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ORIGINAL RESEARCH

A Simplified Screening Model to Predict the Risk of Gestational Diabetes Mellitus in Pregnant Chinese Women

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ABSTRACT

Introduction: This study aimed to develop a simplified screening model to identify pregnant Chinese women at risk of gestational diabetes mellitus (GDM) in the first trimester.

Methods: This prospective study included 1289 pregnant women in their first trimester (6–12 weeks of gestation) with clinical parameters and laboratory data. Logistic regression was performed to extract coefficients and select predictors. The performance of the prediction model was assessed in terms of discrimination and calibration. Internal validation was performed through bootstrapping (1000 random samples).

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Results: The prevalence of GDM in our study cohort was 21.1%. Maternal age, prepregnancy body mass index (BMI), a family history of diabetes, fasting blood glucose levels, the alanine transaminase to aspartate aminotransferase ratio (ALT/AST), and the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) were selected for inclusion in the prediction model. The Hosmer–Lemeshow goodness-of-fit test showed good consistency between prediction and actual observation, and bootstrapping indicated good internal performance. The area under the receiver operating characteristic curve (ROC-AUC) of the multivariate logistic regression model and the simplified clinical screening model was 0.825 (95% confidence interval [CI] 0.797–0.853, $P < 0.001$) and 0.784 (95% CI 0.750–0.818, $P < 0.001$), respectively. The performance of our prediction model was superior to that of three other published models.
Conclusion: We developed a simplified clinical screening model for predicting the risk of GDM in pregnant Chinese women. The model provides a feasible and convenient protocol to identify women at high risk of GDM in early pregnancy. Further validations are needed to evaluate the performance of the model in other populations.
Trial Registration: ClinicalTrials.gov identifier: NCT03246295.

Keywords: Gestational diabetes mellitus; Prediction model; Early pregnancy; Predictors

Key Summary Points

Why carry out this study?

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and the prevalence of GDM has increased in the past few years. However, a feasible method to screen GDM risk in early pregnancy is lacking.

We aimed to develop a convenient clinical prediction model to identify pregnant women at high risk of GDM in early pregnancy that could be applicable in most areas of China.

What was learned from the study?

Three clinical characteristics (maternal age, prepregnancy body mass index, and a family history of diabetes) and three laboratory parameters (fasting blood glucose level, the triglyceride to high-density lipoprotein cholesterol ratio, and the alanine transaminase to aspartate aminotransferase ratio) in the first trimester were selected and used to develop a simplified clinical screening model. The model showed good discrimination (ROC-AUC 0.784, 95% confidence interval 0.750–0.818, $P < 0.001$) and calibration.

The simplified prediction model in our study provided a simple and feasible tool to predict the risk of GDM in early pregnancy. The performance of our prediction model was superior to that of three other published models, and our prediction model would be applicable in pregnant Chinese women.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common complication of pregnancy and is defined as a condition of glucose intolerance that is first diagnosed during pregnancy [1]. The prevalence of GDM has increased globally in the past few years, possibly because of the rapid societal transitions in nutrition and lifestyles. GDM affects up to 15% of pregnant women worldwide, whereas it affects 18.3–25% of pregnant women in Southeast Asia, demonstrating the higher prevalence of GDM in China [2–4]. Accumulating evidence indicates that GDM can not only increase the risk of perinatal complications (pregnancy-induced hypertension, preeclampsia, stillbirth, etc.) but also lead to

chronic health problems for offspring later in life, including diabetes mellitus, metabolic syndrome, and cardiovascular diseases [5, 6].

According to the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria, the diagnosis of GDM is based on the results of a 2-h, 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation [7]. However, pregnant women with GDM could have hyperglycemia for a longer period of time, even during the first trimester of pregnancy; thus, the diagnosis of GDM at 24–-28 weeks of gestation might be retrospective and may not completely reverse the adverse effects on both mothers and their offspring [2]. Therefore, it is essential to predict the risk of GDM in early pregnancy to improve the hyperglycemic environment.

