0.3)
	Diagnosed with hypertension	2 (0.3)
	Diagnosis of anemia	1 (0.1)
Family medical history#		
	Diabetes mellitus	8 (1.1)
	Hypertension	26 (3.7)
Present illness#		
	Gestational diabetes mellitus	145 (20.8)
	Gestational hypertension	32 (4.6)
	Eclampsia/pre-eclampsia	39 (5.6)
	Group B streptococcal infection	25 (3.6)
	Perinatal Anemia	166 (23.8)
Thyroid treatment during pregnancy#		
Medication	Uncertain	5 (0.7)
	Take medicine	605 (86.7)
Whether TSH reaches the standard after medication#	Uncertain	64 (9.2)
	Reach the standard	446 (73.7)
Delivery mode#		
	Eutocia	332 (47.6)
	Episiotomy	47 (6.7)
	Forceps midwifery	29 (0.3)
	Transverse section / emergency cesarean section	136 (19.5)
	Plan cesarean section	181 (25.9)

(Continued)

Table 1 (Continued).

Data Classification	Variable	Median (IQR)/Number (%)
Neonate		
Sex#	Male	393 (56.3)
	Female	305 (43.7)
Refuse to transfer treatment#		39 (5.6)
Adverse outcome#	Puerpera	492 (70.5)
	Neonate	160 (22.9)

Notes: *Median (interquartile range), #Frequency (percentage).

preeclampsia, current history of GBS, current history of perinatal anaemia, number of hospitalisations and mode of delivery) showed statistical significance (Table 2). Moreover, the entire population was divided into two groups based on the presence or absence of adverse neonatal outcomes. In univariate regression analysis, nine maternal variables (ie gestational age at delivery, cholesterol, gestational age at diagnosis, previous history of thyroid abnormality, previous history of thyroid dysfunction medication, current history of GBS, current history of perinatal anaemia, number of hospitalisations and mode of delivery) were statistically significant (all $p < 0.05$, Table 3).

Table 2 Comparison of Variable Characteristics of Maternal Adverse Outcomes

Variable		No Adverse Outcomes (N=206)	Adverse Outcomes (N=492)	Z/χ^2	P
General information on maternity*					
	Age (years)	29 (5)	28 (6)	−2.492	0.013
	Height (cm)	162 (7.0)	161 (7.0)	−1.335	0.182
	Weight (kg)	70 (11.0)	70 (11.0)	−0.117	0.907
	Gestational week of delivery	39 (2)	39 (2)	−0.902	0.367
	Gravidity	2 (2)	1 (1)	−3.597	<0.001
	Parity	1 (1)	1 (1)	−3.649	<0.001
	Cholesterol (mmol/L)	6.57 (1.60)	6.58 (1.55)	−0.158	0.874
	Platelet (×10^9/L)	198 (70)	198 (72)	−0.268	0.789
	Hemoglobin (g/L)	121 (15)	120 (14)	−2.407	0.016
	Number of hospitalizations	1 (0)	1 (1)	−6.619	<0.001
Thyroid function and treatment during pregnancy*					
	Gestational age at diagnosis	21 (22)	17 (22)	−1.410	0.159
	TSH level at diagnosis Gestational age (mU/L)	4.14 (1.1800)	4.327 (1.3230)	−0.706	0.480
	FT4 level at diagnosis Gestational age (mU/L)	0.7704 (0.1859)	0.7704 (0.1980)	−1.305	0.192
	Number of TSH monitoring during pregnancy	4 (3)	5 (2)	−0.927	0.354
	Time to TSH target if medication (days)	21 (35)	20 (23)	−1.258	0.208
Newborn*	Neonatal Weight (g)	3330 (560)	3300 (570)	−0.854	0.393
Maternal BMI#					
	Obesity (≥23)	122 (59.2%)	313 (63.6%)	1.712	0.440
	Emaciation (<18.5)	1 (0.5%)	5 (1.0%)		
	Normal (18.5–22.9)	83 (40.3%)	174 (35.4%)		

(Continued)

Table 2 (Continued).

Variable		No Adverse Outcomes (N=206)	Adverse Outcomes (N=492)	Z/χ^2	P
Mode of conception[#]					
	Natural conception	198 (96.1%)	455 (92.5%)	3.184	0.074
	Assisted reproduction	8 (3.9%)	37 (7.5%)		
Past medical history (pre-pregnancy)[#]					
	Diagnosis of thyroid dysfunction	22 (10.7%)	79 (16.1%)	3.393	0.065
	Thyroid dysfunction medication	20 (9.7%)	72 (14.6%)	3.078	0.079
	Diagnosed with diabetes	0 (0.0%)	2 (0.4%)	Fisher	1.000
	Diagnosed with hypertension	0 (0.0%)	2 (0.4%)	Fisher	1.000
	Diagnosis of anemia	0 (0.0%)	1 (0.2%)	Fisher	1.000
Family medical history[#]					
	Diabetes mellitus	1 (0.5%)	7 (1.4%)	0.451	0.502
	Hypertension	7 (3.4%)	19 (3.9%)	0.087	0.768
Present illness[#]					
	Gestational diabetes mellitus	49 (23.8%)	96 (19.5%)	1.612	0.204
	Gestational hypertension	8 (3.9%)	24 (4.9%)	0.328	0.567
	Eclampsia/pre-eclampsia	5 (2.4%)	34 (6.9%)	5.533	0.019
	Group B streptococcal infection	13 (6.3%)	12 (2.4%)	6.303	0.012
	Perinatal anemia	0 (0.0%)	166 (33.7%)	91.191	<0.001
Thyroid treatment during pregnancy Medication[#]					
Take medicine	Uncertain	3 (1.5%)	2 (0.4%)	2.687	0.220
	Yes	180 (87.4%)	425 (86.4%)		
Whether it reaches the standard after medication	Uncertain	21 (11.5%)	43 (10.0%)	1.246	0.536
	Reach the standard	128 (69.9%)	318 (74.5%)		
Delivery mode[#]					
	Eutocia	109 (52.9%)	223 (45.3%)	23.591	<0.001
	Episiotomy	9 (4.4%)	38 (7.7%)		
	Forceps midwifery	0 (0.0%)	2 (0.4%)		
	Transverse section / emergency cesarean section	21 (10.2%)	115 (23.4%)		
	Plan cesarean section	67 (32.5%)	114 (23.2%)		
Neonate[#]					
Sex	Male	119 (57.8%)	274 (55.7%)	0.254	0.614
	Female	87 (42.2%)	218 (44.3%)		
Refuse to transfer treatment		11 (5.3%)	28 (5.7%)	0.034	0.854

