A New Model for the Prediction of Preeclampsia in Twin Pregnancy：a Retrospective Cohort Study

Qing Han
Affiliated Hospital of Fujian Medical University
Shuisen Zheng
Affiliated Hospital of Fujian Medical University
Rongxin Chen
Affiliated Hospital of Fujian Medical University
Huale Zhang
Affiliated Hospital of Fujian Medical University
Jianying Yan (yanjy2019@fjmu.edu.cn)
Affiliated Hospital of Fujian Medical University

Research Article

Keywords: Twins, preeclampsia, least absolute shrinkage and selector operator regression, nomogram

Posted Date: September 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-810824/v1

Abstract

Objective: To develop an effective nomogram model with which to predict the risk of preeclampsia in twin pregnancies.

Material and Methods: The study was a retrospective cohort study of women pregnant with twins who attended antenatal care and labored between January 2015 and December 2020 at the Fujian Maternity and Child Health Hospital, China. We extracted Maternal demographic data and clinical characteristics. Then we performed the least absolute shrinkage and selection operator (LASSO) regression combined with clinical significance to screen variables. Thereafter, multivariate logistic regression was used to construct a nomogram that predicted the risk of preeclampsia in twin pregnancies. Finally, the nomogram was validated using C-statistics (C-index) and calibration curves.

Results: A total of 2 469 women with twin pregnancies were included, of whom 325 (13.16%) women had preeclampsia. Multivariate logistic regression models revealed that serum creatinine, uric acid, mean platelet volume, high density lipoprotein, lactate dehydrogenase, fibrinogen, primiparity, pre-pregnancy body mass index, and regular prenatal were independently associated with preeclampsia in twin pregnancies. The constructed predictive model exhibited a good discrimination and predictive ability for preeclampsia in twin pregnancies (concordance index 0.821).

Conclusion: The model for the prediction of preeclampsia in twin pregnancies has high accuracy and specificity. It can be used to assess the risk of preeclampsia in twin pregnancies.

Background

Preeclampsia is a unique complication of pregnancy and occurs in 2–5% of all pregnancies. It is the leading cause of maternal and fetal perinatal morbidity and mortality[1].The etiology and pathogenesis of preeclampsia remain unclear. Therefore, it is particularly important to strengthen the screening and prediction of high-risk groups before delivery. With the development of assisted reproductive technology, the incidence of twin pregnancy is increasing yearly. Clinical studies have shown that the incidence of preeclampsia is two to three times higher in twin than in singleton pregnancies[2, 3]. However, in recent years, research on the risk prediction of preeclampsia is mostly limited to singleton pregnancies, and it is not clear whether the predictors in singletons are equally applicable to twin pregnancies. Therefore, we conducted a retrospective cohort study to explore the high-risk factors associated with preeclampsia in twin pregnancies and built a clinical prediction model to guide early interventions and improve pregnancy outcomes.

Materials And Methods

Research object

We performed a population-based retrospective cohort study on women with twin pregnancies who attended antenatal care and labored at the Fujian Maternity and Child Health Hospital between January 2015 and December 2020. A total of 2 469 women with twin pregnancies were included in the study (Figure 1). According to clinical diagnosis, they were divided into a preeclampsia group (325 cases) and a normal pregnancy group (2 144 cases).

Measurement Methods

Participants underwent routine blood tests when hospitalized for other indications such as childbirth and abnormal fetal heart monitoring. All the blood tests (Blood routine, liver function, kidney function, blood lipid parameters, coagulation parameters) were performed before the clinical diagnosis of preeclampsia. We used an automatic hematology system XE-5000 (Sysmex Corporation, Japan) to measure peripheral blood variables.

Procedures

The following data were collected from electronic medical records of the hospital: (1) basic information and medical history including age, height, weight and body mass index (BMI), gravidty, parity, prenatal visits, chorionicity and in vitro fertilization–embryo transfer [IVF-ET] (2) auxiliary examination findings inclucing routine blood parameters (red blood cell count, platelets, hematocrit, platelet distribution width, mean platelet volume[MPV]), liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], transglutaminase [GGT]), kidney function (serum creatinine [CREm], uric acid [URIC]), blood lipid parameters (cholesterol, triglycerides [TG], apolipoprotein-b, high-density lipoprotein [HDL], low-density lipoprotein[LDL] and coagulation parameters (prothrombin time [PT], fibrin degradation products, thrombin time, D-dimer, fibrinogen [Fib], activated partial thromboplastin time[APTT] and international normalized ratio [INR]). (3) maternal complications: gestational diabetes [GDM], premature rupture of membranes [PROM].