Several risk factors, including advanced maternal age, prepregnancy body mass index (preBMI), a family history of diabetes mellitus, and glucose and lipid profiles in early pregnancy, have been applied for the early identification of GDM [8–10]. Based on our previous work, the triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C), alanine transaminase (ALT) to aspartate aminotransferase (AST) ratio (ALT/AST), and hepatic steatosis index (HSI) are independent risk factors for GDM [11, 12]. In recent years, other novel biomarkers have been reported as potential predictors, including angiopoietin-like protein 8 and plasma fatty acid-binding protein 4 [13, 14]. The use of individual biochemical markers has shown relatively poor sensitivity and specificity and, thus, combinations of risk factors have been taken into consideration for predicting the risk of GDM. Several studies explored the utility of preBMI combined with fasting blood glucose (FBG) in the first trimester as risk factors to predict the risk of GDM [15–17]. However, there were no unified cutoff values among different studies, which limited the practicability of these combined risk factors. Because of the similar pathogenesis between GDM and type 2 diabetes mellitus (T2DM), several genetic variants related to insulin secretion (including glucokinase [GCK] and melatonin receptor 1B [MTNR1B]) and insulin resistance (including insulin receptor substrate 1 [IRS1] and peroxisome proliferator-activated receptor gamma [PPARG]) have been found to be associated with GDM [18]. Although the role of genetic variants in the prediction of GDM risk has been discussed, the conclusions are inconsistent [19, 20]. To achieve early identification of the risk of GDM, there has been a rapid development of prediction models based on sociodemographic characteristics and laboratory data. However, these predictors are mostly evaluated during the second trimester (after 12 weeks of gestation), and it is uncertain whether the models developed by other regions are applicable to Chinese women [21, 22]. In addition, some of the prediction models are too complex, and the variables included in the models are not routinely tested during pregnancy [23].

The aim of the present study was to develop a convenient clinical prediction model to identify pregnant women at high risk of GDM in early pregnancy. A mathematical formula was first established by logistic regression analysis, and then a simplified screening model was derived. The diagnostic utility of our prediction model was compared with that of other published GDM prediction models.

METHODS

Ethical approval

Written informed consent was obtained from each participant, and the study was performed in accordance with the Declaration of Helsinki as revised in 2013. This study was part of an ongoing prospective double-center observational cohort study initiated in 2019, which was conducted at Haidian District Maternal and Child Health Care Hospital and Chaoyang District Maternal and Child Health Care Hospital (Beijing, China) (ClinicalTrials.gov: NCT03246295). The Ethical Review Committee of National Center for Women and Children's Health, Chinese Center for Disease Control and Prevention in Beijing, China approved this study on 3 April 2019 (approval number: FY2019-01).

Participants

Singleton pregnant women aged > 18 years were recruited to the study at their first prenatal visit during the first trimester of pregnancy (between 6 and 12 weeks). The inclusion criteria were: (1) < 12 weeks gestation, and the ability to follow-up regularly; (2) natural conception; (3) no medication use before or during pregnancy, except for vitamins; and (4) agreement to participate in the study and to provide a signed consent form. The exclusion criteria were: (1) twin or multiple pregnancy; (2) impaired glucose tolerance or diabetes mellitus before pregnancy; (3) severe chronic diseases or infectious diseases (e.g., liver disease, kidney failure, cardiovascular disease, autoimmune disease, hematological disease, AIDS, and other diseases before pregnancy); and (4) the inability to understand and complete the study. The enrollment flow chart is shown in Electronic Supplementary Material (ESM) Fig. 1. Because a previous study revealed that an FBG level ≥ 6.1 mmol/L in early pregnancy could predict the risk of GDM with a specificity of 100%, participants with an FBG level ≥ 6.1 mmol/L at the first visit were excluded from our study [10]. Baseline anthropometric and sociodemographic characteristics of the eligible women were collected at the first visit.

Clinical and Laboratory Measurements

Body height and weight were measured, and the BMI was calculated as (weight [kg])/(height [m])^2. Body weight, systolic blood pressure and diastolic blood pressure were measured at each follow-up visit. Blood pressure was measured twice at 5-min intervals using an automatic BP monitor and averaged.

Laboratory tests were performed at the first visit. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as (FBG [mmol/L] × fasting insulin [μU/mL])]/22.5 [24]. All participants were offered a 2-h, 75-g OGTT between 24 and 28 weeks of gestation for GDM screening. GDM was diagnosed according to the 2010 IADPSG criteria [25]. Overall, 1289 pregnant women were included in the present study. All available data were recorded and verified by two investigators simultaneously.

Data were collected on the following pregnancy outcomes from electronic medical records: gestational age at birth, type of delivery, infant birth weight, and the 10-min Apgar score. Preterm delivery was defined as delivery before gestational week 37 [26]. Large for gestational age (LGA) and small for gestational age (SGA) were defined as birth weights above the 90th percentile and below the 10th percentile of the mean weight for gestational age and sex, respectively [27]. Delivery data were available for 1064 of the 1289 participants.

Statistical Analysis

Missing data accounted for < 10% of all data, and were handled by multiple imputations of 5. Continuous variables are presented as the mean ± standard deviation if normally distributed and as medians (interquartile range) if nonnormally distributed; categorical variables are presented as percentages. Categorical variables were evaluated using the Pearson Chi-squared test (χ^2). Comparisons between outcome groups for continuous variables were assessed by two-sample Student's *t*-test or the Mann–Whitney *U*-test as appropriate.