Notes: *Median (interquartile range) and Nonparametric Rank Sum Test, [#]Frequency (percentage) and Chi-Square Test.

Nomogram Construction

The training set included the nine screened variables to establish logistic regression models for maternal and neonatal adverse outcomes. Tables 4 and 5 present the model regression coefficients, and the nomograms are shown in Figures 2 and 3.

Model Validation and Evaluation

In this study, a logistic model was developed, and the protocol was analysed for all variables with $p < 0.05$. Therefore, four prediction models for predicting adverse outcomes were established, two for maternal and two for neonatal: logistic-all and logistic-partial variables. Tables 6 and 7 list the results of the model evaluation, where indicators included the AUC, sensitivity, specificity and Brier score. According to the model, the cut-off referred to the prediction probability p:

Table 3 Comparison of Variable Characteristics of Neonatal with or Without Adverse Outcomes

		No Adverse Outcomes (N=538)	Adverse Outcomes (N=160)	Z/χ^2	P
General information on maternity*					
	Age (years)	29 (6)	29 (5)	−0.212	0.832
	Height (cm)	161 (7.0)	162 (7.0)	−0.951	0.341
	Weight (kg)	70 (10.7)	70 (13.8)	−0.659	0.510
	Gestational week of delivery	39 (2)	39 (3)	−1.969	0.049
	Gravidity	1 (1)	1 (2)	−0.378	0.705
	Parity	1 (1)	1 (1)	−0.166	0.868
	Cholesterol (mmol/L)	6.58 (1.47)	6.58 (1.83)	−2.304	0.021
	Platelet (×10⁹/L)	202 (72)	199 (64)	−0.717	0.473
	Hemoglobin (g/L)	120 (14)	118.5 (15)	−1.265	0.206
	Number of hospitalizations	1 (1)	1 (1)	−3.461	0.001
Thyroid function and treatment during pregnancy*					
	Gestational age at diagnosis	25 (20)	20 (29)	−3.257	0.001
	TSH level at diagnosis Gestational age (mU/L)	4.39 (1.2260)	4.3595 (1.4425)	−1.204	0.229
	FT4 level at diagnosis Gestational age (mU/L)	0.7704 (0.1750)	0.7704 (0.2330)	−0.282	0.778
	Number of TSH monitoring during pregnancy	4 (2)	4 (3)	−1.266	0.206
	Time to TSH target if medication (days)	21 (28)	20 (35)	−1.330	0.184
Newborn*	Neonatal Weight (g)	3300 (470)	3240 (1023)	−0.346	0.729
Maternal BMI#					
	Obesity (≥23)	328 (61.0%)	107 (66.9%)	4.941	0.077
	Emaciation (<18.5)	3 (0.6%)	3 (1.9%)		
	Normal (18.5–22.9)	207 (38.5%)	50 (31.3%)		
Mode of conception#					
	Natural conception	507 (94.2%)	146 (91.3%)	1.825	0.177
	Assisted reproduction	31 (5.8%)	14 (8.8%)		
Past medical history (pre-pregnancy)#					
	Diagnosis of thyroid dysfunction	68 (12.6%)	33 (20.6%)	6.354	0.012
	Thyroid dysfunction medication	59 (11.0%)	33 (20.6%)	10.053	0.002
	Diagnosed with diabetes	0 (0.0%)	2 (1.3%)		0.052
	Diagnosed with hypertension	1 (0.2%)	1 (0.6%)		0.406
	Diagnosis of anemia	1 (0.2%)	0 (0.0%)		1.000
Family medical history#					
	Diabetes mellitus	6 (1.1%)	2 (1.3%)	0.000	1.000
	Hypertension	21 (3.9%)	5 (3.1%)	0.208	0.648
Present illness#					
	Gestational Diabetes Mellitus	103 (19.1%)	42 (26.3%)	3.783	0.052
	Gestational hypertension	25 (4.6%)	7 (4.4%)	0.021	0.885
	Eclampsia/pre-eclampsia	26 (4.8%)	13 (8.1%)	2.534	0.111
	Group B streptococcal infection	15 (2.8%)	10 (6.3%)	4.280	0.039
	Perinatal anemia	117 (21.7%)	49 (30.6%)	5.362	0.021
Thyroid treatment during pregnancy Medication#					
Take medicine	Uncertain	3 (0.6%)	2 (1.3%)	2.960	0.204
	Yes	462 (85.9%)	143 (89.4%)		

(Continued)

Table 3 (Continued).

