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ORIGINAL RESEARCH

Estimating the Risk of Insulin Requirement in Women Complicated by Gestational Diabetes Mellitus: A Clinical Nomogram

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Purpose: This study sought to develop a nomogram for the prediction of insulin requirement in a Chinese population with gestational diabetes mellitus (GDM).

Materials and Methods: We performed a retrospective cohort study involving 626 Chinese women with GDM, of whom 188 were treated with insulin. "Least absolute shrinkage and selection operator" regression was used to optimize the independent predictors of insulin requirement during pregnancies complicated with GDM. Cox proportional hazards regression analysis was performed to establish a prediction model incorporating the selected predictors, and the nomogram was constructed to achieve individual prediction. The C-index, calibration plot and decision curve analysis were used to validate the model.

Results: Maternal age, family history of type 2 diabetes mellitus in a first-degree relative, a prior GDM history, fasting plasma glucose, hemoglobin A1c, gestational age, and body mass index values at the time of GDM diagnosis were the risk factors for insulin treatment. The model displayed medium predictive power with a C-index of 0.77 (95% confidence interval: 0.73–0.81) and relatively good calibration accuracies. The decision curve demonstrated a positive net benefit with a threshold between 0.09 and 0.70.

Conclusion: The findings suggest that our nomogram, incorporating seven indicators, is useful in predicting individualized survival probabilities of insulin requirement.

Keywords: pregnancy, glycemic control, insulin therapy, prediction

Introduction

Gestational diabetes mellitus (GDM), one of the most common complications during pregnancy, potentially causes short-term and long-term adverse effects in both the mother and offspring.[1] It has been reported that GDM affects 8–19.7% of pregnancies in China due to the increased obesity rate and growth of the childbearing age.[1,2] Current guidelines have recommended that controlling blood glucose levels should be the primary goal in managing women with GDM.[2–4] Diet and lifestyle interventions are the mainstay of GDM treatment. When the basic intervention fails, drug therapy is initiated to achieve the desired glucose level.[2] It has been reported that 20–30% of pregnancies complicated by GDM require drug treatment.[5] To date, insulin is the only drug that has been approved by the Food and Drug Administration for use in glycemic control during pregnancy and by almost all guidelines.[2–4]

Various risk factors underlying the introduction of insulin therapy in GDM have been reported, including higher fasting glucose levels, abnormal blood glucose

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levels from 75-g oral glucose tolerance tests (OGTT), hemoglobin A1c (HbA1c) concentration at diagnosis, an early gestational age at diagnosis, obesity, and family history (FH) of diabetes.[6–10] The timely and proper treatment of GDM can reduce the risk of complications significantly[3] and avoid the financial burden caused by overtreatment. The use of risk factors to identify patients at risk of insulin requirement may be effective if their diagnostic value is specified appropriately in a statistical model.

Nomograms are used in predicting survival as well as determining individualized therapy planning and follow-up intervals. A nomogram for the prediction of insulin requirement during the treatment of early-diagnosed GDM in the Brazilian population has been developed.[11] However, different populations have different risk profiles, and the previous nomogram was exclusively for the prediction of insulin requirement in early-diagnosed GDM without survival-time (gestational age at initiation of insulin therapy) prediction. In the present study, we aimed to construct a nomogram for the estimation of individualized survival probabilities of insulin requirement in Chinese GDM patients.

Materials and Methods

Participants and Data

An observational, retrospective cohort study was conducted using clinical and laboratory data from electronic medical charts of pregnant women with hyperglycemia who underwent prenatal care at the Endocrinology Outpatient Clinic of Shengjing Hospital of China Medical University between May 2016 and December 2019. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Shengjing Hospital affiliated to China Medical University (Approval number: 2016PS360K). All the participants provided written informed consent for the viewing of their medical records.

According to the Chinese Current Care Guidelines for GDM, GDM was diagnosed if one or more of the following pathological glucose values in a 75-g OGTT were presented at any time during pregnancy: 5.1 mmol/L≤ fasting plasma glucose (FPG) <7.0 mmol/L, 1-h plasma glucose (1hPG) ≥10.0 mmol/L, or 8.5 mmol/L≤ 2-h plasma glucose (2hPG) <11.1 mmol/L.[12] Additionally, we included women with praecox GDM diagnosed by abnormal FPG before 24 gestational weeks.

Eligible women were requested to self-monitor blood glucose after receiving lifestyle-intervention counseling. An individualized balanced diet on the basis of pre-gestational BMI and regular physical activity were recommended to all patients. The recommended physical activity included aerobic and resistance exercises for less than 45 mins per day. Insulin therapy was administered in the event of uncontrolled glucose (capillary fasting blood glucose >3.3–5.3 mmol/L, 1-h postprandial blood glucose <7.8 mmol/L, and 2-h postprandial blood glucose <6.7 mmol/L). The retrospective cohort study included 2308 women: women with a reported diagnosis of overt diabetes mellitus during pregnancy or pregestational diabetes mellitus (PGDM) (n=1629), multifetal pregnancies (n=41), and missing multiple data (n=12) were excluded. Finally, a total of 626 singleton pregnant women with GDM, aged 20 years or older, were included for further analysis.