Univariate and multivariate logistic regression analyses were performed to identify the risk factors for GDM by computing diagnostic odds ratios (ORs) and their 95% confidence intervals (95% CIs). A backward stepwise entry procedure was used to preliminarily select the variables to be retained in the multivariate logistic regression model with a statistical significance cutoff of $P = 0.05$. The variables included in the predictive model were selected on the basis of the Akaike information criterion. The coefficient estimates in the prediction model were normalized to construct a simplified GDM screening model. The diagnostic accuracy of the GDM prediction model and simplified screening model were evaluated by receiver operating characteristic (ROC) analysis. The optimal cutoff values were defined by obtaining the maximum Youden index

calculated by the following formula: (sensitivity + specificity) − 1 [28]. The area under the curve (AUC) with the 95% CI, sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were used as measures of overall performance. Calibration was evaluated by the Hosmer–Lemeshow goodness-of-fit test and internally validated with bootstrapping (1000 random samples) to reduce overfitting bias. Statistical analyses were performed using the IBM SPSS statistical program (version 26.0; SPSS IBM Corp, Armonk, NY, USA),, GraphPad Prism (version 9.5.1, GraphPad Software, San Diego, CA, USA), and R software (version 4.3.1, packages Hmisc, rms, and caret; R Foundation for Statistical Computing, Vienna, Austria). A P value of < 0.05 (two-tailed) was considered to be statistically significant.

The similar methodologies described in this study have been presented in our previous work [29].

RESULTS

Clinical and Laboratory Characteristics

Of the 1289 participants enrolled in the present study, 272 (21.1%) developed GDM. The maternal and pregnancy characteristics of all participants are shown in Table 1. Compared to those in the normal glucose tolerance (NGT) group, women in the GDM group were older and heavier ($P < 0.05$). A family history of diabetes and a history of adverse pregnancy did not significantly differ between the two subgroups. The majority of participants in this study were nulliparous (64.0% and 72.4% for the GDM and NGT groups, respectively), but more women with GDM were multiparous ($P = 0.024$). Women who developed GDM had significantly higher levels of FBG and HOMA-IR in the first trimester of pregnancy ($P < 0.01$); in addition, other metabolic measures, including ALT, the ALT/AST ratio, and lipid profiles (TC, TG, HDL-C, low-density lipoprotein-cholesterol [LDL-C] levels, and the TG/HDL-C ratio) were also significantly different between the two groups ($P < 0.05$). Regarding pregnancy outcomes, most of the participants had a term delivery, and there was no significant difference in the incidence of preterm delivery between the GDM and NGT groups. However, the proportion of LGA was higher in the GDM group than in the NGT group (5.4% vs. 2.0%, respectively; $P = 0.006$).

Predictors of GDM

The potential predictors of GDM were included in the logistic regression analysis. All clinical variables were included, and laboratory variables in early pregnancy were screened to simplify the prediction model (the FBG was substituted for the HOMA-IR, the ALT/AST ratio was substituted for the ALT and AST levels, respectively, and the TG/HDL-C ratio was substituted for other lipid measures). After using the backward (LR) method for preliminary predictor selection, five variables remained in the model, including two clinical variables and three laboratory variables. Although a family history of diabetes was not significantly different between the GDM and NGT subgroups in our cohort, it has been reported to be an important risk factor for GDM in previous studies [9]. Therefore, we added a family history of diabetes to the prediction model. The univariate and multivariate logistic regression analyses for the final six variables are presented in Table 2, including the coefficients (β), ORs (95% CIs), and P values. Except for family history of diabetes, maternal age (adjusted OR 1.070, 95% CI 1.027–1.114), preBMI (adjusted OR 1.607, 95% CI 1.484–1.739), FBG (adjusted OR 1.881, 95% CI 1.425–2.482), the ALT/AST ratio (adjusted OR 3.345, 95% CI 1.969–5.683), and the TG/HDL-C ratio (adjusted OR 1.754, 95% CI 1.204–2.553) remained independent factors associated with GDM.

Based on the above variables included in the multivariate regression analysis, a prediction model was established. The probability (P) of GDM could be calculated according to the following formula: Logit $P = -18.263 + (0.067 \times$ maternal age [years]) $+ (0.474 \times$ preBMI [kg/m^2]) $- (0.088 \times$ family history of diabetes [1 if yes, 0 if no]) $+ (0.632 \times$ FBG [mmol/L]) $+ (1.208 \times$ ALT/AST) $+ (0.562 \times$ TG/HDL-C). ROC

Table 1 Baseline characteristics and pregnancy outcomes of the pregnant women enrolled in the study