Statistical Analysis

We compared the differences between the two groups using the independent sample t-test or nonparametric tests. Qualitative data are expressed as frequencies and percentages, and the Pearson's chi-square test or Fisher’s exact test were conducted to analyse differences between groups. All women in the study were randomly divided into a training cohort and a test cohort. The training cohort (n = 1470) account for 70% of the participants and the test cohort (n = 729) account for 30%. Then the least absolute shrinkage and selection operator (LASSO) regression, with 10-fold cross-validation were used to select the most useful predictive variables via 1se criteria in the training cohort, whereas internal validation was performed in the test cohort. Thereafter, combining with clinical significance, we built the model with multivariate logistic regression; in order to visualize the efficiency of these models, a nomogram of the combined models was formulated. The calibration curves and Harrell’s concordance index (C-Index) were used to assess the ability of various models to predict the risk of preeclampsia in twin pregnancies. Bootstrap resampling (1 000 resamples) was used for plotting calibration curves.

Quantitative data are presented as mean ± standard deviation, denoted as X±SD or medians with interquartile range (IQR). We collected data for this study in Excel (Microsoft ® Excel ® 2010), and analyzed and graph them using the SPSS 25.0 (IBM, Armonk, NY, USA) and R software (V3.6.2).

Results

Baseline characteristics

Totally, 2 469 women with twin pregnancies were included, of whom 325 (13.16%) women had preeclampsia. There were no statistically significant differences of clinical characteristics between training cohort (n = 1470) and test cohort (n =729) (Table 1).

We compared the general baseline data of the preeclampsia and the normal pregnancy groups and found there were no statistically significant differences in age, height, in vitro fertilization–embryo transfer, choriocarcinoma, and gestational diabetes between the two groups. The proportion of primipara in the preeclampsia group was greater than in the normal pregnancy group (P=0.006), while the proportion of pregnant women who received regular check-ups was significantly lower in the preeclampsia group than in the normal pregnancy group (P=0.007). There was also a statistically significant difference in the incidence of premature rupture of membranes between the two groups (P=0.003). A comparison of the serological indicators in the two groups revealed that, in terms of renal function parameters, URIC and CREm were significantly higher in the preeclampsia than in the normal pregnancy group, and the difference was statistically significant. As for liver function indicators, the differences in AST and LDH were statistically significant, while the difference in ALT and GGT between the two groups was not statistically significant. In terms of blood lipid indices, HDL was significantly lower in the preeclampsia group than in the normal pregnancy group (P<0.001), but the difference in TG between the two groups was not statistically significant. With respect to coagulation indicators, the differences in fibrinogen degradation products, thrombin time, D-dimer, Fib, and activated partial thromboplastin time between the two groups were statistically significant, while the differences in PT and INR were not statistically significant. In terms of routine blood indicators, red blood cell count, platelet count, and hematocrit were lower in the preeclampsia than in the normal pregnancy group, while MPV and platelet distribution width were higher in the preeclampsia than in the normal pregnancy group, the difference was statistically significant (Table 2).

Predictors of preeclampsia in twin pregnancies

We used LASSO regression to screen the peripheral blood parameter variables via 1se criteria (λ=0.02671711) in the training set, and finally seven high-risk factors (CREm, URIC, MPV, HDL, AST, LDH, Fib) were included in the prediction model (Figure 2). The seven variables (CREm, URIC, MPV, HDL, AST, LDH, Fib) initially screened by the LASSO regression model have an area under the receiver operating characteristic (ROC) curve of 0.7955 in the training cohort and the area under the ROC curve in the test cohort is 0.7868. There is thus good specificity and sensitivity (Figure 3).

The seven variables were included in the multivariate logistic together with clinically significant variables (primipara, regular prenatal visits, pre-pregnancy BMI). Multivariate logistic regression analysis of the selected variables showed that primipara (odds ratio [OR], 1.343; 95% confidence intervals [CI], 1.024 - 1.762), pre-pregnancy BMI (OR, 1.071; 95% CI, 1.030 - 1.114), regular prenatal visits (OR, 0.626; 95% CI, 0.466 - 0.842), CREm (OR, 1.033; 95% CI, 1.022 - 1.044), URIC (OR, 1.004; 95% CI, 1.003 - 1.006), MPV (OR, 1.275; 95% CI, 1.119 - 1.453), LDH (OR, 1.004; 95% CI, 1.002 - 1.005), HDL (OR, 0.472; 95% CI, 0.388 - 0.567), and Fib (OR, 0.794; 95% CI, 0.688 - 0.916) were independently associated with preeclampsia in twin pregnancies (Table 3).