		No Adverse Outcomes (N=538)	Adverse Outcomes (N=160)	Z/χ^2	P
Whether it reaches the standard after medication	Uncertain	52 (11.2%)	12 (8.3%)	2.374	0.305
	Reach the standard	333 (71.5%)	113 (77.9%)		
Delivery mode[#]					
	Eutocia	270 (50.2%)	62 (38.8%)	14.276	0.005
	Episiotomy	27 (5.0%)	20 (12.5%)		
	Forceps midwifery	2 (0.4%)	0 (0.0%)		
	Transverse section / emergency cesarean section	106 (19.7%)	30 (18.8%)		
	Plan cesarean section	133 (24.7%)	48 (30.0%)		
Neonate[#]					
Sex	Male	296 (55.0%)	97 (60.6%)	1.576	0.209
	Female	242 (45.5%)	63 (39.4%)		
Refuse to transfer treatment		19 (3.5%)	20 (12.5%)	18.803	<0.001

Notes: *Median (interquartile range) and Nonparametric Rank Sum Test, #Frequency (percentage) and Chi-Square Test.

Table 4 Logistic Regression Model for Adverse Maternal Outcomes

Independent Variable	B	SE	Z	P	OR	95% CI Lower	95% CI Upper
(Intercept)	3.750	1.782	2.105	0.035	42.541	1.326	1469.157
Age	−0.025	0.032	−0.782	0.434	0.975	0.915	1.039
Gravidity	0.011	0.295	0.038	0.970	1.011	0.565	1.799
Parity	0.484	0.337	1.438	0.150	1.623	0.841	3.160
Number of hospitalizations	−1.976	0.356	−5.556	<0.001	0.139	0.066	0.268
Hemoglobin	−0.013	0.011	−1.171	0.242	0.987	0.965	1.009
Eclampsia/pre-eclampsia	1.132	0.699	1.619	0.105	3.103	0.872	14.741
Pregnancy with group b streptococcus infection	−1.420	0.653	−2.176	0.030	0.242	0.060	0.812
Perinatal anemia	19.093	903.131	0.021	0.983	1.96E+8	5.12E+98	3.22E+167
Delivery mode eutocia	–	–	–	–	–	–	–
Episiotomy/Forceps midwifery	1.275	0.545	2.338	0.019	3.578	1.305	11.534
Transverse section / emergency cesarean section	1.209	0.365	3.316	0.001	3.350	1.676	7.049
Plan cesarean section	0.109	0.284	0.385	0.701	1.115	0.639	1.952