Characteristics	NGT (n = 1017)	GDM (n = 272)	P value
Maternal baseline information			
Age (years)	30.0 [28.0, 32.0]	32.0 [29.0, 34.0]	< **0.001****
preBMI (kg/m^2)	21.0 [19.5, 22.5]	22.9 [21.3, 25.0]	< **0.001****
Gravidity			
1	559 (55.0%)	134 (49.3%)	0.246
2	263 (25.9%)	79 (29.0%)	
≥ 3	195 (19.2%)	59 (21.7%)	
Parity			
0	736 (72.4%)	174 (64.0%)	**0.024***
1	269 (26.5%)	93 (34.2%)	
≥ 2	12 (1.2%)	5 (1.8%)	
Family history of diabetes	138 (13.6%)	47 (17.3%)	0.121
History of adverse pregnancy[a]	99 (9.7%)	32 (11.8%)	0.325
Laboratory data between 6 and 12 weeks of pregnancy			
FBG (mmol/L)	4.4 [4.1, 4.8]	4.7 ± 0.6	< **0.001****
HOMA-IR	1.2 [0.8, 1.6]	1.8 [1.1, 2.4]	< **0.001****
ALT (U/L)	12.1 [9.8, 16.4]	15.0 [11.0, 19.6]	< **0.001****
AST (U/L)	16.0 [14.0, 18.2]	16.0 [14.0, 18.1]	0.634
ALT/AST	0.8 [0.6, 0.9]	0.9 [0.8, 1.2]	< **0.001****
TC (mmol/L)	3.9 [3.4, 4.5]	4.1 [3.7, 4.6]	**0.019***
TG (mmol/L)	0.8 [0.6, 1.1]	1.0 [0.8, 1.4]	< **0.001****
HDL-C (mmol/L)	1.5 ± 0.3	1.43 [1.2, 1.6]	**0.003****
LDL-C (mmol/L)	1.9 [1.6, 2.3]	2.2 [1.8, 2.6]	< **0.001****
TG/HDL-C	0.6 [0.4, 0.7]	0.7 [0.5, 1.0]	< **0.001****
75-g OGTT between 24 and 28 weeks of pregnancy			
Fasting glucose OGTT (mmol/L)	4.6 [4.4, 4.8]	5.1 [4.8, 5.3]	< **0.001****
1 h glucose OGTT (mmol/L)	7.2 [6.3, 8.2]	9.7 [8.5, 10.5]	< **0.001****
2 h glucose OGTT (mmol/L)	6.3 [5.6, 6.9]	8.2 ± 1.5	< **0.001****
Characteristics in the third trimester of pregnancy (n = 1064)			
SBP (mmHg)	117.0 [110.0, 120.0]	116.5 [110.0, 120.0]	**0.004****
DBP (mmHg)	72.0 [70.0, 80.0]	72.0 [70.0, 80.0]	**0.043***
Preterm delivery[b]	27 (3.2%)	13 (5.8%)	0.07
Birth weight (g)	3290 [3000, 3530]	3350 [3023, 3608]	0.128

Table 1 continued

Characteristics	NGT (n = 1017)	GDM (n = 272)	P value
LGA	17 (2.0%)	12 (5.4%)	**0.006****
SGA	19 (2.3%)	4 (1.8%)	0.663

Data are presented as a number (n) with the percentage in parentheses, as the median with the interquartile range (IQR) in square brackets, or as the mean ± standard deviation (SD)

NGT Normal glucose tolerance, *GDM* gestational diabetes mellitus, *preBMI* prepregnancy body mass index, *FBG* fasting blood glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALT/AST* ALT-to AST ratio *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG/HDL-C* TG-to HDL-C ratio, *OGTT* oral glucose tolerance test, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LGA* large for gestational age (defined as a birth weight > 90th percentile of the mean weight for gestational age), *SGA* small for gestational age (defined as a birth weight < 10th percentile of the mean weight for gestational age)

*, **Significant difference between subgroups at $^{*}P < 0.05$ and $^{**}P < 0.01$

[a]Defined as embryo damage, spontaneous abortion, or preterm delivery in a previous pregnancy

[b]Defined as delivery at < 37 completed weeks of gestation

analysis in this prediction model showed an area under the curve (AUC) of 0.825 (95% CI 0.797–0.853, $P < 0.001$), with a sensitivity of 76% and a specificity of 72% (Fig. 1). This prediction model was assessed by the Hosmer–Lemeshow goodness-of-fit test and was internally validated by bootstrapping. Hosmer–Lemeshow goodness-of-fit testing indicated good consistency between the predicted and actual data ($\chi^2 = 9.756$, $P = 0.283$) (Fig. 2a). The calibration curve after bootstrapping indicated good internal performance in terms of discrimination, with an adjusted C-statistic of 0.821 (Fig. 2b).