In order to facilitate clinical evaluation and application, we use R's lrm package to draw the nomogram of the multi-factor logistics regression model. The nomogram provides a practical tool to identify the risk of developing preeclampsia in pregnant women with twin pregnancies (Figure 4).

Nomogram validation

After 1000 Bootstrap self-sampling internal verifications were performed on the model in the data set, this study showed a predictive accuracy of 0.821 (measured by C-index). There was a moderate correlation between the actual outcome and the outcome predicted by the nomogram. This was shown by the calibration plot of the probability of preeclampsia in twin pregnancies (Figure 5).

Discussion

We found that the probability of twin pregnancy being complicated with preeclampsia was 13.16%, slightly higher than in previous reports[4]. We performed a more comprehensive screening of high-risk factors for preeclampsia in twin pregnancies through the acquisition of clinical medical records of patients. The results of logistic multivariate analysis showed that primiparity, regular obstetric visits, pre-pregnancy BMI, CREm, URIC, MPV, HDL, LDH, Fib, Primipara, Pre-pregnancy BMI and Regular prenatal were independently associated with preeclampsia in twin pregnancies. The nomogram prediction model (concordance index 0.821) was further constructed with good accuracy and conformity, and was able to make individualized predictions for pregnant women with twin pregnancies complicated by preeclampsia, so as to allow for timeous clinical interventions and thus reduce the number of adverse outcomes in mothers and children.

The expert consensus published by the American College of Obstetricians and Gynecologists showed that primiparity, obesity, advanced age, and assisted reproductive technology were high-risk factors for pregnancies complicated by preeclampsia in singletons[5]. Taguchi et al. found that pre-pregnancy BMI and primiparity were independent risk factors for preeclampsia in twin pregnancies[6].Similarly, in another prospective cohort study, Chen et al. [7]reported that pre-pregnancy BMI was significantly associated with the risk of preeclampsia in twin pregnancies, which is consistent with our findings. In addition, regular antenatal check-ups, strengthening the monitoring for risk factors, and timely intervention can reduce the incidence of preeclampsia in twin pregnancies.

Various biochemical factors in maternal serum play an important role in the pathophysiological development of preeclampsia, and the composition, source and mechanism is different for each of these factors. At present, the serum markers used to screen for preeclampsia in twin pregnancies mainly include pregnancy-associated plasma protein A, placental protein 13, placental growth factor[8], inhibin A, and unconjugated estriol[9]; however, widespread roll-out of these indicators is difficult to develop and promote in underdeveloped areas. Therefore, this study measures peripheral blood parameters, screens out predictive indicators with high sensitivity and specificity, and provides a basis for the development of economical and efficient screening programs for twin pregnancies with preeclampsia.

Previous studies on the relation between MPV and preeclampsia were based on pregnant women with singleton pregnancies, while there were fewer studies involving those with twin pregnancies. In a cohort study by they found that the peripheral blood MPV value of pregnant women with preeclampsia was significantly higher than that of normal pregnant women[10]. A cross-sectional comparative study by Tesfay et al. showed that MPV had a good predictive value for the development of preeclampsia[11]. However, these studies were based on singleton pregnancies; we found that an increase in peripheral blood MPV was associated with an increased risk of preeclampsia in twin pregnancies as well. The increase in MPV reflects the enhancement of platelet activation. In patients with preeclampsia, due to the increase in platelet consumption and destruction, the bone marrow produces and releases a large quantity of platelets, which leads to an increase in MPV[12]. Conversely, preeclampsia may cause complex diseases in the endogenous blood coagulation pathway and consumes Fib, resulting in a decrease in Fib[13]. We found an increase in the risk of preeclampsia in twin pregnancies with decreasing Fib, which is similar to the results reported in related studies[14].

Some studies have shown that, as pregnancy progresses, serum total cholesterol, TG, and LDL-C concentrations increase, and this abnormal dyslipidemia during pregnancy is related to preeclampsia and other adverse pregnancy outcomes[15]. The pathophysiological basis may be that the increase in circulating lipid levels leads to an accumulation of lipids in endothelial cells, which reduces the release of prostacyclin and leads to oxidative stress[16]. A meta-analysis by Spracklen et al. showed that low levels of HDL-C are significantly associated with the risk of preeclampsia[17] and our study found that women with twin pregnancies who have low HDL-C also have this risk.