The following maternal information was collected from the medical records: last menstrual period, insulin therapy, maternal age, gestational age at GDM diagnosis, weight at GDM diagnosis, pregestational weight, height, a history of polycystic ovary syndrome (PCOS), gravity, parity, an FH of type 2 diabetes mellitus (T2DM, defined as a first- or second-degree relative with T2DM), a history of GDM in a prior pregnancy, a history of macrosomia in a prior pregnancy, use of assisted reproductive technology (ART), glycated albumin and HbA1c at GDM diagnosis, value of blood glucose measurement that resulted in the diagnosis, survival status (insulin therapy or lifestyle intervention), and survival time (gestational age at initiation of insulin therapy)/follow-up time in days. The follow-up time of patients not on insulin therapy defaulted to 280 days (40 weeks). Data on pregnancy and neonatal adverse outcomes were collected through postpartum follow-up visits (12–14 weeks after delivery): prenatal weight, delivery time and methods, insulin dosage at the end of pregnancy, insulin requirement after delivery, birth weight and sex of newborns, and adverse neonatal outcomes. Data on variable adverse neonatal outcomes included mortality, malformations, neonatal intensive care requirement, hypoglycemia, pathologic jaundice, and respiratory distress. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Low-birth-weight infant and macrosomia referred to newborns with birth weight <2500 g and >4000 g, respectively.

Statistical Analysis

The Shapiro test was used to determine the normal distribution of each variable and Levene's test to assess

homogeneity. Quantitative variables are presented as mean ± standard deviation, whereas qualitative variables are presented as counts and/or percentages. Associations between quantitative variables were assessed using the Student's *t*-test or the Mann–Whitney *U*-test. Qualitative variables were compared using the Chi-square test. The least absolute shrinkage and selection operator (LASSO) is a linear regression model penalized with the L1 norm and widely used in variable selection in the field of medicine due to its tendency to prefer solutions with fewer non-zero coefficients.[13,14] Lambda is a tuning parameter that controls the number of coefficients with a value of zero. To select the optimal lambda value, 10-fold K cross-validations for the centralization and normalization of selected variables were run using R software. We constructed a forest plot to describe the P-value, hazard ratio, and 95% confidence interval (CI) of selected validation visually. Subsequently, Cox proportional hazards (CPH) regression analysis was performed to establish a prediction model by introducing the variables based on the LASSO regression, and the nomogram was constructed to achieve individual predictions. The concordance index (C-index) was used to evaluate the predictive accuracy of the prediction model, which ranges from 0.5 (completely random prediction) to 1 (perfect prediction).[15] Internal validation was analyzed using a bootstrapping approach and by randomly repeating 1000 times with replacement. Calibration was visually examined using a calibration curve. To determine the clinical usefulness of the nomogram, decision curve analysis was applied to GDM patients by quantifying the net benefits at different threshold probabilities. Data processing and statistical analyses were performed using R software (version 4.0.3). LASSO regression, Cox regression, nomogram development, and validation were conducted using "glmnet," "survival," and "rms" packages, respectively. P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

All data for the patients on insulin therapy (n = 188) and those implementing simple lifestyle interventions (n = 438), including demographics, physical examination results, and biochemical test results, are presented in Table 1. The mean gestational age for insulin initiation was 23.4 ± 9.1 gestational weeks, and 22.3% of the women started insulin therapy once they were diagnosed. Compared to women with simple lifestyle interventions, those on insulin therapy were more likely to be older, have a family history of diabetes, be using ART, and have a significantly higher pre-pregnancy BMI as well as a higher BMI at GDM diagnosis. FPG, 1hPG, and HbA1c at the time of GDM diagnosis were significantly higher in the insulin group than in the lifestyle-intervention group. A total of 155 women attended the postpartum follow-up visit, of whom 44 were treated with insulin during pregnancy. Information on pregnancy and neonatal outcomes are reported in Table 2. At the end of pregnancy, the mean insulin dosage was 52.5 ± 55.3 IU per day, and 5 patients discontinued insulin. Most patients discontinued insulin after delivery, and only 2 patients continued to require insulin. Patients on insulin therapy terminated pregnancy earlier and had higher rates of cesarean sections as well as preterm births. One neonatal death, one neonatal hypoglycemia, and two malformations were recorded in the insulin group. Furthermore, there were no significant differences in maternal weight at delivery and no other adverse neonatal outcomes.

