

Nomogram-Based Prediction of the Risk of Macrosomia: A Prospective Cohort Study in a Chinese Population

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Abstract

Objective: This study aimed to establish a nomogram for predicting the risk of macrosomia in early pregnancy.

Methods: We performed a prospective cohort study involving 1,549 pregnant women. According to the birth weight of newborn, the subjects were divided into two groups: macrosomia group and non-macrosomia group. Multivariate logistic regression was used to analyze the risk factors for macrosomia.

Results: The prevalence of macrosomia was 6.13% (95/1549) in our hospital. Multivariate logistic regression analysis showed the risk factors of macrosomia were prepregnancy overweight (OR: 2.126, 95% CI: 1.181-3.826)/obesity (OR: 3.536, 95% CI: 1.555-8.036), multiparity (OR:1.877, 95% CI: 1.160-3.039), the history of macrosomia (OR: 36.971, 95% CI: 19.903-68.674), the history of GDM/DM (OR: 2.285, 95% CI: 1.314-3.976), the higher levels of HbA1c (OR: 1.763, 95% CI: 1.004-3.097) and TC (OR: 1.360, 95% CI: 1.004-1.842). A nomogram was developed for predicting macrosomia based on maternal factors related to the risk of macrosomia in early pregnancy. The area under the receiver operating characteristic (ROC) curve of the nomogram was 0.807 (95% CI: 0.755–0.859), the sensitivity and specificity of the model were 0.716 and 0.777, respectively.

Conclusion: The nomogram model provides an accurate method for clinicians to early predict macrosomia.

Introduction

Macrosomia is one of the most common neonatal adverse outcomes, which is defined as the absolute birth weight of newborn > 4,000 g or 4,500 g, regardless of the gestational age¹. Recent studies have showed that macrosomia increases adverse maternal and fetal outcomes. For pregnant women, delivery of macrosomia is associated with significantly increased risks of cesarean section, prolonged labor, postpartum hemorrhage, chorioamnionitis, soft birth canal injury, even uterus and bladder rupture²⁻⁶. For the newborns, macrosomia increases the risk of shoulder dystocia, clavicle fractures, brachial plexus injury, respiratory distress, meconium aspiration, perinatal infection, hypoglycemia, polycythemia, hypoxic-ischemic encephalopathy and increases the need for admission to neonatal intensive care units^{3-5, 7, 8}. In addition, macrosomic newborns have more health problems such as overweight/obesity, diabetes mellitus, high blood pressure, cardiovascular disease and other chronic diseases later in life⁹⁻¹¹. Early predicting the risk of macrosomia and taking preventive measures can avoid or reduce the occurrence of adverse complications. Accurate diagnosis of macrosomia can only be made by weighing the newborn after birth, but the opportunity of early intervention is lost. Currently, the prenatal estimation of fetal weight is carried out by maternal physical examination or ultrasonographic measurement. However, these methods are based on maternal and fetal data during the later stage of pregnancy, and the accuracy of them is not very high^{12, 13}. Hence, establishing a simple, noninvasive, practical, accurate model for predicting the risk of macrosomia in the first trimester of pregnancy is of great important. In the

present study, we attempted to set up a predictive model of macrosomia based on clinical indicators in first trimester to enable early identification and prevention of macrosomia.

Results

Subjects' characteristics

Among the 1,549 pregnant women, 95 mothers gave birth to the newborn whose weight was more than 4,000g. The rate of macrosomia was 6.13%. There was no significant difference in the mean age and the proportion of pregnant women older than 35-year-old between the macrosomia group and the non-macrosomia group ($P > 0.05$). The prepregnancy BMI and weight gain during pregnancy in the macrosomia group were higher than those in the non-macrosomia group, and the proportions of overweight and obese participants before pregnancy were higher in the macrosomia group compared with the non-macrosomia group ($P < 0.05$). Comparison with the non-macrosomia group, the proportions of multipara, the history of macrosomia and the history of GDM/DM in the macrosomia group was higher ($P < 0.05$); while, there was no significant difference in the proportion of HDP between the two groups ($P > 0.05$). In the first trimester, the levels of TC, TG, HbA1c and CRP of pregnant women in the macrosomia group were higher than those in the non-macrosomia group ($P < 0.05$), while, there were no significant differences on the levels of SBP, DBP, NLR, HGB, PLT, ALT, AST, ALB, HDL, LDL, Lpa, FPG, Hcy, FT4, FT3, TSH, ferritin, Cu, Zn, Ca, Mg, Fe and Al between the two groups ($P > 0.05$) (Table 1).