The main energy supply pathway to the placenta occurs through glycolysis. LDH is an intracellular enzyme required for glycolysis. Under hypoxic conditions, LDH is activated to promote glycolysis and produce large amounts of lactic acid. Therefore, elevated LDH levels often indicate cell damage and dysfunction. Studies have shown that peripheral blood LDH levels in patients with preeclampsia are significantly increased[18]. Our study found this feature in twin pregnancies with preeclampsia. In addition, some scholars have found that high levels of LDH are significantly related to the occurrence of adverse perinatal outcomes in patients with preeclampsia[19]. It is necessary to explore in future studies whether there is a dose-response relationship between high levels of LDH and the occurrence of adverse preeclampsia outcomes.

The kidney is an important organ involved in preeclampsia. Damage to glomerular endothelial cells and destruction of the relation between endothelial cells and podocytes are the main underlying pathogenetic mechanisms of preeclampsia[20].Patients with preeclampsia are prone to renal dysfunction caused by extensive renal arteriolar spasm. This causes glomerular swelling, decreased glomerular filtration rate, and decreased renal blood flow, which leads to obstruction of the excretion and clearance of renal metabolites such as URIC and CREm; this results in an increase in serum URIC and CREm. In a prospective case-control study, Enaruna et al. found that the URIC level of patients with preeclampsia was significantly increased, and that higher levels reflected disease severity[21]. Jhee et al. developed models using machine learning to predict late-onset preeclampsia and found that CREm levels were one of the most influential variables included in the prediction models[22]. Our study was in agreement with this, demonstrating that URIC and CREm levels were independent risk factors for preeclampsia in twin pregnancies.

We are aware of the limitations of our study. Our study is a single-center retrospective cohort study which may result in a risk of overestimating model performance. However, as a tertiary hospital in Southeast China, our number of cases is still representative and we believe the model would be useful in pregnancy supervision. Further prospective cohort and multi-center joint research will help to further expand the research results, improve the prediction accuracy of the model, and confirm the conclusions.

In summary, the prediction model of preeclampsia in twin pregnancies constructed in this study has good accuracy and high clinical application value, and can be used as a reference for obstetricians. We should pay attention to twin pregnancies with high-risk factors in clinical practice and perform careful screening, early intervention and active treatment, so as to reduce the occurrence of adverse pregnancy outcomes.

Conclusion

This study performed a more comprehensive screening of high-risk factors for preeclampsia in twin pregnancies through the acquisition of clinical medical records of patients. The model for the prediction of preeclampsia in twin pregnancies has high accuracy and specificity. It can be used to assess the risk of preeclampsia in twin pregnancies.

Abbreviations

ALT, alanine aminotransaminase

AST, aspartame aminotransferase

BMI, body mass index

CI, confidence intervals

CREm, creatinine

Fib, fibrinogen

GGT, transglutaminase

HDL, high-density lipoprotein

INR, international normalized ratio

LASSO, least absolute shrinkage and selection operator

LDH, lactate dehydrogenase

MPV, mean platelet volume

OR, odds ratio

PT, prothrombin time

ROC, receiver operating characteristics

TG, triglycerides

URIC, uric acid

Declarations

Ethical approval

This study obtained an ethical approval from the ethical committee of Fujian Maternity and Child Health Hospital. An informed written consent for the patients was not required because only information from unidentifiable patient was used.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the data used in our research acquired administrative permissions. An informed written consent for the patients was not required, because of the nature of the retrospective setting for our study and only information from unidentifiable patient was used. Consent waiver obtained from the institutional ethics committee of Fujian Maternity and Children's Hospital. The study was legally approved by the institutional ethics committee of Fujian Provincial Maternity and Children's Hospital and conducted in accord with the guidelines of the Declaration of Helsinki, and the rights of all participants were protected.

Consent for publication

The requirement for individual patient consent was waived as data were extracted from an anonymized database and our study did not influence patient care.

Availability of data and materials

Data were anonymized, and no patient information was included to preserve confidentiality. All data used to reach the aforementioned conclusions is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported in part by grants from Fujian Science and Technology Project(2019J01514) Guide Fund for the Development of Local Science and Technology from the Central Government (2020L3019), Fujian provincial Health and Family Planning Commission Youth Research Project (2019-2-10).