Variable Selection

Based on LASSO regression analysis, seven potential predictors had nonzero coefficients, and the coefficient of lambda was 0.02831 (Figure 1). These variables included maternal age, gestational age at GDM diagnosis, BMI at GDM diagnosis, FH of T2DM in first-degree relative, history of GDM, FPG, and HbA1c. The results of the CPH regression analysis based on 406 subjects (excluding data missing any of the seven foregoing features) are presented in Figure 2.

Development of an Individualized Prediction Model

A model incorporating maternal age, gestational age at GDM diagnosis, BMI at GDM diagnosis, FH of T2DM in first-degree relative, history of GDM, FPG, and HbA1c was developed and presented as a nomogram (Figure 3). The C-index of the nomogram was 0.77 (95% CI: 0.73–0.81).

Calibration Results and Clinical Use

The probability of 40-week survival (where insulin therapy was not initiated until the 40th week of pregnancy) was accurately predicted from the calibration curve (Figure 4). The decision curve analysis for the 40-week survival nomogram is presented in Figure 5.

Table 1 Characteristics of GDM Patients with and without Insulin Therapy

	Insulin Group (n = 188)	Lifestyle-Intervention Group (n = 438)	*P value*
Maternal age (years)	32.2 ± 4.2***	30.9 ± 3.9	<0.001
Pregestational BMI (kg/m^2)	25.5 ± 4.6***	24.0 ± 4.1	<0.001
BMI at diagnosis (kg/m^2)	27.7 ± 5.0***	25.9 ± 4.4	<0.001
History of PCOS, n (%)	34 (18.1)	62 (14.2)	0.211
Gravity, n (%) 1 2 ≥3	 84 (44.7) 48 (25.5) 56 (29.8)	 219 (50.0) 111 (25.3) 108 (24.7)	0.607
Parity, n (%) 0 1 ≥2	 148 (78.7) 38 (20.2) 2 (1.1)	 362 (82.6) 70 (16.0) 6 (1.4)	0.475
Gestational age at diagnosis of GDM (days)	129.7 ± 62.7***	153.1 ± 54.0	<0.001
Gestational age at initiation of insulin therapy (days)	163.7 ± 64.0	-	
Insulin treatment started at diagnosis of GDM, n (%)	42 (22.3%)	-	
FH of T2DM, n (%) In first-degree relative In second-degree relative	* 54 (28.7) 44 (23.4)	 101 (23.1) 83 (19.0)	0.017
History of GDM, n (%)	19 (10.1)	29 (6.6)	0.128
History of macrosomia, n (%)	6 (3.2)	6 (1.4)	0.125
Use of ART, n (%)	34 (18.1)*	52 (11.9)	0.038
FPG (mmol/L)	5.8 ± 0.6***	5.4 ± 0.5	<0.001
1hPG (mmol/L)	10.5 ± 1.6**	9.9 ± 1.8	0.003
2hPG (mmol/L)	8.7 ± 1.7	8.4 ± 1.5	0.059
HbA1c (%)	5.6 ± 0.5***	5.3 ± 0.4	<0.001
GA (%)	12.4 ± 2.1	12.5 ± 1.9	0.757

Notes: Values are presented as mean ± SD or number (percentage). *P < 0.05; **P < 0.01; ***P < 0.001.
Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; FH, family history; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; ART, assisted reproductive technology; FPG, fasting plasma glucose; 1hPG, 1-h plasma glucose; 2hPG, 2-h plasma glucose; HbA1c, hemoglobin A1c; GA, glycated albumin.

The decision curve revealed that our model demonstrated a positive net benefit with a threshold between 0.09 and 0.70, without increasing the number of false positives.

A dynamic nomogram of a random patient was established to predict the risk of insulin therapy (Figure 6). The patient features were as follows: age = 35 years, gestational age at GDM diagnosis = 160 days, BMI at GDM diagnosis = 28 kg/m^2, GDM history = yes, first-degree FH of T2DM = no, FPG = 6.1 mmol/L, and HbA1c = 5.4%. Therefore, this tool provides an individualized estimate of insulin usage during pregnancy and should be useful to patients and healthcare providers in counseling patients regarding treatment decisions and follow-up. The team developed a dynamic nomogram online software to facilitate the clinical use of this nomogram (https://doctordu.shinyapps.io/insulin_risk_in_gdm/).