Table 1

Comparison of maternal characteristics between the non-macrosomia group and the macrosomia group

Index	Non-macrosomia group (n = 1454)	Macrosomia group (n = 95)	t(χ^2)	<i>p</i>
Age (years)	30.91 ± 3.64	31.46 ± 3.65	-1.466	0.148
< 25	30(2.06%)	1(1.05%)		
25–34	1175(80.81%)	73(76.84%)		
≥ 35	249(17.13%)	21(22.11%)	1.898	0.387
Prepregnancy BMI (kg/m ²)	21.84 ± 2.97	23.13 ± 3.12	-4.091	0.000
< 24	1169(80.40%)	60(63.16%)		
24–28	225(15.47%)	22(23.16%)		
≥ 28	60(4.13%)	13(13.68%)	23.927	0.000
Gestational weight gain (kg)	12.53 ± 5.62	14.97 ± 5.09	-4.112	0.000
Parity				
0	906(62.31%)	46(48.42%)		
> 1	548(37.69%)	49(51.58%)	7.263	0.007
History of macrosomia				
Yes	30(2.06%)	34(35.79%)		
No	1424(97.94%)	61(64.21%)	247.63	0.000
History of GDM/DM				
Yes	278(19.12%)	29(30.53%)		
No	1176(80.88%)	66(69.47%)	7.301	0.007
History of HDP				
Yes	18(1.24%)	3(3.16%)		
No	1436(98.76%)	92(96.84%)	1.232	0.267
SBP (mmHg)	109.73 ± 9.97	111.64 ± 9.43	-1.810	0.071
DBP (mmHg)	65.92 ± 9.15	67.53 ± 9.85	-1.647	0.100
NLR	3.24 ± 1.12	3.33 ± 1.15	-0.729	0.466
HGB (g/L)	129.94 ± 12.76	129.03 ± 13.65	0.675	0.500

Index	Non-macrosomia group (n = 1454)	Macrosomia group (n = 95)	t(χ^2)	p
PLT (10 ⁹ /L)	243.03 ± 51.38	242.76 ± 53.76	0.050	0.960
ALT (U/L)	17.01 ± 3.59	17.92 ± 8.51	-1.035	0.303
AST (U/L)	18.27 ± 8.96	19.08 ± 15.27	-0.813	0.416
ALB (g/L)	44.18 ± 2.50	43.72 ± 2.28	1.725	0.085
TC (mmol/L)	3.93 ± 0.70	4.13 ± 0.91	-2.018	0.046
TG (mmol/L)	0.99 ± 0.60	1.18 ± 0.69	-2.641	0.010
HDL-C (mmol/L)	1.42 ± 0.36	1.41 ± 0.26	0.246	0.805
LDL-C (mmol/L)	2.55 ± 10.66	2.23 ± 0.62	0.295	0.768
Lpa (mg/L)	153.87 ± 185.01	141.13 ± 201.11	0.647	0.518
SCr (umol/L)	49.97 ± 12.41	49.72 ± 6.41	0.195	0.845
UA (umol/L)	213.58 ± 50.81	222.13 ± 54.16	-1.583	0.114
HbA1c (%)	5.12 ± 0.27	5.27 ± 0.71	-2.013	0.047
FPG (mmol/L)	4.91 ± 0.27	5.00 ± 0.59	-1.447	0.151
Hcy (umol/L)	6.79 ± 5.78	6.32 ± 1.32	0.776	0.438
CRP (mg/L)	2.00 ± 2.30	3.05 ± 3.56	-2.840	0.005
FT4 (pmol/L)	17.45 ± 7.65	16.51 ± 2.51	1.195	0.232
FT3 (pmol/L)	4.79 ± 2.29	4.65 ± 0.57	0.605	0.545
TSH (mU/L)	1.89 ± 1.72	1.92 ± 1.33	-0.186	0.852
Ferritin (ng/ml)	62.62 ± 55.12	58.66 ± 38.30	0.690	0.491
Cu (umol/L)	26.93 ± 48.61	25.62 ± 3.91	0.262	0.793
Zn (umol/L)	86.37 ± 6.78	87.26 ± 8.20	-1.223	0.222
Ca (mmol/L)	1.49 ± 0.05	1.49 ± 0.05	0.104	0.917
Mg (mmol/L)	1.49 ± 0.17	1.49 ± 0.06	0.221	0.825
Fe (mmol/L)	7.97 ± 0.47	7.95 ± 0.29	0.385	0.700
Al (ug/L)	25.39 ± 4.38	25.22 ± 3.08	0.358	0.721

Logistic regression analysis of the influencing factors of macrosomia

Multivariate logistic regression was adopted to assess the influencing factors of macrosomia. The dependent variable was delivery of macrosomia, and the independent variables included prepregnancy BMI, gestational weight gain, parity, history of macrosomia, history of GDM/DM, HbA1c, TC, TG and CRP which were statistically significant parameters from univariate regression analysis. After adjusting for the weight gain during pregnancy, the results showed that macrosomia was significantly associated with prepregnancy overweight (OR: 2.126, 95% CI: 1.181–3.826)/obesity (OR: 3.536, 95% CI: 1.555–8.036), multiparity (OR:1.877, 95% CI: 1.160–3.039), the history of macrosomia (OR: 36.971, 95% CI: 19.903–68.674), the history of GDM/DM (OR: 2.285, 95% CI: 1.314–3.976), the levels of HbA1c (OR: 1.763, 95% CI: 1.004–3.097) and TC (OR: 1.360, 95% CI: 1.004–1.842) (Table 2).