Simplified Clinical Screening Model for GDM

In according to the CHARMS recommendations [30], we extracted coefficients from the multivariate logistic regression and used these to calculate the GDM risk score. The fitted model and simplified scores are reported in Table 3, and details on the variables included in the screening model are as follows:

- *Maternal age*. The cutoff values were set according to the standards for advanced maternal age and extremely advanced maternal age [31]: age < 35 years (score of 0), age between 35 and 40 years (score of 2), and age ≥ 40 years (score of 4).
- *preBMI*. The cutoff values were set according to China's standards for overweight or obesity [32]: preBMI < 24 kg/m^2 (score of 0), preBMI between 24 and 28 kg/m^2 (score of 10), and preBMI ≥ 28 kg/m^2 (score of 20).
- *Family history of diabetes*. A family history of diabetes was defined as at least one family member having been diagnosed with diabetes, with a score of 1 for yes and a score of 0 for none.
- *Fasting blood glucose*. The cutoff values were set according to the threshold for elevated blood glucose levels in the first trimester as recommended by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) studies [33]: FBG < 5.1 mmol/L (a score of 0), FBG between 5.1 and 5.6 mmol/L (a score of 2), and FBG ≥ 5.6 mmol/L (a score of 4).
- *ALT/AST ratio*. The cutoff value was set according to our previous work [12]: ALT/AST ratio < 0.825 (a score of 0) and ALT/AST ratio ≥ 0.825 (score of 5).
- *TG/HDL-C ratio*. The cutoff value was set according to our previous work [12]: TG/

Table 2 Potential predictors of gestational diabetes mellitus in the logistic regression analysis

Variables	Univariate logistic model			Multivariate logistic model		
	β	OR (95% CI)	*P* value	*β*	OR (95% CI)	*P* value
Maternal age (years)	0.110	1.117 (1.079, 1.156)	<0.001**	0.067	1.070 (1.027, 1.114)	0.001**
preBMI (kg/m^2)	0.541	1.717 (1.591, 1.854)	<0.001**	0.474	1.607 (1.484, 1.739)	<0.001**
Family history of diabetes	0.286	1.331 (0.926, 1.911)	0.122	− 0.088	0.916 (0.591, 1.421)	0.916
FBG (mmol/L)	0.756	2.130 (1.686, 2.691)	<0.001**	0.632	1.881 (1.425, 2.482)	<0.001**
ALT/AST	1.842	6.310 (3.968, 10.036)	<0.001**	1.208	3.345 (1.969, 5.683)	<0.001**
TG/HDL-C	1.268	3.555 (2.469, 5.118)	<0.001**	0.562	1.754 (1.204, 2.553)	0.003**
Intercept	–	–	–	− 18.263	–	<0.001**

GDM gestational diabetes mellitus, *OR* odds ratio, *preBMI* prepregnancy body mass index, *FBG* fasting blood glucose, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol
**Independent factors significantly associated with GDM at $^{**}P < 0.01$

HDL-C ratio < 0.676 (score of 0) and TG/HDL-C ratio ≥ 0.676 (score of 3).

ROC curves were used to analyze the performance and discrimination of the simplified screening model (Fig. 1). The simplified screening model had an AUC of 0.784 (95% CI 0.750–0.818, $P < 0.001$), demonstrating a well-accepted predictive and discriminative performance. The optimal cutoff of the scoring model was 5.5, with a sensitivity of 71% and a specificity of 74%; the LR+) was 2.73, and the LR− was 0.39. As shown in ESM Table 1, when the cutoff point was ≥ 12.5, the specificity of GDM prediction was > 95%; when the cutoff point was ≥ 18.5, the specificity of GDM prediction was > 99%. The diagnostic capacity of this prediction model at different cutoff points is described in Fig. 3 and ESM Table 1.

Sensitivity Analysis by Different preBMI Cutoff Values

As the findings of previous studies suggested lower preBMI cutoff values for application in pregnant Chinese women [16, 17], we used different preBMI cutoff values ranging from 21 to 24 kg/m^2 for overweight stratification (Fig. 4; ESM Table 3). When the preBMI cutoff value was 22 kg/m^2, the ROC-AUC of our prediction model was 0.789 (0.756–0.821); the two other preBMI cutoff values (21 and 23 kg/m^2) did not show better ROC-AUC values than the cutoff value of 24 kg/m^2. The pairwise comparisons of different preBMI cutoff values did not show statistically significant differences ($P > 0.05$).

Comparison of the Performance of Our model with other GDM Prediction Models

The performance of our model was compared with that of other prediction models published in the last 10 years. The screening and selection process of these models are given in ESM Fig. 2. Of the 886 records retrieved through the database search, we selected three published clinical risk models to compare with our model [34–36]. As shown in Fig. 1 and ESM Table 2, our current model was superior to the other established GDM prediction models, with AUCs of 0.752 (95% CI 0.721–0.784) for Gao et al.'s model [34], 0.672 (95% CI 0.636–0.708) for Zheng et al.'s model [35], and 0.736 (95% CI 0.704–0.768) for Guo et al.'s model [36]. For two of the three published models (those of Gao et al. and Guo et al.), the performance in our participants was better than the original models, whereas in Zheng et al.'s model it was worse.