Table 5 Logistic Regression Model for Adverse Neonatal Outcomes

| Independent Variable	B	SE	Z	P	OR	95% CI Lower	95% CI Upper
(Intercept)	−0.250	0.694	−0.360	0.719	0.779	0.199	3.039
Gestational week of delivery	2.142	0.467	4.585	<0.001	8.515	3.497	22.315
Cholesterol	−0.144	0.093	−1.545	0.122	0.866	0.720	1.038
Number of hospitalizations	−0.297	0.270	−1.100	0.271	0.743	0.441	1.274
Gestational age at diagnosis	−0.012	0.012	−1.010	0.312	0.988	0.966	1.011
Previous thyroid dysfunction	−13.942	590.126	−0.024	0.981	<0.001	NA	3.15E+18
Previous medication for thyroid dysfunction	14.203	590.126	0.024	0.981	1.47E+6	<0.001	NA
Pregnancy with group b streptococcus infection	1.429	0.508	2.811	0.005	4.175	1.499	11.315
Perinatal anemia	0.283	0.272	1.039	0.299	1.327	0.770	2.244
Delivery mode eutocia	–	–	–	–	–	–	–
Episiotomy/Forceps midwifery	1.059	0.438	2.415	0.016	2.882	1.185	6.714
Transverse section / emergency cesarean section	−0.034	0.318	−0.106	0.915	0.967	0.509	1.783
Plan cesarean section	−0.109	0.302	−0.361	0.718	0.897	0.489	1.606
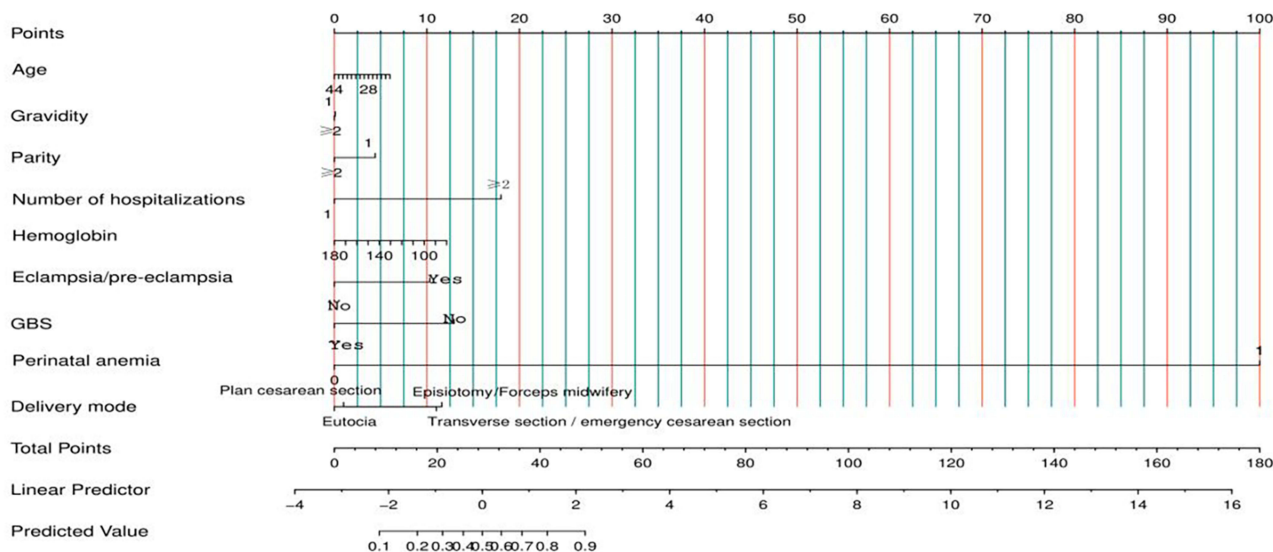
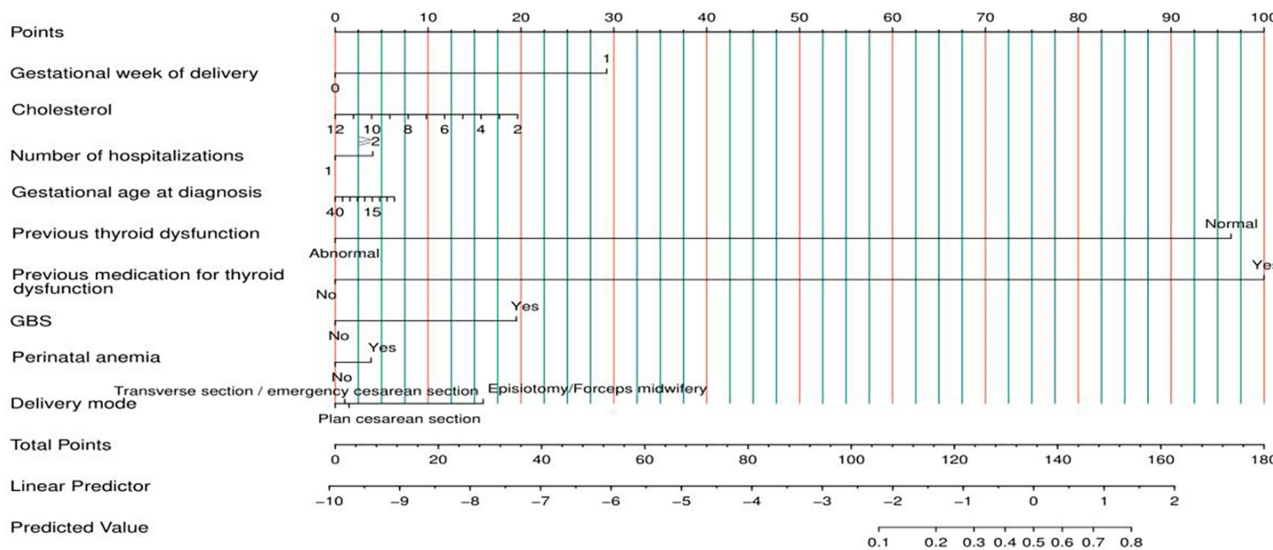**Figure 2** Nomogram of adverse maternal outcomes.

Figure 3 Nomogram of adverse neonatal outcomes.

if $p \geq$ Cut-off, the prediction was positive; otherwise, the prediction was negative. Figures 4–6 depict the ROC, calibration and DCA curves, respectively.

The AUC of the ROC curve of the partial variable nomogram for the parturient and neonates demonstrated good discriminatory ability. Regarding the maternal model (Table 6), the AUC of the logistic-partial variables model in the

Table 6 Discrimination and Calibration of Predictive Models for Adverse Maternal Outcomes

Model	Model	AUC	Cut-off	Sensitivity	Specificity	Brier Score	95% CI
Training sets (N=488)	Logistic-all variables	0.869	0.703	0.730	0.864	0.135	0.839–0.900
	Logistic-partial variables	0.845	0.755	0.666	0.905	0.147	0.811–0.879
Validation set (N=210)	Logistic-all variables	0.765	0.769	0.570	0.864	0.180	0.699–0.830
	Logistic-partial variables	0.779	0.687	0.669	0.780	0.169	0.717–0.842

Notes: Discrimination indicators include AUC, sensitivity and specificity. The measurement of calibration refers to the Brier score.

Table 7 Discrimination and Calibration of Prediction Models for Adverse Neonatal Outcomes

Model	Model	AUC	Cut-off	Sensitivity	Specificity	Brier Score	95% CI
Training sets (N=488)	Logistic-all variables	0.735	0.188	0.702	0.680	0.143	[0.680–0.789]
	Logistic-partial variables	0.685	0.229	0.500	0.818	0.148	[0.622–0.747]
Validation set (N=210)	Logistic-all variables	0.776	0.222	0.714	0.727	0.156	[0.702–0.849]
	Logistic-partial variables	0.787	0.193	0.732	0.714	0.150	[0.716–0.857]

Notes: Discrimination indicators include AUC, sensitivity and specificity. The measurement of calibration refers to the Brier score.

training set was 0.845 [95% CI: 0.811–0.879], and that of the logistic-partial variables model in the validation set was 0.779 [95% CI: 0.717–0.842], which was higher than the AUC value of the logistic-all variables model (0.765 [95% CI: 0.699–0.830]). Concerning the neonatal model (Table 7), the AUC of the logistic-partial variables model in the validation set was 0.787 [95% CI: 0.716–0.857], higher than the AUC value of the logistic-all variables model (0.776 [95% CI: 0.702–0.849]).