Table 2
Multivariate logistic regression analysis of influencing factors of macrosomia

	β	SE.	Wald χ^2	OR (95%CI)	P
Prepregnancy BMI (kg/m ²)					
< 24	Ref.				
24–28	0.754	0.300	6.328	2.126 (1.181,3.826)	0.012
\geq 28	1.263	0.419	9.086	3.536 (1.555, 8.036)	0.003
Parity					
0	Ref.				
> 1	0.630	0.246	6.564	1.877 (1.160, 3.039)	0.010
History of macrosomia					
No	Ref.				
Yes	3.610	0.316	130.560	36.971 (19.903, 68.674)	0.000
History of GDM/DM					
No	Ref.				
Yes	0.827	0.283	8.560	2.285 (1.314, 3.976)	0.003
HbA1c (%)	0.567	0.287	3.895	1.763(1.004, 3.097)	0.048
TC (mmol/L)	0.307	0.155	3.942	1.360 (1.004, 1.842)	0.047

Nomogram for macrosomia and evaluation of the predictive model

In the study, the nomogram for predicting the risk of macrosomia was established based on the risk factors including prepregnancy BMI, parity, history of macrosomia, history of GDM/DM, the levels of

HbA1 and TC in the first trimester of pregnancy (Figure 1). The accuracy of the predictive model for macrosomia was good assessed by the AUC equal to 0.807 (95% CI: 0.755–0.859). The sensitivity and specificity were 0.716 and 0.777, respectively; and the positive predictive value and the negative predictive value was 0.174 and 0.977, respectively (Figure 2).

Each individual's risk for macrosomia was estimated by plotting on each variable axis. A vertical line should be drawn from the correct location of each independent risk factor to the top points scale. Then, total points, which could be calculated by adding all points of the axis to the bottom axes vertically, made the conversion into the incidence probability of macrosomia.

Discussion

In recent years, with the rapid development of social economy, the lifestyle and nutritional status of women before and during pregnancy has been significantly changed. Along with these changes, the birth weight of newborn is increasing and the incidence of macrosomia is increasingly common. However, with the gradual improvement in the quality of health care during pregnancy and the awareness of the adverse effects of macrosomia, the incidence of macrosomia has been controlled to a certain extent in China. Data from a retrospective study including 63,661 singleton newborns showed that the percentages of macrosomia in Beijing, China, increased from 6.6% in 1996 to 9.5% in 2000 and declined to 7.0% in 2010¹⁴. In the study, the results showed that the prevalence of macrosomia was 6.13%, which was close to 5.96% reported in the tertiary hospitals and lower than the total prevalence (7.069%) in Beijing¹⁵. The rate of newborns weighing at least 4,000 g was lower than 7.8% in the United States, which had been reported by the National Center for Health Statistics¹⁶.

The occurrence of macrosomia is closely related to a variety of maternal factors, such as genetic factors, environment, constitutional healthy condition. Constitutional factors of pregnant women like prepregnancy BMI, excessive weight gain during pregnancy, and preexisting GDM/DM, are recognized as independent risk factors for macrosomia. GDM/DM, overweight/obesity and excess gestational weight gain have common metabolic characteristics such as increased insulin resistance, hyperglycemia, and hyperinsulinemia, which play an important role in macrosomia^{17–20}. Our study found that prepregnancy BMI, weight gain during pregnancy, the proportion of preexisting GDM/DM in the macrosomia group were significantly higher than those in the non-macrosomia group ($P < 0.05$). The result of multivariate logistic regression showed the risk of macrosomia were significantly associated with prepregnancy overweight /obesity, the history of GDM/DM and weight gain during pregnancy, which was consistent with the above findings.

With the implementation of the two-child policy in China, the proportion of multipara and the age of pregnant women may be obviously increasing. A multi-centre, cross-sectional survey involving 101,723 singleton term infants in China showed that risk of macrosomia was positively associated with maternal age, parity²¹. In this study, the mean age and the proportion of pregnant women ≥ 35 -year-old in the macrosomia group were higher than those in the non-macrosomia group, but the difference was not

statistically significant. And there was no association between age and macrosomia by univariate logistic regression analysis ($P > 0.05$). The proportion of multipara in the macrosomia group were higher than that in the non- macrosomia group, and the risk of macrosomia in multiparas was 1.8 times than that in primiparas($P < 0.05$). These results were not completely consistent with the previous studies.

Data from a prospective cohort study including 54,371 singleton pregnancies at 12 centers in the US showed that women who had delivered a macrosomic newborn in the past had a high risk to have another macrosomia in the subsequent pregnancy with the recurrence rate of 23.2% (95% CI: 21.2%-25.2%), and the number of prior macrosomic infants was positively associated with the risk of recurrent macrosomia²². Previous studies demonstrated that the previous delivery of macrosomia was the single strongest individual risk factor for macrosomia controlling for prepregnancy BMI, excess weight gain, DM/GDM and other risk factors^{19; 20}. In this study, the result from multivariate logistic regression analysis showed that the adjusted OR (39.021) of the previous delivery of macrosomia was the highest among the risk factors of macrosomia($P < 0.05$), which suggested the previous history of macrosomia was the most influencing risk factor for macrosomia. Although these factors are non-modifiable, they are helpful in screening for macrosomia. Obstetricians should pay attention to inquire the previous histories, and provide more close monitoring and effective intervention to these pregnant women.