Authors' contributions

QH and J-YY were responsible for conception and design of the study. H-LZ, S-SZ and R-XC participated in the collection of data and performed the statistical analysis. S-SZ and QH drafted the manuscript. H-LZ and J-YY helped to refine the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all participants in this study and the staff from the Department of Obstetrics, Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University for their work on patients enrollment and follow-up.

References

1. Ree PH, Hahn WB, Chang SW, Jung SH, Kang JH, Cha DH, Kang MS, Huh JY: **Early detection of preeclampsia using inhibin a and other second-trimester serum markers**. *Fetal Diagn Ther* 2011, **29**(4):280–286.
2. Baha M. Sibai M, John Hauth M, Steve Caritis M, Marshall D. Lindheimer M, PhD,, Cora MacPherson P, Mark Klebanoff M, J. Peter VanDorsten M, Mark Landon M, Menachem Miodovnik M, Richard Paul M *et al*: **Hypertensive disorders in twin versus singleton gestations**. *Am J Obstet Gynecol* 2000, **182**(4):938–942.
3. Bdolah Y, Lam C, Rajakumar A, Shivalingappa V, Mutter W, Sachs BP, Lim KH, Bdolah-Abram T, Epstein FH, Karumanchi SA: **Twin pregnancy and the risk of preeclampsia: bigger placenta or relative**

ischemia? *Am J Obstet Gynecol* 2008, **198**(4):428 e421-426.

4. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides KH: **Hidden high rate of pre-eclampsia in twin compared with singleton pregnancy**. *Ultrasound Obstet Gynecol* 2017, **50**(1):88–92.
5. **Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222**. *Obstet Gynecol* 2020, **135**(6):e237-e260.
6. Taguchi T, Ishii K, Hayashi S, Mabuchi A, Murata M, Mitsuda N: **Clinical features and prenatal risk factors for hypertensive disorders in twin pregnancies**. *J Obstet Gynaecol Res* 2014, **40**(6):1584–1591.
7. Chen J, Zhao D, Liu Y, Zhou J, Zou G, Zhang Y, Guo M, Duan T, Van Mieghem T, Sun LA-O: **Screening for preeclampsia in low-risk twin pregnancies at early gestation**. 2020(1600 – 0412 (Electronic)).
8. Maymon R, Trahtenherts A, Svirsky R, Melcer Y, Madar-Shapiro L, Klog E, Meiri H, Cuckle H: **Developing a new algorithm for first and second trimester preeclampsia screening in twin pregnancies**. *Hypertens Pregnancy* 2017, **36**(1):108–115.
9. Kim YR, Jung I, Heo SJ, Chang SW, Cho HY: **A preeclampsia risk prediction model based on maternal characteristics and serum markers in twin pregnancy**. *J Matern Fetal Neonatal Med* 2019:1–6.
10. Dundar O, Yoruk P, Tutuncu L, Erikci AA, Muhcu M, Ergur AR, Atay V, Mungen E: **Longitudinal study of platelet size changes in gestation and predictive power of elevated MPV in development of pre-eclampsia**. *Prenat Diagn* 2008, **28**(11):1052–1056.
11. Tesfay F, Negash M, Alemu J, Yahya M, Teklu G, Yibrah M, Asfaw T, Tsegaye A: **Role of platelet parameters in early detection and prediction of severity of preeclampsia: A comparative cross-sectional study at Ayder comprehensive specialized and Mekelle general hospitals, Mekelle, Tigray, Ethiopia**. *PLoS One* 2019, **14**(11):e0225536.
12. Kaito K, Otsubo H, Usui N, Yoshida M, Tanno J, Kurihara E, Matsumoto K, Hirata R, Domitsu K, Kobayashi M: **Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia**. *Br J Haematol* 2005, **128**(5):698–702.
13. Han L, Liu X, Li H, Zou J, Yang Z, Han J, Huang W, Yu L, Zheng Y, Li L: **Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia**. *PLoS One* 2014, **9**(12):e114488.
14. Liu Z, Zhang H, Chen L, Lin L, Yan J: **Blood Coagulation Indices in Twin Pregnancy Complicated with Preeclampsia**. *J Coll Physicians Surg Pak* 2020, **30**(3):276–281.
15. Jin WY, Lin SL, Hou RL, Chen XY, Han T, Jin Y, Tang L, Zhu ZW, Zhao ZY: **Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: a population-based study from China**. *BMC Pregnancy Childbirth* 2016, **16**:60.
16. Ghio A, Bertolotto A, Resi V, Volpe L, Di Cianni G: **Triglyceride metabolism in pregnancy**. *Adv Clin Chem* 2011, **55**:133–153.
17. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK: **Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis**. *Am J Epidemiol* 2014, **180**(4):346–358.