Discussion

Nomograms, which integrate diverse risk predictors and directly reflect the relative importance of predictors, allow for the seamless incorporation of risk prediction into clinical

Table 2 Comparison of Pregnancy and Neonatal Outcomes

Outcomes	Insulin Group (n = 44)	Lifestyle-Intervention Group (n = 111)	*P value*
Gestational age at delivery (days)	261.0 ± 24.6*	271.4 ± 9.9	0.010
Cesarean section (%)	79.5*	63.1	0.048
Weight at delivery (kg)	79.8 ± 1.6	77.8 ±13.8	0.453
Insulin dosage at end of pregnancy (IU/d)	52.5 ± 55.3	–	
Insulin requirement after delivery (n)	2	–	
Gender of newborns (Female) (%)	37.8	45.7	0.411
Birth weight of newborns (g)	3168.8 ± 719.0	3405.3 ± 552.2	0.068
Preterm birth (%)	25.0**	9.0	0.009
Macrosomia (>4000 g) (%)	7.5	12.3	0.411
Low-birth-weight infant (<2500 g) (%)	7.5	5.7	0.680
Mother death (n)	0	0	-
Neonatal death (n)	1	0	-
Neonatal hypoglycemia (n)	1	0	-
Neonatal intensive care unit need (%)	6.8	4.5	0.557
Malformation (n)	2	0	-
Respiratory distress (%)	4.5	3.6	0.784
Other neonatal adverse outcomes (n)	0	0	-

Notes: Values are presented as mean ± SD, number or percentage. *P < 0.05; **P < 0.01.

decision making. Nomograms are widely used as personalized risk-prediction tools, with user-friendly digital interfaces and increased accuracy. This is the first study to develop a nomogram for predicting individualized survival probabilities of insulin requirement in Chinese GDM patients. In the present study, the nomogram incorporated seven risk factors, including maternal age, gestational age at GDM diagnosis, BMI at GDM diagnosis, FH of T2DM in first-degree relative, history of GDM, FPG, and HbA1c. Once diagnosed, the nomogram could stratify GDM patients in need of more frequent follow-up and more medical resources according to accessible risk factors. Its prediction was supported by the C-index (0.77), calibration, and decision curve. The use of a 0.09–0.70 threshold to identify individuals at high risk of requiring insulin therapy among pregnant women with GDM always had a positive net benefit.

In our study, the percentage of insulin requirement among patients with GDM was 30.3%, which is consistent with that in previous studies.[11,16–18] Many studies have been performed to identify risk indicators for insulin requirement among GDM patients,[7,10,19] including a previous study by our group.[9] Only a few studies have integrated multiple indicators in a prediction model or scoring system in order to predict the risk of insulin requirement of every GDM-complicated pregnancy individually. Sapienza et al[8] developed a scoring system to establish the probability of insulin therapy in pregnant women with GDM based on pre-pregnancy BMI, FH of diabetes, number of abnormal 100-g/3-h OGTT values, and HbA1c concentration. Several indicators were consistent with ours (eg, FH of diabetes and HbA1c concentration). In this scoring system, all the factors were evaluated equally, ignoring the magnitudes of the various risk indicators. A prediction model based on maternal age, pre-pregnancy BMI, FBG value, prior GDM, and FH of diabetes was developed from a retrospective cohort study in the Brazilian population.[11] Similarly, they also suggested maternal age, FBG value, prior GDM, and FH of diabetes as indicators of insulin requirement. However, the study focused exclusively on the need for insulin therapy in women with early GDM diagnosis, thereby ignoring GDM development in later trimesters. Considering the influence of ethnicity on the development of GDM, the model had reduced applicability to other populations.

According to our results, FPG and HbA1c at the time of GDM diagnosis were important predictors of insulin requirement, which is consistent with previous findings.[6,8,10,20] However, a risk-stratification approach based solely on baseline measures of glycemia had reportedly exhibited poor predictive utility.[20] Factors such as maternal age, FH of diabetes, BMI at GDM diagnosis, and a prior GDM history have also been reported to increase the probability of insulin therapy.[11,19] We also observed that women with early-diagnosed GDM were more likely to require insulin