The blood lipid level of pregnant women is one of the important factors affecting the birth weight of newborns. Maternal TG and TC can be taken up by the placenta, metabolized and transported to the fetus in various forms for providing energy for the fetus and helping the fetus to build cell membrane²³. Increased levels of these two lipids in a certain range during pregnancy are beneficial to the development and growth of the fetus. However, excessive increased of lipid can induce fetal overgrowth²⁴. Previous studies showed that maternal TG level in the first term of pregnancy was positively associated with higher birth weight, and an independent predictor of neonatal birth weight, but maternal TG level was not associated with birth weight^{24, 25}. While, Kulkarni et al. reported a positive correlation between maternal TC level and neonatal birth weight²⁶. In this study, we found that the levels of maternal TC, TG in the first trimester in the macrosomia group were significantly higher than those in the non-macrosomia group ($P < 0.05$). The results of univariate logistic regression analysis showed the levels of maternal TC, TG in the first trimester were related to the occurrence of macrosomia. But after adjusting for prepregnancy BMI, gestational weight gain, parity, history of macrosomia delivery, history of GDM/DM, HbA1c, and CRP, the results of multivariate logistic regression analysis showed maternal TC level was an independent risk factors of macrosomia. However, the increase of TG was not an independent risk factor for macrosomia.

Given the increased morbidity and mortality for infants and mothers caused by macrosomia, early predicting macrosomia and taking effective interventions should be performed to reduce the adverse outcomes. Before 1976, fetal weight was estimated mainly by measuring the height of uterus and abdominal circumference of pregnant women. This method was easy and rapid, but it was easily affected by many factors, such as uterine tension, amniotic fluid volume, fetal position and abdominal

wall thickness. Hence, the accuracy of clinical measurement to predict macrosomia is not very good. In recent 40 years, with the extensive use of ultrasound examination in obstetrics, ultrasonography has been currently an important measure to predict fetal weight in many countries. Sonographic estimated fetal weight (EFW) uses 2-dimensional ultrasound imaging to record fetal biometric parameters (such as abdominal circumference, head circumference, femur length, and biparietal diameter), which are incorporated into a formula to estimate fetal weight²⁷. Comparison with maternal physical examination, ultrasonography is superior in assessing normal fetal weight, but its accuracy of predicting macrosomia is not better²⁸. A meta-analysis of 29 studies showed that the sensitivity and specificity of 2-dimensional (2D) ultrasound predicting birth weight more than 4,000 g were 0.56 (95% CI 0.49–0.61) and 0.92 (95% CI 0.90–0.94), respectively²⁹, and its accuracy decreased with increasing fetal weight²⁸. In addition, 3-dimensional (3D) ultrasound and magnetic resonance imaging (MRI) have been used to estimate fetal macrosomia. There is not enough evidence to conclude that 3D ultrasound and MRI are superior to 2D ultrasound^{29,30}, and these examinations are more expensive than 2D ultrasound. So they are not widely used in clinical practice. Furthermore, these methods for predicting macrosomia are all carried out near to and at term, which may result in missing the best opportunity to intervene. Therefore, it is of great clinical significance to develop a simple, cheap and accurate method to predict the risk of macrosomia in early pregnancy.

As a reliable risk prediction tool, nomogram model has been widely used in clinical cohort studies due to its high accuracy, efficiency and stability. It solves the complexity of balancing different factors through statistical modeling so that patients and doctors can quantify risk based on the chart. In the study, we constructed a nomogram model based on the risk factors of macrosomia including maternal BMI before pregnancy, parity, a prior macrosomic newborn, preexisting GDM/DM, the levels of HbA1 and TC in the first trimester. The AUC of the nomogram model indicated an overall predictive performance of 0.807 (95% CI: 0.755–0.859) in the internal validation, which showed good predictive ability. The sensitivity, specificity, positive predictive value, and negative predictive value were 0.716, 0.777, 0.174, and 0.977, respectively. Compared to traditional predictive models^{31,32}, the nomogram model realizes visualized and individualized prediction, which can help obstetricians to more easily access the risk of macrosomia according to the score of each pregnant woman, then provide personalized healthcare service, such as lifestyle changes, dietary adjustments, exercise interventions, weight reduction and medical treatment. Meanwhile, the nomogram model can help pregnant women to more easily and clearly understand personal risk of macrosomia, which can enable pregnant women to more actively cooperate with the treatment to achieve better clinical effects. The predictive model of this study was established based on maternal general characteristics before pregnancy and the clinical data in early pregnancy, which can be used to screen pregnant women for macrosomia in the early pregnancy so that effective intervention and treatment can be earlier implemented for these gestational women to prevent macrosomia. In our study, the variables of the screening tool were easily available, which was conducive to the wide promotion and application in clinical practice. In addition, previous studies mostly were cross-sectional retrospective. In this study, we conducted a longitudinal cohort study, and included more reliable and comprehensive clinical indicators observed in the first trimester in order to improve the accuracy of prediction

There were some limitations in the current study. The data was from a single center, the sample size was small, and the model was only internally validated. Therefore, multi-center, larger sample studies and further external validation should be carried out to assure the generalizability of our predictive model.

Currently, macrosomia has become an important clinical and public health problem that needs to be urgently solved all over the world. In this study, the nomogram established based on the independent risk factors of macrosomia in early pregnancy has good accuracy, sensitivity and specificity. It provides a simple, convenient, economic, accurate model for clinicians to early predict macrosomia.

Materials And Methods

Subjects

This study was approved by the Ethics Committee of Peking University International Hospital. All participants signed the written informed consent. All procedures were performed in accordance with the Declaration of Helsinki.