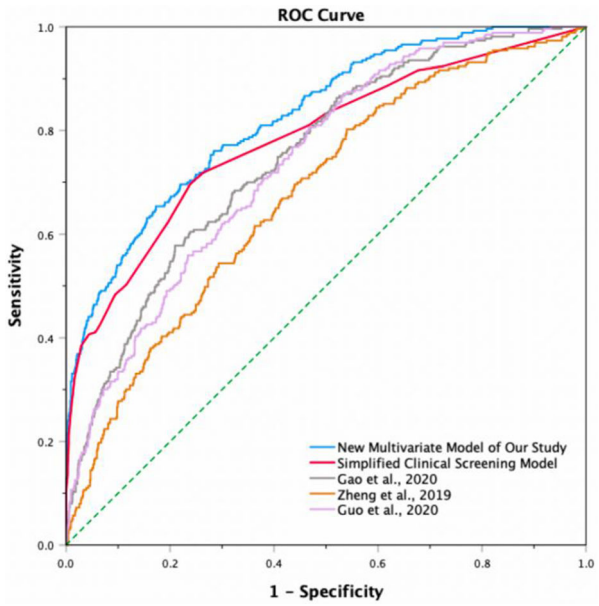

Fig. 1 The performance of our prediction model compared to that of the other published models for gestational diabetes mellitus prediction within our cohort. *ROC* Receiver operating characteristic

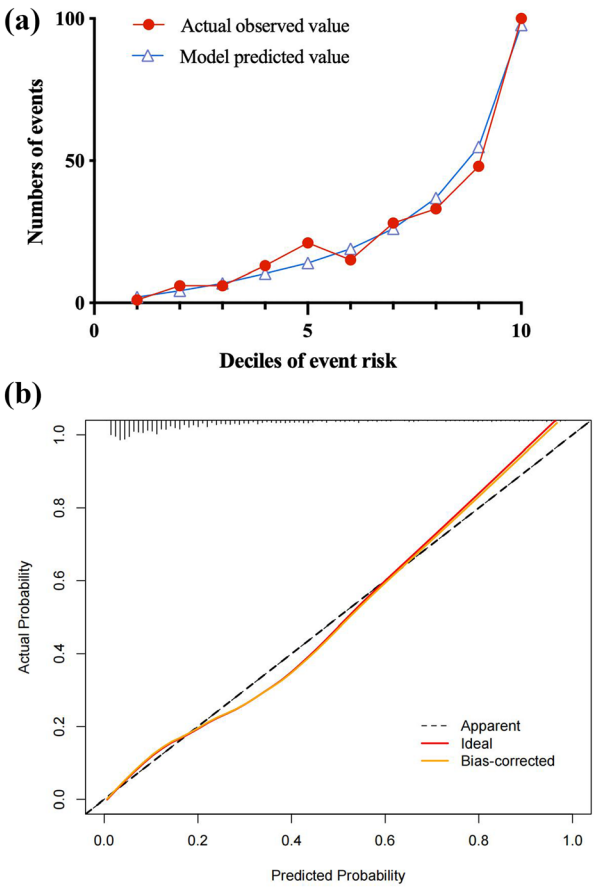

Fig. 2 Assessment of the multivariate logistic model. **a** Hosmer–Lemeshow goodness-of-fit test (χ^2 = 9.756, P = 0.283). **b** Bootstrap-validated calibration curve (β = 1000 repetitions, boot, mean absolute error = 0.018, n = 1289). The x-axis represents the predicted probability of the multivariate logistic model, and the y-axis represents the actual probability of gestational diabetes mellitus. Perfect prediction would correspond to the 45° dashed line. The red line represents the entire cohort, and the orange line indicates bias correction by bootstrapping

DISCUSSION

In the present study, we developed a simplified clinical screening model for predicting the risk of GDM in early pregnancy. Using three clinical characteristics (maternal age, preBMI, and a family history of diabetes) and three laboratory parameters (FBG, the ALT/AST ratio, and the TG/HDL-C ratio) measured in the first trimester, the model showed good discrimination (a sensitivity of 71% and a specificity of 74%, with an AUC of 0.784) and calibration (as shown in Fig. 2a, b). This prediction model provided earlier screening for the risk of GDM, which would be applicable in pregnant Chinese women.

Pregnant women with GDM have an increased risk of pregnancy complications. A systematic review and meta-analysis including 156 studies revealed that women with GDM had increased odds of cesarean section, preterm delivery, macrosomia, and LGA infants. Among pregnant women with GDM requiring insulin therapy, the odds of having an infant with respiratory distress syndrome were also higher [37]. Based on the results of these studies, it is necessary to identify the risk of GDM as early as possible. Although numerous risk factors for GDM have been reported, the ability to precisely identify women at high risk for GDM before or early in pregnancy remains limited. The IADPSG recommended using an FBG range of 5.1–6.9 mmol/L before 24 weeks of gestation to define early GDM, and pregnant women with FBG levels in this range should be referred for immediate intervention [25]. However, it has been reported that FBG is related to gestational