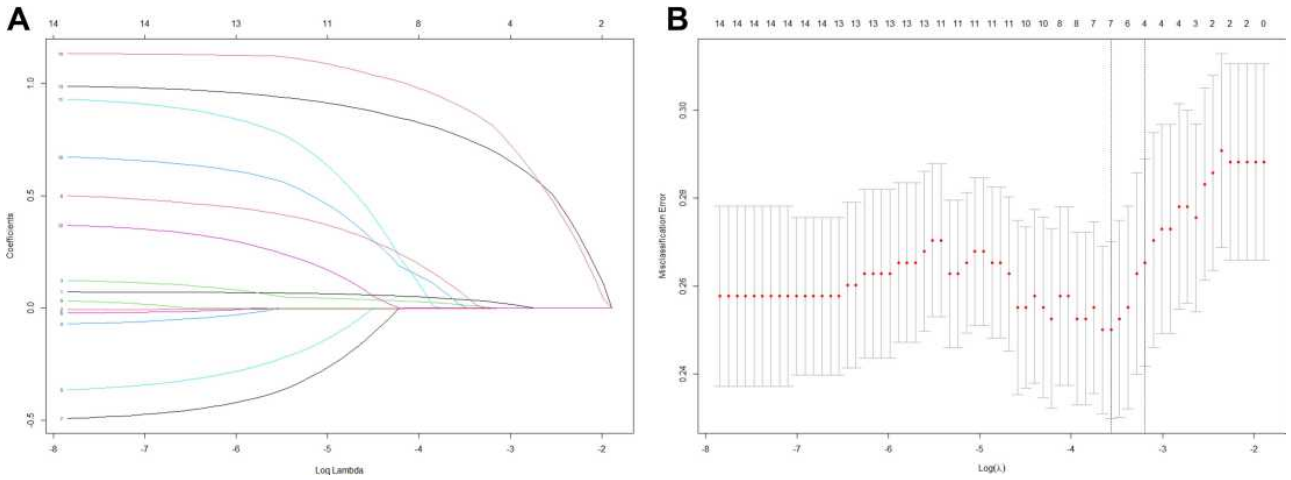

Figure 1 Feature selection using LASSO regression (**A**) LASSO coefficient profile plot was produced against the log(lambda). (**B**) The misclassification error curve was plotted versus log(lambda) to verify the optimal lambda value. The dotted vertical line left represents the optimal lambda value that gives minimum mean cross-validated error. The dotted vertical line right indicates the largest value of lambda such that error is within 1 standard error of the minimum. Seven features with nonzero coefficients were selected by optimal lambda.

intervention, which corroborates the findings of Alunni et al.-[21] Evidently, it would be imprecise to evaluate the risk of insulin requirement using isolated risk factors while ignoring individual differences. Our study quantified the above factors in a statistical prediction model, which we converted to a clinically usable nomogram that potentially illustrates the extent to which individual risk indicators contribute to the risk of insulin requirement. As depicted in our example, a 35-