The calibration of both models showed that the predicted probabilities were close to the actual observations and that the calibration of the partial variables model was better (Figure 5). We used a quantitative calibration measure, the Brier score, with values ranging from 0 to 0.25. The closer the Brier score to 0, the better the model calibration; when the score equals 0.25, the model has no predictive power.[18] Regarding the maternity model (Table 6), the Brier score was 0.169 for the logistic-partial variables model in the training set, lower than the Brier score of 0.18 for the logistic-all variables model in the training set. Concerning the neonatal model (Table 7), the Brier score of 0.150 for the logistic-partial variables model in the training set was lower than the Brier score of 0.156 for the logistic-all variables model in the training set.

The entire range threshold of the DCA curve analysis model is 0–1. The DCA curve (Figure 6B) illustrated that the clinical benefit of the logistics-partial variables model was greater than that of the logistics-all variables model when the probability exceeded 0.5 in the validation group. Moreover, the clinical benefit of the logistics-partial variables model (Figure 6D) was greater than that of the logistics-all variables model when the probability exceeded 0.4 in the validation group. Regarding clinical decision-making, if the maternal nomogram predicted a probability higher than the cut-off value (0.755) and the newborn nomogram predicted a probability greater than the cut-off value (0.229), it was advisable to provide active therapy based on the significant net benefit (Tables 6 and 7).

Discussion

Using conveniently collected clinical data of 698 pregnant women with hypothyroidism, predictive models for maternal and neonatal adverse outcomes were developed and validated. The final models for predicting the risk of maternal and neonatal adverse outcomes included several routine variables, such as number of hospitalisations, GBS and delivery mode. Both models demonstrated high levels of predictive discrimination in the derivation and validation cohorts. The pregnant participants were assessed by the model during antenatal examinations in primary health care, and those at risk were recommended to be transferred to tertiary centres for appropriate management and further care.

The logistic regression model for adverse maternal outcomes identified the mode of delivery, which encompassed lateral episiotomy / forceps delivery as well as caesarean section / emergency caesarean section, as the independent risk factor. Compared with normal labour, the risk of adverse outcomes of lateral episiotomy / forceps delivery was 3.578 times higher than that of normal labour, whereas the risk of adverse outcomes of antegrade caesarean section / emergency caesarean section was 3.35 times higher than that of normal labour. The logistic regression model identified gestational age and lateral incision / forceps delivery as the independent risk variables for adverse neonatal outcomes. Conversely, neonates delivered via lateral episiotomy / forceps exhibited a 2.882-fold increased risk of adverse outcomes in comparison to those delivered via natural delivery. In this study, mothers who experienced adverse results had a higher proportion of deliveries that were not vaginal compared to those who did not experience adverse outcomes (54.7% vs 47.1%, respectively). Similarly, a greater percentage of neonates with adverse outcomes were delivered non-vaginally compared to those without adverse outcomes (61.2% vs 49.8%, respectively). These findings were consistent
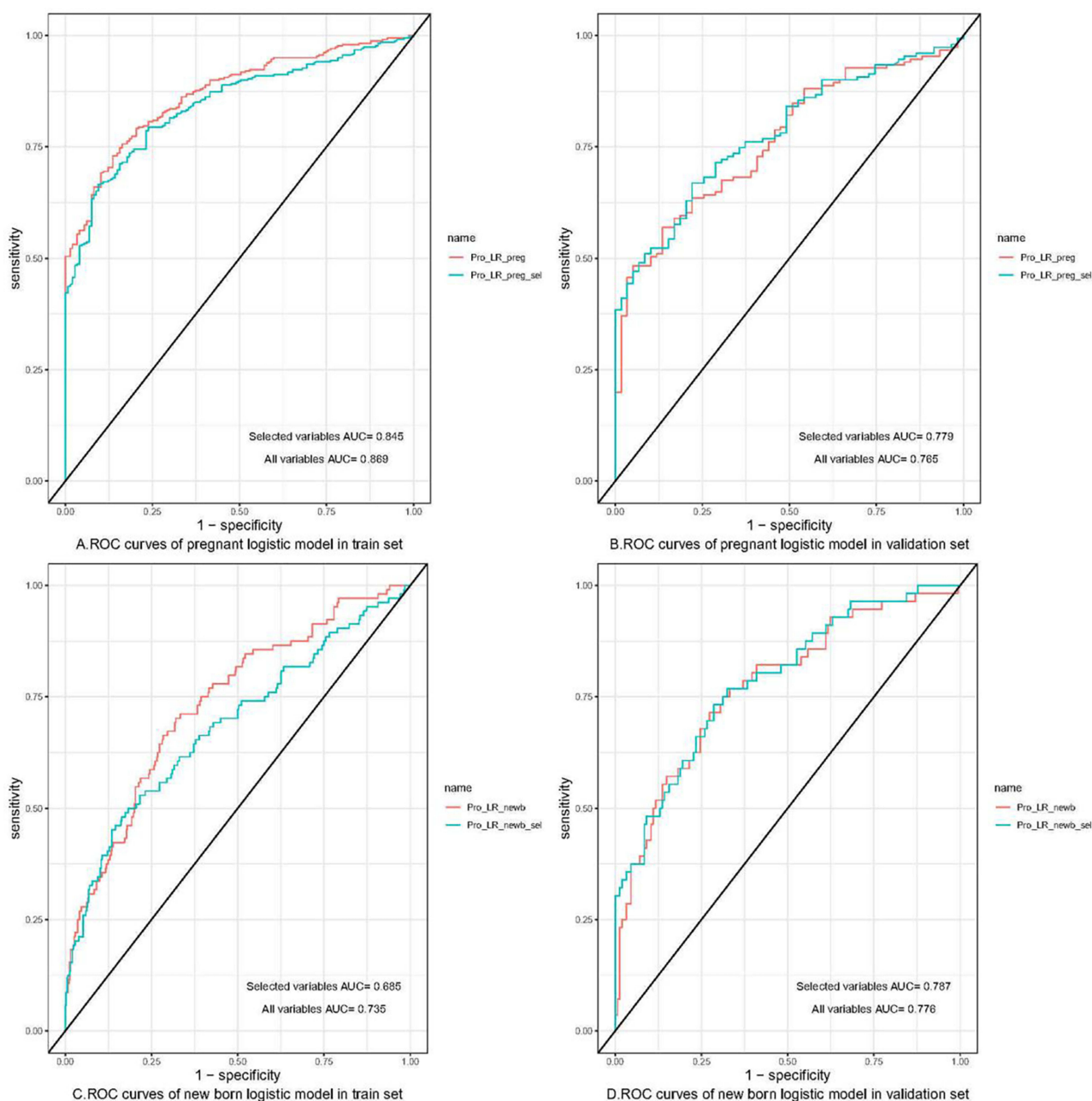
Figure 4 ROC curve of logistic regression model for adverse outcomes. (**A**) Training set-adverse maternal outcomes; (**B**) Validation set-adverse maternal outcome; (**C**) Training set-neonatal adverse outcomes; (**D**) Validation set-neonatal adverse outcome.