This was a single-center, prospective, cohort study. Pregnant women who were admitted to the Department of Gynaecology and Obstetrics of Peking University International Hospital from December 2017 to June 2019 were enrolled to participate in this study. Inclusion criteria were as follows: (1) subjects' age \geq 18 years old; (2) the gestational weeks < 12 weeks diagnosed by last menstrual period (LMP) and human chorionic gonadotropin (HCG); (3) single pregnancy; (4) planning to undergo examine and give birth at our hospital. Exclusion criteria were as follows: (1) multiple pregnancy; (2) subjects with cardiovascular and cerebrovascular diseases, respiratory diseases, liver and kidney diseases, hematological diseases, autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome), and tumors; (3) subjects who did not deliver in our hospital. Finally, a total of 1,549 subjects with complete data were included in this study.

Methods

Each subject's demographic and medical data (e.g., age, parity, gestational week, history of macrosomia, history of gestational diabetes mellitus (GDM) or diabetes mellitus (DM), past history of hypertensive disorders of pregnancy (HDP), prepregnancy weight, etc.) were recorded as enrolling into the study, and all patients underwent anthropometric assessment, including height and blood pressure. Body mass index (BMI) was calculated using the following formula: $BMI = \text{weight (kg)}/\text{square of height (m}^2\text{)}$.

Venous blood samples were drawn from subjects who had been fasting for 8 hours to evaluate whole blood count, as well as the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein-a (Lpa), serum creatinine (Scr), uric acid (UA), glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), homocysteine (Hcy), C-reactive protein (CRP), free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH), ferritin, copper

(Cu), zinc (Zn), calcium (Ca), magnesium (Mg), ferrum (Fe), aluminum (Al). HbA1c was measured using high performance liquid chromatography (HPLC) with Dongcao G8 glycosylated hemoglobin analyzer. The serum levels of TSH, FT4 and FT3 were measured using electrochemical luminescence immunoassay by Roche Cobas Elesys 601 analyzer.

The subjects were followed up regularly during pregnancy until delivery. Gestational weight gain of pregnant women and birth weight of newborns were measured and recorded by uniform-trained nurses.

Definitions

Macrosomia was defined as an absolute birth weight was more than 4000g¹⁴. Overweight was defined as BMI was 24-28kg/m², obesity was defined as BMI \geq 28kg/m³³. GDM was diagnosed based on the guidelines of the International Association of Diabetes and Pregnancy Study Groups as fasting plasma glucose (FPG) \geq 5.1 mmol/L, and/or 1-hour plasma glucose (1hPG) \geq 10.0 mmol/L, and/or 2-hour plasma glucose (2hPG) \geq 8.5mmol/L in a 75 g oral glucose tolerance test (OGTT) ³⁴. DM was defined based on the criteria presented by the World Health Organization (WHO) in 1999 as FPG \geq 7.0 mmol/L and/or 2hPG \geq 11.1 mmol/L in OGTT. HDP included gestational hypertension, preeclampsia-eclampsia, chronic hypertension (of any cause diagnosed before 20 weeks of gestation), and chronic hypertension with preeclampsia superimposed ³⁵.

Statistical Analysis

SPSS 20.0 software (IBM, Armonk, NY, USA) was used to perform statistical analysis. Normality was assessed with the Shapiro-Wilk test. Continuous variables were expressed as mean \pm standard deviation or median (Q1, Q3). Categorical variables were expressed as absolute numbers and percentages. To compare differences related to continuous variables between groups, the independent t-test or the Mann-Whitney U test was used, and chi-square test was employed for comparing differences related to categorical variables. Univariate regression analysis logistic regression and unconditional multivariate logistic regression were used to analyze the associations between variables and the risk of macrosomia. All statistical tests were two-sided, and differences were considered statistically significant when $P < 0.05$.

In this study, the nomogram was internally validated in cohorts of this study by using 500 bootstrap resamplings. We created a receiver operating characteristic (ROC) curve and calculated the area under the ROC curve (AUC) to assess the discriminatory ability of the nomogram. The value of AUC closer to 1 implied a better predictive accuracy. Statistical analyses were performed with statistical packages R (<http://www.R-project.org>) and EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA).

Declarations

Author contributions statement

J.D. and X.Z. conceived and designed the research. J.D., S.C., X.Z., J.S., N.Y., X.Y. and Q.Z. contributed to data acquisition and input. J.D. analyzed and interpreted data. J.D. wrote the initial paper. J.D. and Z.X. finally revised the manuscript. All authors read and approved the final manuscript.

Additional information

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Competing interests

The authors declare no competing interests.