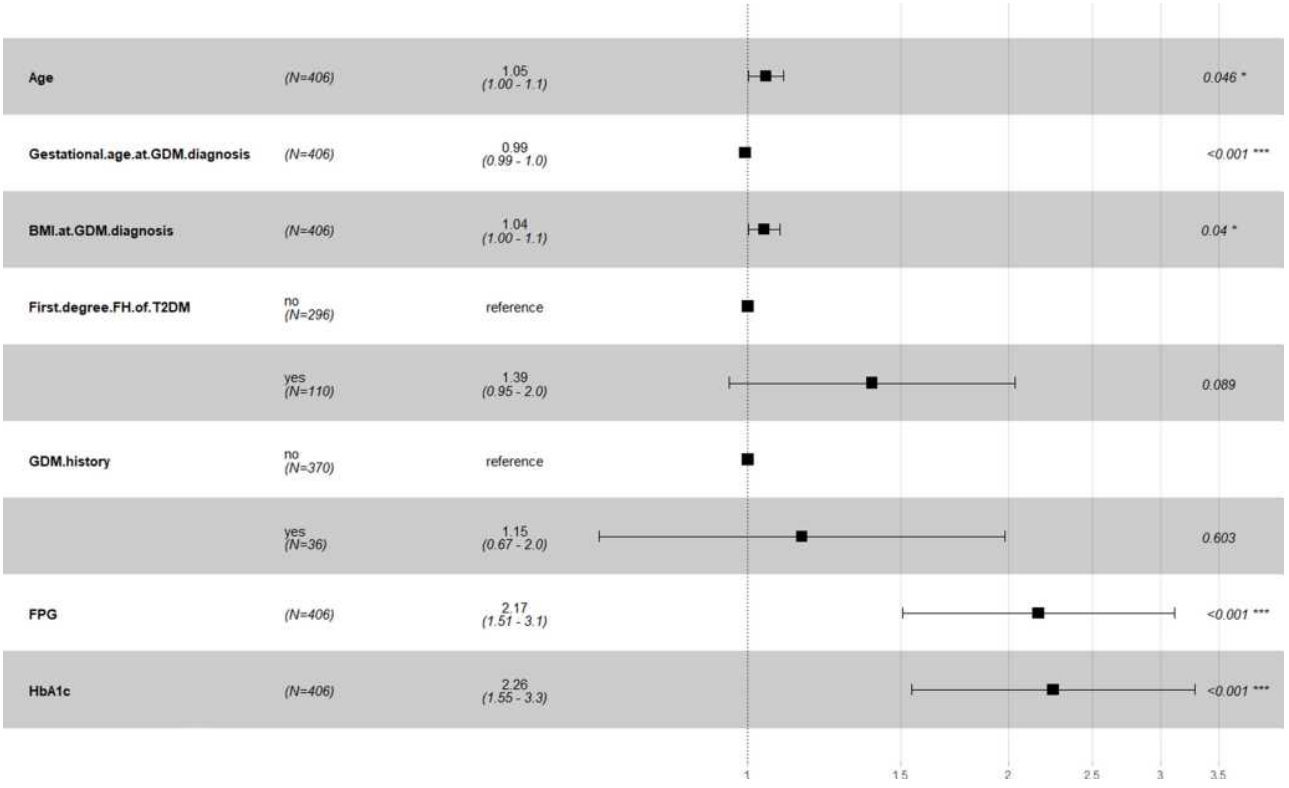

Figure 2 The forest plot of the seven predictors selected using LASSO regression. The forest plot of the hazard ratio (95%confidence interval) and *P*-value of the selected features. *$P < 0.05$; ***$P < 0.001$.

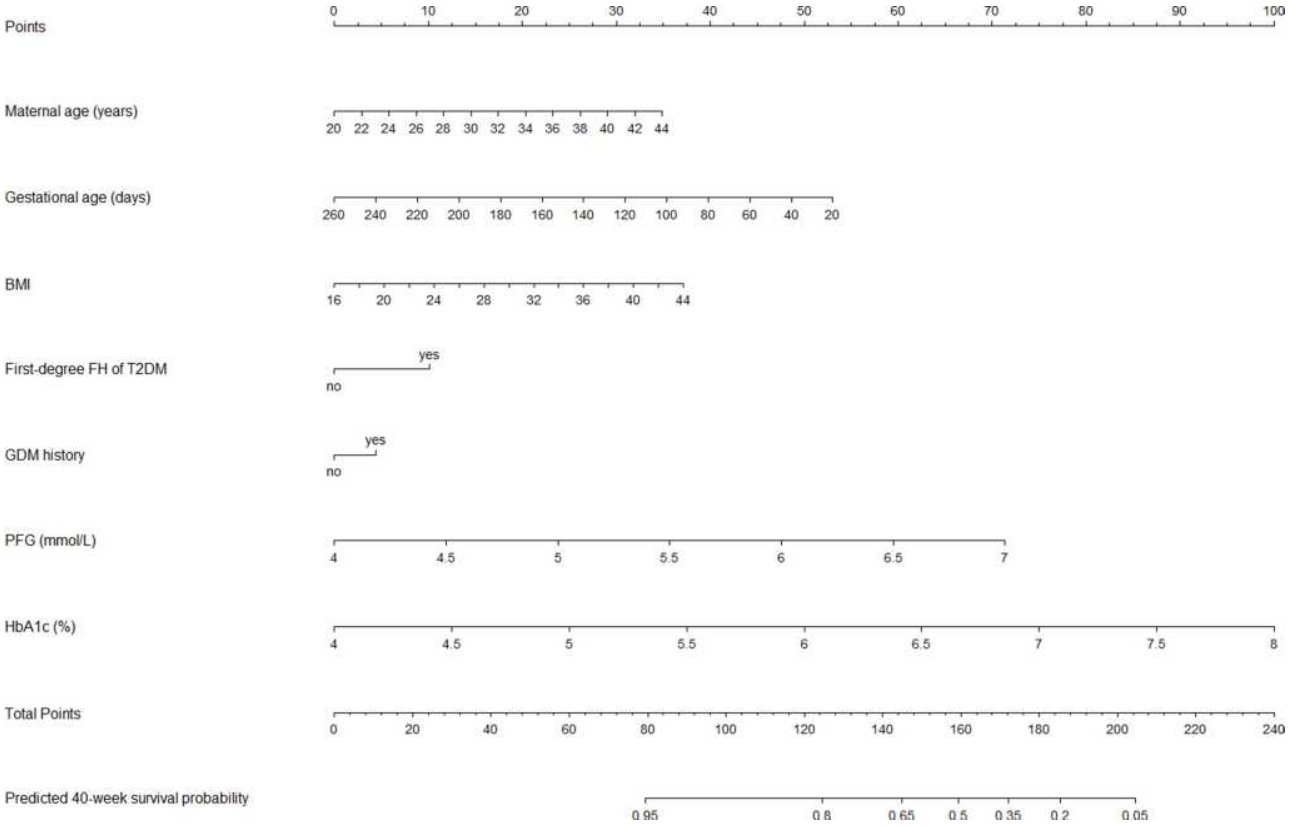

Figure 3 Nomogram for the prediction of insulin requirement in patients with GDM.

year-old woman with 6.1 mmol/L FBG, 5.4% HbA1c, and 28 kg/m^2 BMI was diagnosed with GDM at 160 days of gestation, with a prior GDM history, and no first-degree FH of T2DM; hence, she may have a 61% probability of requiring insulin therapy. This is the first study to predict individualized survival probabilities of insulin requirement while accounting for the determination of the follow-up interval required and medical-resource allocation.