Abbreviations: Pro_LR_preg, Logistic regression model for adverse maternal outcomes with all variables included; Pro_LR_preg_sel, Logistic regression model for adverse maternal outcomes including variables with p <0.05; Pro_LR_newb; Logistic regression model for adverse neonatal outcomes with all variables included; Pro_LR_newb_sel, Logistic regression model for adverse neonatal outcomes including p <0.05 variables.

with Gil Rosen[19] and Katia Vella.[20] Patients with hypothyroidism and isolated hypothyroidism exhibit a greater prevalence of delivery by lower segment caesarean section than the general population, and more newborns with congenital hypothyroidism (CH) are born by vaginal delivery or caesarean section. Erol et al emphasised that thyroid dysfunction occurring early in pregnancy may affect foetal and placental growth.[21] When there are negative outcomes, such as foetal distress and placental dysfunction, it is clinically recommended to use either vaginal midwifery or emergency caesarean section. This helps to quickly remove the neonate from the unsuitable environment in the uterus and prevents adverse outcomes for the newborn. This is one of the reasons why the proportion of negative outcomes for
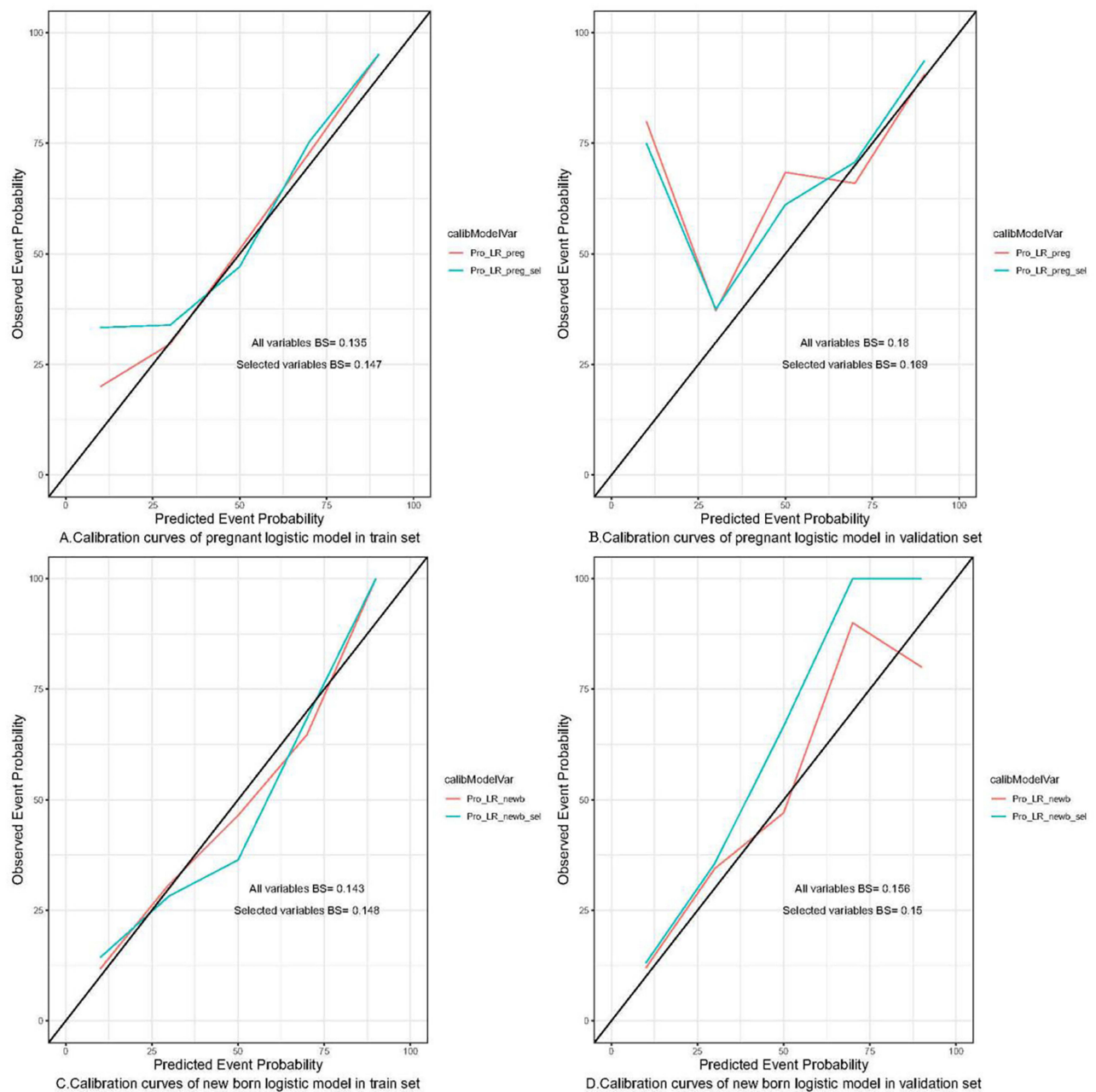
Figure 5 Calibration curve for logistic regression model for adverse outcomes. (**A**) Training set-adverse maternal outcomes; (**B**) Validation set-adverse maternal outcome; (**C**) Training set-neonatal adverse outcomes; (**D**) Validation set-neonatal adverse outcome.
Abbreviations: Pro_LR_preg, Logistic regression model for adverse maternal outcomes with all variables included; Pro_LR_preg_sel, Logistic regression model for adverse maternal outcomes including variables with $p <0.05$; Pro_LR_newb, Logistic regression model for adverse neonatal outcomes with all variables included; Pro_LR_newb_sel, Logistic regression model for adverse neonatal outcomes including $p <0.05$ variables.