Table 3 Simplified clinical screening model for gestational diabetes mellitus

Clinical measures			Laboratory data in the first trimester		
Predictors	**Categories**	**Score**	**Predictors**	**Categories**	**Score**
Maternal age (years)	< 35	0	FBG (mmol/L)[b]	< 5.1	0
	35–40	2		5.1–5.6	2
	≥ 40	4		≥ 5.6	4
preBMI (kg/m^2)	< 24	0	ALT/AST ratio	< 0.825	0
	24–28	10		≥ 0.825	5
	≥ 28	20			
Family history of diabetes[a]	None	0	TG/HDL-C ratio	< 0.676	0
	Yes	1		≥ 0.676	3

GDM gestational diabetes mellitus, *preBMI* prepregnancy body mass index, *FBG* fasting blood glucose, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol

[a]Defined as at least 1 family member having been diagnosed with diabetes

[b]Participants with an FBG level ≥ 6.1 mmol/L in the first trimester were excluded from this prediction model because of probable impaired glucose intolerance before pregnancy

age and body weight, and several women with GDM have normal FBG levels in early pregnancy [38]. In addition, one study reported that even among pregnant women with FBG levels > 5.6 mmol/L before 24 weeks of gestation, > 50% did not develop GDM, indicating that it was inaccurate to predict the risk of GDM by FBG levels alone [39]. Heterogeneity of physiological processes underlying hyperglycemia has been revealed among women with GDM [40]. In a proportion of pregnant women with GDM, the pathophysiological mechanism of GDM was dominated by insulin secretion defects without impaired insulin sensitivity, whereas other patients had predominant insulin sensitivity defects with hyperinsulinemia and were more likely to develop altered adipokine profiles. The association between lipid profiles and liver function in early pregnancy and GDM has gradually been elucidated, but the diagnostic ability of each study was different with disparate cutoff points [41, 42]. Our previous work identified clinically useful biomarkers in early pregnancy for the prediction of GDM risk, which were used as variables in the prediction model reported in the present study and to determine cutoff values [11, 12].

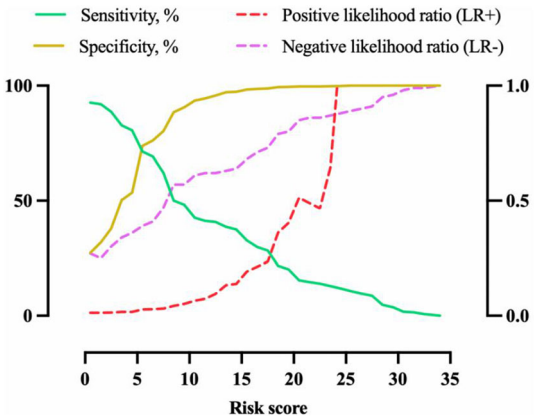

Fig. 3 The diagnostic capacity of this prediction model at different risk scores. Sensitivity, specificity, and positive likelihood ratio (LR+) are described by the *y*-axis on the left, and the negative likelihood ratio (LR−) is described by the *y*-axis on the right

The parameters included in our scoring model have been reported in previous studies, providing the theoretical basis of the model.

Race is one of the risk factors for GDM [9]. The incidence of GDM in Chinese individuals is significantly higher than that in white individuals; thus, prediction models based on European or North American populations are not

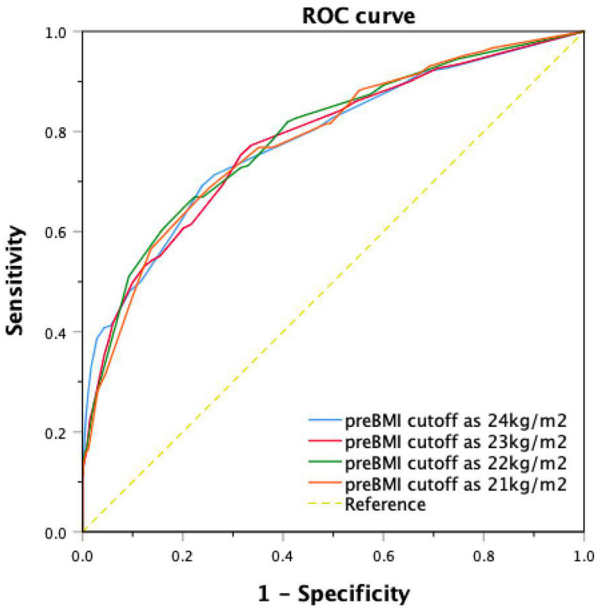

Fig. 4 The performance of our gestational diabetes mellitus prediction model stratified by different prepregnancy body mass index (*preBMI*) cutoff values. *ROC* Receiver operating characteristic

applicable for Chinese women. Several GDM prediction models have been established in China. Wu et al. developed a clinical model for gestational women in the first trimester by selecting seven variables via advanced machine learning, which demonstrated a promising predictive value [43]. However, the model was too complicated to use in routine clinical care, especially in rural areas. Wang et al. found that FBG and TG levels during gestational weeks 14–20 were independent predictors for GDM and built a risk score using these two variables [44]. The prediction model based on laboratory data ignored the relationship between sociodemographic characteristics and GDM. More studies devoted to predicting the risk of GDM by novel biomarkers, including genetic variants and proteomic analysis, have been implemented in most institutions in China [45, 46]. The aim of this study was to establish a practical and propagable method to identify the risk of GDM in Chinese women in early pregnancy, and the simplified screening model presented herein achieved high accuracy. Three published models with variables similar to ours were contrasted with our prediction model, but none of them had better predictive values than our model, neither the original AUC values nor the derived ones [34–36].