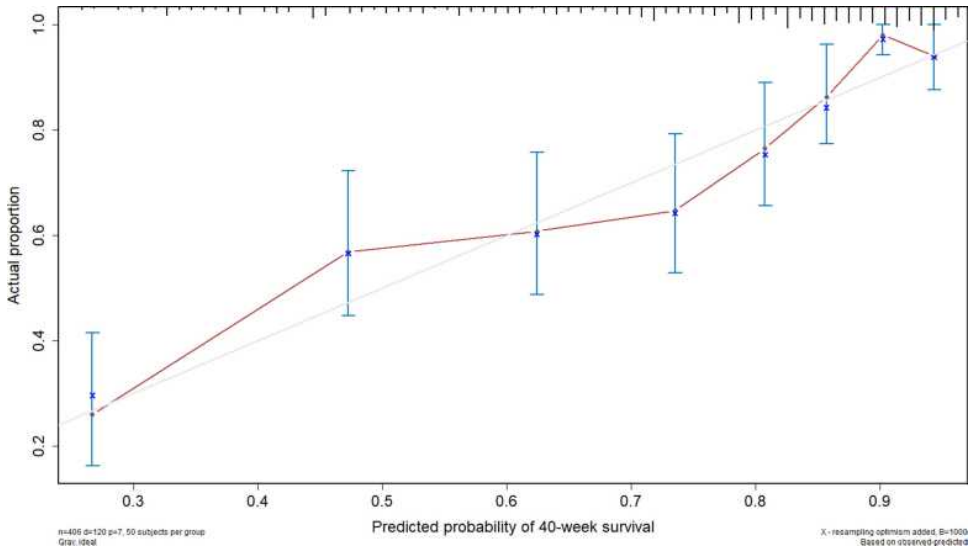

Figure 4 The calibration results. The x-axis represents the nomogram-predicted survival probability of insulin requirement. The y-axis represents the actual proportion of insulin therapy. The grey line represents an ideal calibration line. The red line represents the performance of the nomogram, of which a more favorable performance is reflected by a closer fit to the ideal calibration line.

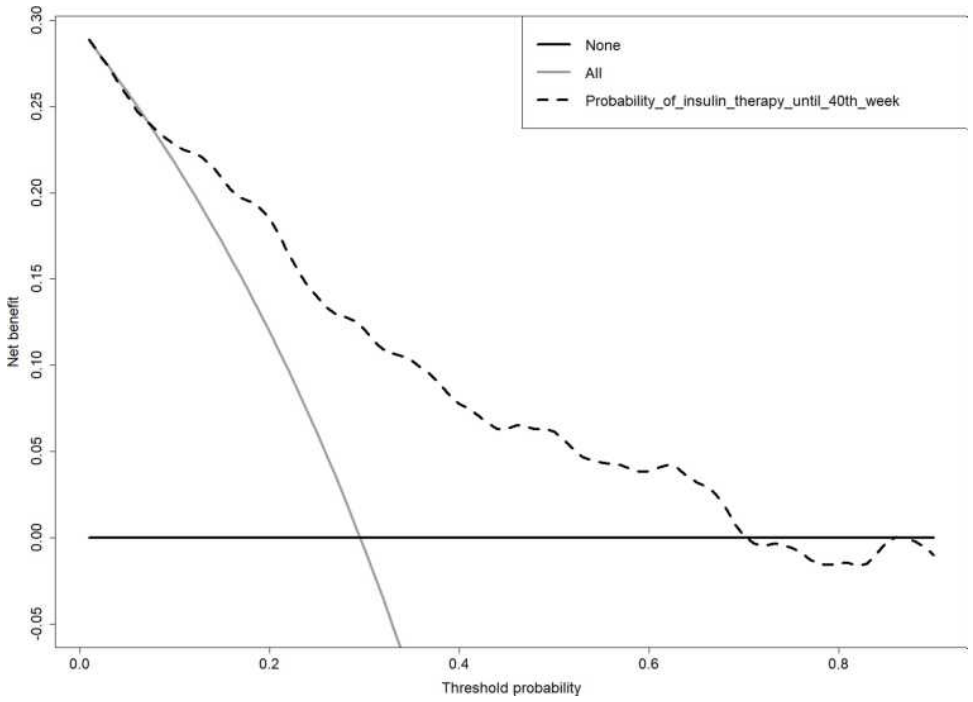

Figure 5 Decision curve analysis. The solid black line represents the net benefit when no one is at risk of requiring insulin therapy. The solid grey line indicates the net benefit when all are at risk of requiring insulin treatment. The dashed line represents the nomogram. The y-axis represents the net benefit.