newborns in this study was low (22.9%), suggesting that it is imperative to prioritise the monitoring and management of postpartum complications related to hypothyroidism and neonatal thyroid function.

The present study found that preterm birth is both an adverse outcome and an independent risk factor for neonatal outcomes. There is compelling data from recent decades indicating a significant correlation between hypothyroidism during pregnancy and preterm birth.[22] Currently, while the likelihood of premature infants surviving has been on the rise, there has also been a steady increase in the occurrence of CH each year.[23,24] However, due to the immaturity of the hypothalamic–pituitary–thyroid axis in preterm infants, CH diagnosed by TSH assessment in heel blood screening may
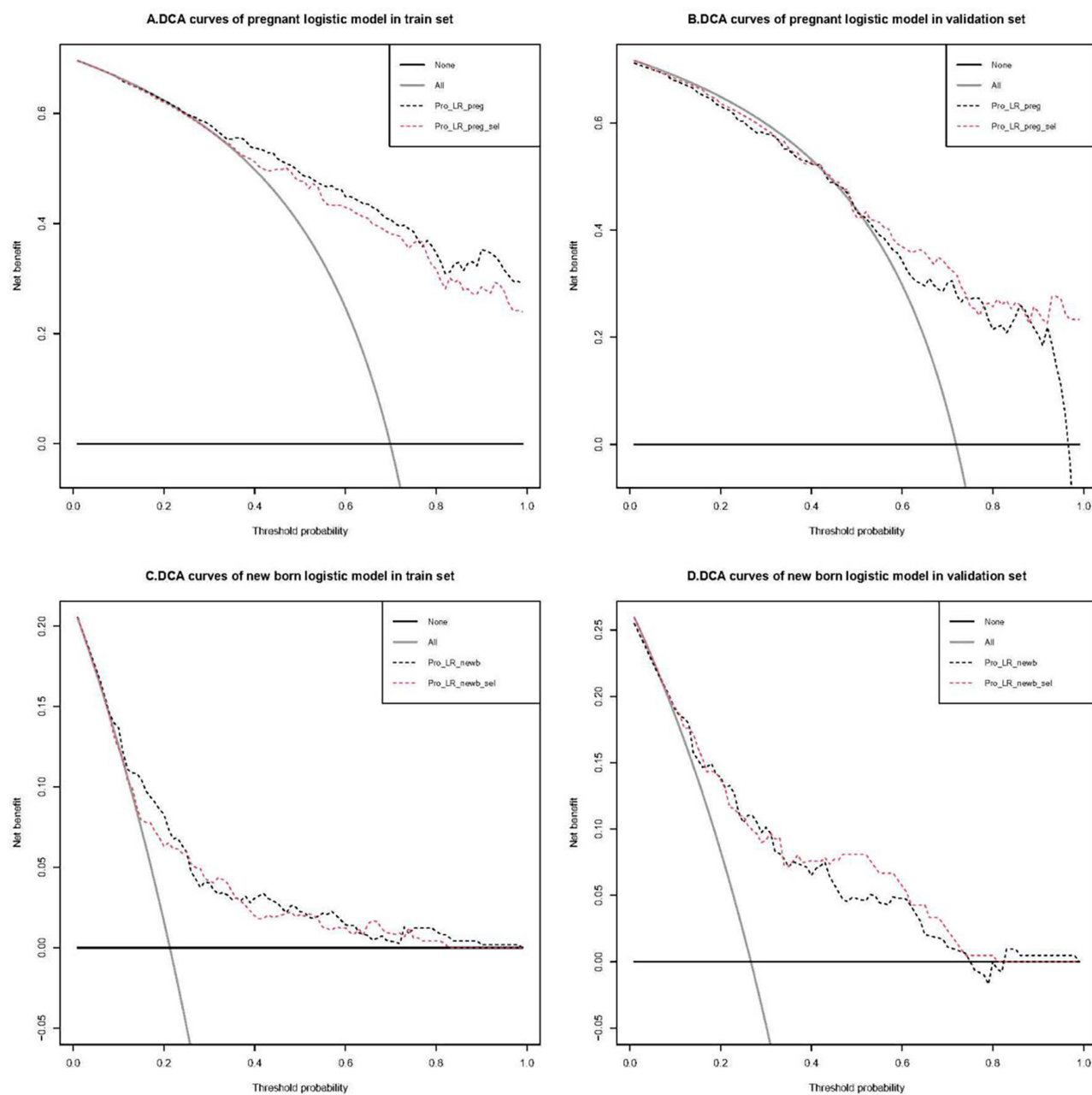
Figure 6 DCA curve from logistic regression model for adverse outcomes. (**A**) Training set-adverse maternal outcomes; (**B**) Validation set-adverse maternal outcome; (**C**) Training set-neonatal adverse outcomes; (**D**) Validation set-neonatal adverse outcome.