The diagnostic utility of our prediction model was satisfactory, with an AUC of 0.784 (95% CI 0.750–0.818, $P < 0.001$). The optimal cutoff value of the model was 5.5, with a sensitivity of 71% and a specificity of 74%, which indicates that it could be a simplified and low-cost screening tool for clinical use. As shown in ESM Table 1, when the cutoff point was $\geq$ 12.5, the specificity was > than 95%; when the cutoff point was $\geq$ 18.5, the specificity was > than 99%. Therefore, we recommend that if the score is > 12.5, intervention measures should be taken immediately because of the high probability of GDM. In addition, women with FBG levels $\geq$ 6.1 mmol/L in the first trimester were excluded from our prediction model. Patients with FBG levels $\geq$ 6.1 mmol/L were defined as having impaired fasting glucose (IFG), which indicated that they may already have abnormal glucose metabolism. Zhu et al. found that an fasting plasma glucose cutoff values of 6.1 mmol/L at the first prenatal visit had a specificity of 1 for predicting the risk of GDM [10]. Based on the above, we recommend that pregnant women with an FBG level $\geq$ 6.1 mmol/L in the first trimester should be treated as women with GDM and receive lifestyle intervention or even insulin treatment.

There are several limitations to our study. First, some missing data were missing during early pregnancy in this prospective cohort. However, the proportion of missing data was < 10%, and multiple imputations were conducted to develop the prediction model. Second, as our study was derived and internally validated only in pregnant Chinese women, it may not be applicable to other populations. Performing external validation in other populations and different settings would have been the optimal approach, but this was not feasible in this cohort. Moreover, although the screening model showed good discrimination, it could not identify all women at high risk of GDM in the first trimester. When the cutoff point was 5.5, the screening model failed to identify 78 of the 272 (28.6%) pregnant women with GDM in

this study. Further studies on GDM risk factors are needed to establish more accurate prediction models.

CONCLUSIONS

In conclusion, we developed a simplified screening model that can predict the risk of GDM in early pregnancy in the Chinese population based on sociodemographic characteristics and laboratory data; this model is easy to implement in most medical centers in China. The diagnostic utility of our prediction model showed better discrimination than other published models using similar biomarkers, with an ROC-AUC of 0.784 (95% CI 0.750–0.818). This model could help identify women at high GDM risk earlier than the 75-g OGTT, which may reduce the rate of perinatal complications in pregnant women as well as the economic burden of society.

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Author Contributions. Yanbei Duo, Tao Yuan, Weigang Zhao, Wei Sun, and Ailing Wang conceptualized the study. Yuemei Zhang, Shuoning Song, Jiyu Xu, Yan Chen, Xiaorui Nie, Qiujin Sun, Xianchun Yang, and Zechun Lu performed the investigation. Yanbei Duo, Xiaolin Qiao, Zhenyao Peng, Jing Zhang, Tao Yuan, Yong Fu, and Yingyue Dong determined the methodology. Yanbei Duo, Shuoning Song, Yuemei Zhang, Xiaolin Qiao, Jiyu Xu, and Yan Chen collected the clinical data. Yanbei Duo wrote the original draft. Yanbei Duo, Tao Yuan, Weigang Zhao, Wei Sun, and Ailing Wang edited the manuscript. Weigang Zhao supervised the study. All authors approved the final draft of the manuscript.

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Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Yanbei Duo, Shuoning Song, Xiaolin Qiao, Yuemei Zhang, Jiyu Xu, Jing Zhang, Zhenyao Peng, Yan Chen, Xiaorui Nie, Qiujin Sun, Xianchun Yang, Ailing Wang, Wei Sun, Yong Fu, Yingyue Dong, Zechun Lu, Tao Yuan, and Weigang Zhao have nothing to disclose.

Ethical Approval. Written informed consent was obtained from each participant, and the study was performed in accordance with the Declaration of Helsinki as revised in 2013. This study was part of an ongoing prospective double-center observational cohort study started in 2019, which was conducted at Haidian District Maternal and Child Health Care Hospital and Chaoyang District Maternal and Child Health Care Hospital (Beijing, China) (ClinicalTrials.gov: NCT03246295). The Ethical Review Committee of National Center for Women and Children's Health, Chinese Center for Disease Control and Prevention in Beijing, China approved this study on 3 April 2019 (approval number: FY2019-01).

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