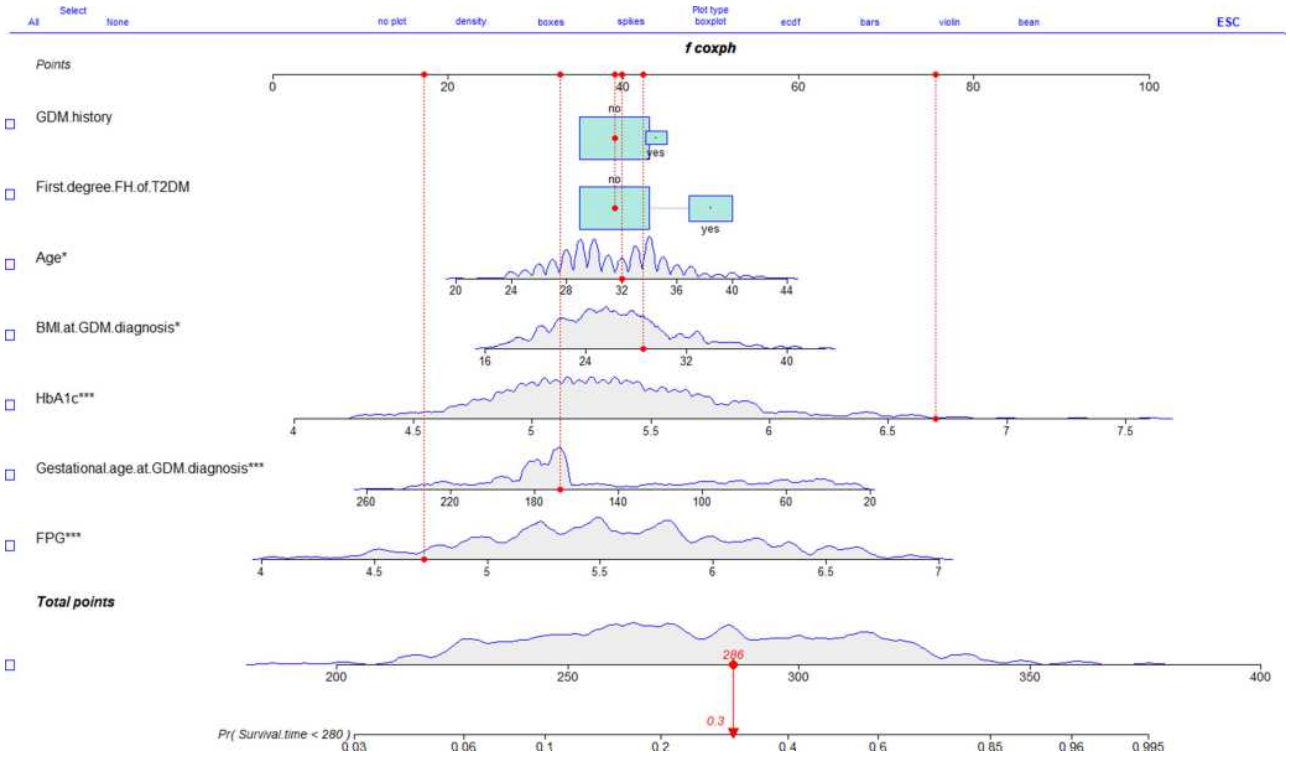

Figure 6 Dynamic nomogram. A GDM patient was randomly selected from the population, and the risk of insulin therapy was predicted on the basis of the 7 characteristic indicators of the nomogram. The indicators with statistical differences between the two groups were marked with asterisk. *$P < 0.05$; ***$P < 0.001$.

The present study has some limitations. The risk-factor analysis did not include all potential factors that affect insulin requirement during pregnancy due to data loss owing to incomplete medical records. Further, our study involved a single-center cohort, which was not representative of the entire Chinese GDM population. Further external evaluation of the nomogram in large-scaled, multicenter-study populations is imperative.

Conclusion

We developed a nomogram for the prediction of insulin requirement in a Chinese population with GDM. The nomogram, which incorporated seven indicators, including maternal age, gestational age at GDM diagnosis, BMI at GDM diagnosis, FH of T2DM in first-degree relative, history of GDM, FPG, and HbA1c, potentially illustrates the extent to which the individual risk indicators contribute to the risk of requiring insulin therapy.

Data Sharing Statement

The processed data are available from the corresponding author upon reasonable request.

Acknowledgments

The authors thank all the physicians at the Department of Endocrinology, Shengjing Hospital of China Medical University, for their assistance in recruiting participants.

Funding

The study was supported by the Clinical Research Project of Liaoning Diabetes Medical Nutrition Prevention Society (grant number LNSTNBYXYYFZXH-RS01A). The sponsor is one of the corresponding authors of this study.

Disclosure

The authors report no conflicts of interest in this work.

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