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References

1. Macrosomia ACOG Practice Bulletin, Number 216. *Obstet. Gynecol.***135**, e18–e35 (2020).
2. Fuchs, F., Bouyer, J., Rozenberg, P. & Senat, M. V. Adverse Maternal Outcomes Associated with Fetal Macrosomia: What are the Risk Factors Beyond Birthweight? *BMC Pregnancy Childbirth.***13**, 90 (2013).
3. Beta, J. *et al.* Maternal and Neonatal Complications of Fetal Macrosomia: Cohort Study. *Ultrasound Obstet Gynecol.***54**, 319–325 (2019).
4. Beta, J. *et al.* Maternal and Neonatal Complications of Fetal Macrosomia: Systematic Review and Meta-Analysis. *Ultrasound Obstet Gynecol.***54**, 308–318 (2019).
5. King, J. R., Korst, L. M., Miller, D. A. & Ouzounian, J. G. Increased Composite Maternal and Neonatal Morbidity Associated with Ultrasonographically Suspected Fetal Macrosomia. *J Matern Fetal Neonatal Med.***25**, 1953–1959 (2012).
6. Fukami, T. *et al.* Incidence and Risk Factors for Postpartum Hemorrhage Among Transvaginal Deliveries at a Tertiary Perinatal Medical Facility in Japan. *PLoS One.***14**, e208873 (2019).
7. Kc, K., Shakya, S. & Zhang, H. Gestational Diabetes Mellitus and Macrosomia: A Literature Review. *Ann. Nutr. Metab.***66** (Suppl 2), 14–20 (2015).
8. Rowe, R., Soe, A., Knight, M. & Kurinczuk, J. J. Neonatal Admission and Mortality in Babies Born in UK Alongside Midwifery Units: A National Population-Based Case-Control Study Using the UK Midwifery Study System (UKMidSS). *Arch Dis Child Fetal Neonatal Ed.* (2020).
9. Sparano, S. *et al.* Being Macrosomic at Birth is an Independent Predictor of Overweight in Children: Results From the IDEFICS Study. *Matern Child Health J.***17**, 1373–1381 (2013).

10. Palatianou, M. E., Simos, Y. V., Andronikou, S. K. & Kiortsis, D. N. Long-Term Metabolic Effects of High Birth Weight: A Critical Review of the Literature. *Horm. Metab. Res.***46**, 911–920 (2014).
11. Hemachandra, A. H. *et al.* Postnatal Growth, and Risk for High Blood Pressure at 7 Years of Age: Results From the Collaborative Perinatal Project. *Pediatrics*.**119**, e1264–e1270 (2007).
12. Pretscher, J. *et al.* Influence of Sonographic Fetal Weight Estimation Inaccuracies in Macrosomia on Perinatal Outcome. *Ultraschall Med.*(2020).
13. Noumi, G., Collado-Khoury, F., Bombard, A., Julliard, K. & Weiner, Z. Clinical and Sonographic Estimation of Fetal Weight Performed During Labor by Residents. *Am. J. Obstet. Gynecol.***192**, 1407–1409 (2005).
14. Shan, X. *et al.* Secular Trends of Low Birthweight and Macrosomia and Related Maternal Factors in Beijing, China: A Longitudinal Trend Analysis. *BMC Pregnancy Childbirth*.**14**, 105 (2014).
15. Ren, J. H., Wang, C., Wei, Y. M. & Yang, H. X. [Incidence of Singleton Macrosomia in Beijing and its Risk Factors]. *Zhonghua Fu Chan Ke Za Zhi*.**51**, 410–414 (2016).
16. Martin, J. A., Hamilton, B. E., Osterman, M., Driscoll, A. K. & Drake, P. Births: Final Data for 2017. *Natl Vital Stat Rep*.**67**, 1–50 (2018).
17. Jolly, M. C., Sebire, N. J., Harris, J. P., Regan, L. & Robinson, S. Risk Factors for Macrosomia and its Clinical Consequences: A Study of 350,311 Pregnancies. *Eur J Obstet Gynecol Reprod Biol*.**111**, 9–14 (2003).
18. Black, M. H., Sacks, D. A., Xiang, A. H. & Lawrence, J. M. The Relative Contribution of Prepregnancy Overweight and Obesity, Gestational Weight Gain, and IADPSG-defined Gestational Diabetes Mellitus to Fetal Overgrowth. *Diabetes Care*.**36**, 56–62 (2013).
19. Bowers, K. *et al.* Gestational Diabetes, Pre-Pregnancy Obesity and Pregnancy Weight Gain in Relation to Excess Fetal Growth: Variations by Race/Ethnicity. *Diabetologia*.**56**, 1263–1271 (2013).
20. Nkwabong, E. & Nzalli, T. G. Risk Factors for Macrosomia. *J Obstet Gynaecol India*.**65**, 226–229 (2015).
21. Li, G. *et al.* Prevalence of Macrosomia and its Risk Factors in China: A Multicentre Survey Based On Birth Data Involving 101,723 Singleton Term Infants. *Paediatr Perinat Epidemiol*.**28**, 345–350 (2014).
22. Fang, F. *et al.* Risk Factors for Recurrent Macrosomia and Child Outcomes. *World J. Pediatr*.**15**, 289–296 (2019).
23. Khaire, A., Wadhwani, N., Madiwale, S. & Joshi, S. Maternal Fats and Pregnancy Complications: Implications for Long-Term Health. *Prostaglandins Leukot Essent Fatty Acids*.**157**, 102098 (2020).
24. Vrijkotte, T. G., Algera, S. J., Brouwer, I. A., van Eijsden, M. & Twickler, M. B. Maternal Triglyceride Levels During Early Pregnancy are Associated with Birth Weight and Postnatal Growth. *J Pediatr*.**159**, 736–742 (2011).
25. Mossayebi, E., Arab, Z., Rahmaniyan, M., Almassinokiani, F. & Kabir, A. Prediction of Neonates' Macrosomia with Maternal Lipid Profile of Healthy Mothers. *Pediatr. Neonatol*.**55**, 28–34 (2014).