Abbreviations: Pro_LR_preg, Logistic regression model for adverse maternal outcomes with all variables included; Pro_LR_preg_sel, Logistic regression model for adverse maternal outcomes, including variables with p <0.05; Pro_LR_newborn, Logistic regression model for adverse neonatal outcomes with all variables included; Pro_LR_newborn selection, Logistic regression model for adverse neonatal outcomes including p <0.05 variables.

be overlooked.[23] Furthermore, TSH levels may be elevated, so it is necessary to repeat screening for CH in premature infants after a short-term treatment and maintain long-term follow-up and regular monitoring.[25]

The present analysis revealed that the number of hospitalisations during pregnancy and pregnancy with GBS were independent safety factors for adverse maternal outcomes. Multiple hospitalisations during pregnancy reduced the risk of adverse maternal outcomes by 0.139 times compared with one hospitalisation. Within the general population, 25.4% of hospitalisations were due to repeated occurrences, 9.9% were caused by threatening preterm labour or abortion, and 5.4% were a result of premature labour. Clinically, pregnant women who experience threatening premature delivery or abortion, such as premature membrane rupture, are typically admitted to the hospital for tocolysis treatment. This

intervention aims to prevent or delay labour contractions and ultimately improve the outcome of the pregnancy. Consequently, the number of hospitalisations is increased. Nevertheless, the probability of adverse pregnancy results could potentially enhance adherence to treatment among pregnant women who decline hospitalisation.

In this study, the pregnant women who had GBS had a 0.242-fold reduced risk of adverse outcomes compared to those who did not. Among the most common invasive diseases in both pregnant women and newborns, GBS can cause bacteraemia, meningitis, pneumonia and urinary tract infections.[26] Previous studies have found no association between GBS and thyroid dysfunction.[27] Conversely, the present study showed that the presence of GBS in the pregnant women with hypothyroidism was associated with a reduced maternal adverse outcome. However, more trials are required to investigate the association between pregnancy and hypothyroidism, GBS and pregnancy outcome.

Anaemia is also a common complication of pregnancy. The foetus requires large amounts of iron, folic acid and other nutrients from the mother for its own growth and development. Inadequate iron supplementation can lead to anaemia during pregnancy, impairing foetal intelligence, miscarriage, preterm delivery and other serious complications. Although the causal relationship between thyroid dysfunction and anaemia remains unclear, most studies have demonstrated that hypothyroidism is associated with higher anaemia prevalence.[28–30] In this study, the results showed that perinatal anaemia was a risk factor of maternal and neonatal adverse outcomes in pregnant women with hypothyroidism. Therefore, monitoring and controlling perinatal anaemia contribute to the prevention of adverse outcomes of hypothyroidism in pregnancy.

This research had various limitations, such as reliance on a singular centre, a small cohort size and the possibility of selection bias. The sample size of the validation cohort was comparatively small, and the populations of the training and validation cohorts were distinct. While the validation exhibited satisfactory calibration, its validation effectiveness was constrained. In addition, to obtain the highest possible level of evidence in clinical practice, each nomogram should demonstrate validity in prospective randomised clinical trials, leading to further generalisation in primary health care. Finally, it is imperative to conduct larger prospective multicentre studies involving pregnant patients with hypothyroidism to precisely identify the risk factors that are linked to unfavourable outcomes for both the mother and the infant.

Conclusions

In this study, two models to predict the risk probability of maternal and neonatal adverse outcomes in pregnant women with hypothyroidism were developed and validated. According to DCA, using this model to stratify pregnancies involving hypothyroidism could enhance maternal and neonatal outcomes, facilitate clinician decision-making and provide clinical utility. Therefore, clinicians should actively evaluate pregnant women through this model during pregnancy. Pregnant women at high risk of hypothyroidism should be timely intervention and whole-process supervision.

Statement Covering Patient Data Confidentiality

In order to protect patients' personal information and maintain the security of Jiangnan University Affiliated Hospital's patient information, we are committed to fulfilling our obligation to keep patients' personal information confidential.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Jiangnan University Affiliated Hospital, and the requirement for obtaining informed consent was exempted due to retrospective with minimal risk nature of the study. Ethic Reference Number: (JNU20230301IRB02).

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Disclosure

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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