26. Kulkarni, S. R. *et al.* Maternal Lipids are as Important as Glucose for Fetal Growth: Findings From the Pune Maternal Nutrition Study. *Diabetes Care*.**36**, 2706–2713 (2013).
27. Zafman, K. B., Bergh, E. & Fox, N. S. Accuracy of Sonographic Estimated Fetal Weight in Suspected Macrosomia: The Likelihood of Overestimating and Underestimating the True Birthweight. *J Matern Fetal Neonatal Med*.**33**, 967–972 (2020).
28. Weiner, E. *et al.* Comparison between Three Methods of Fetal Weight Estimation during the Active Stage of Labor Performed by Residents: A Prospective Cohort Study. *Fetal Diagn. Ther*.**42**, 117–123 (2017).
29. Malin, G. L., Bugg, G. J., Takwoingi, Y., Thornton, J. G. & Jones, N. W. Antenatal Magnetic Resonance Imaging Versus Ultrasound for Predicting Neonatal Macrosomia: A Systematic Review and Meta-Analysis. *BJOG*.**123**, 77–88 (2016).
30. Mazzone, E. *et al.* Prediction of Fetal Macrosomia Using Two-Dimensional and Three-Dimensional Ultrasound. *Eur J Obstet Gynecol Reprod Biol*.**243**, 26–31 (2019).
31. Yuan, X. *et al.* Fibrin/Fibrinogen Degradation Products in Late Pregnancy Promote Macrosomia Prediction in Normal Uncomplicated Pregnancy. *Placenta*.**96**, 27–33 (2020).
32. Shigemi, D., Yamaguchi, S., Aso, S. & Yasunaga, H. Predictive Model for Macrosomia Using Maternal Parameters without Sonography Information. *J Matern Fetal Neonatal Med*.**32**, 3859–3863 (2019).
33. Zhou, B. Predictive Values of Body Mass Index and Waist Circumference to Risk Factors of Related Diseases in Chinese Adult Population. *Chin J Epidemiol*.**23**, 5–10 (2002).
34. Gupta, Y., Kalra, B., Baruah, M. P., Singla, R. & Kalra, S. Updated Guidelines On Screening for Gestational Diabetes. *Int J Womens Health*.**7**, 539–550 (2015).
35. Lowe, S. A. *et al.* SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy 2014. *Aust N Z J Obstet Gynaecol*.**55**, e1–e29 (2015).

Figures

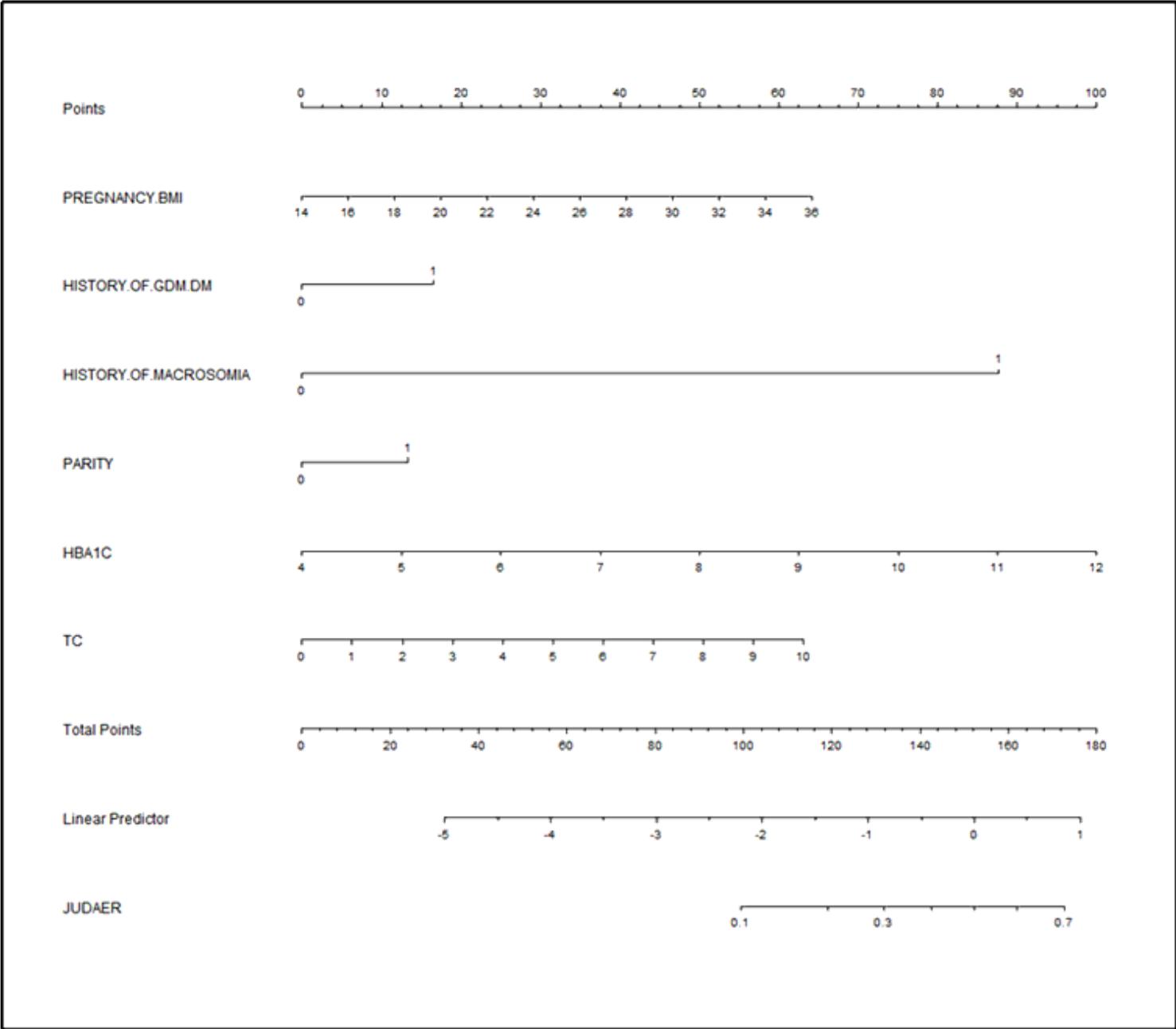


Figure 1
 Nomogram for predicting macrosomia in first trimester

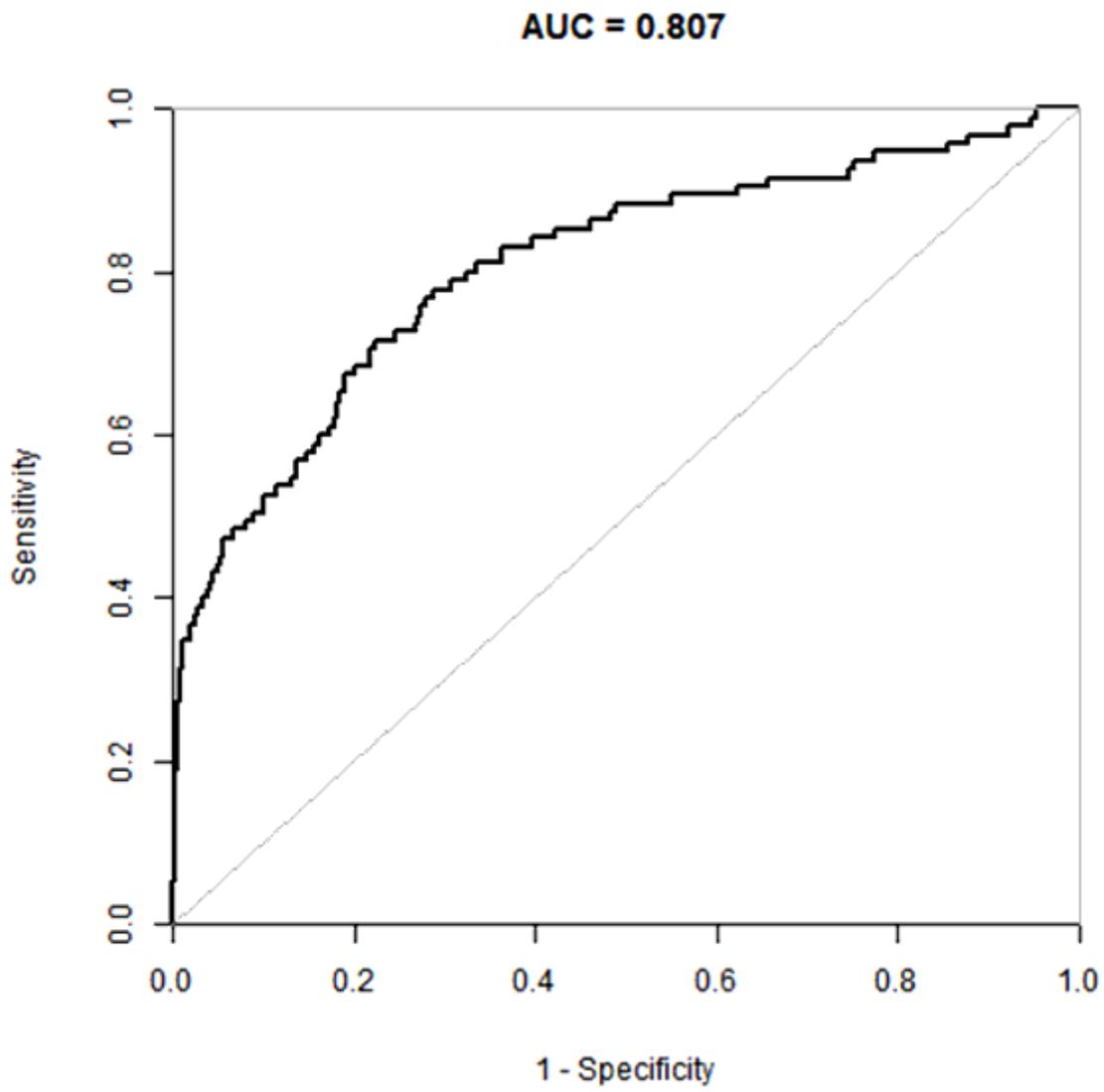


Figure 2

ROC curve for the accuracy of the nomogram for macrosomia.