18. Wu Y, Lu C, Pan N, Zhang M, An Y, Xu M, Zhang L, Guo Y, Tan L: **Serum lactate dehydrogenase activities as systems biomarkers for 48 types of human diseases**. *Sci Rep* 2021, **11**(1):12997.
19. Dave A, Maru L, Jain A: **LDH (Lactate Dehydrogenase): A Biochemical Marker for the Prediction of Adverse Outcomes in Pre-eclampsia and Eclampsia**. *J Obstet Gynaecol India* 2016, **66**(1):23–29.
20. Moghaddas Sani H, Zununi Vahed S, Ardalan M: **Preeclampsia: A close look at renal dysfunction**. *Biomed Pharmacother* 2019, **109**:408–416.
21. Enaruna NO, Idemudia JO, Aikoriogie PI: **Serum lipid profile and uric acid levels in preeclampsia in University of Benin Teaching Hospital**. *Niger Med J* 2014, **55**(5):423–427.
22. Jhee JH, Lee S, Park Y, Lee SE, Kim YA, Kang SW, Kwon JY, Park JT: **Prediction model development of late-onset preeclampsia using machine learning-based methods**. *PLoS*

Tables

Table 1: Clinical characteristics of the training and test cohort

	Training cohort（n=1 470）	Test cohort（n=729）	*P* value
Age (y)	29.9±4.41[a]	30.12±4.38 [a]	0.286
Height (cm)	160.17±4.99[a]	160.30±5.17 [a]	0.565
Pre-pregnancy weight (kg)	54.46±14.35[a]	54.67±8.56 [a]	0.703
Pre-pregnancy BMI (kg/m2)	27.71±6.46[a]	27.64±3.27 [a]	0.774
Gravidity	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.157
Parity	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.438
Primipara (n (%))	881 (50.6)	393 (53.9)	0.149
Regular prenatal visits (n (%))	1217 (69.9)	537 (73.7)	0.07
IVF-ET (n (%))	582 (33.4)	230 (31.6)	0.385
Chorionicity (n (%))			0.642
Monochorionic	545 (31.3)	236 (32.4)	
Dichorionic	1195 (68.7)	493 (67.6)	
GDM (n (%))	1357 (78.0)	548 (75.2)	0.142
PROM (n (%))	430 (24.7)	164 (22.5)	0.261

[a]Mean and standard deviation;

BMI, body mass index; IVF-ET, in vitro fertilization- embryo transfer; GDM, gestational diabetes mellitus; PROM, premature rupture of membranes

Table 2: General baseline information

	Normal pregnancy（n=2 144）	Preeclampsia（n=325）	*P* value
Age (y)	29.97±4.40[a]	30.09±4.64[a]	0.597
Height (cm)	160.18±5.03[a]	160.43±5.15[a]	0.396
Pre-pregnancy weight (kg)	54.24±8.07[a]	56.34±28.92[a]	0.006
Pre-pregnancy BMI (kg/m2)	22.94±3.36[a]	23.70±3.65[a]	<0.001
Gravidity	2.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.014
Parity	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.004
Primipara (n (%))	1014 (47.3%)	181 (55.7%)	0.006
Regular prenatal visits (n (%))	1544 (72.0%)	210 (64.6%)	0.007
IVF-ET (n (%))	690 (32.2%)	122 (37.5%)	0.064
Chorionicity (n (%))			0.391
Monochorionic	671 (31.3%)	110 (33.8%)	
Dichorionic	1473 (68.7%)	215 (66.2%)	
GDM (n (%))	491 (22.9%)	73 (22.5%)	0.916
PROM (n (%))	538 (25.1%)	56 (17.2%)	0.003
HDL (mmol/L)	1.63 [1.37, 1.96]	1.40 [1.15, 1.13]	<0.001
ALT （U/L）	11.86 [8.69, 17.68]	12.60 [8.85, 18.95]	0.062
AST （U/L）	18.50 [15.00, 22.70]	22.40 [17.60, 29.60]	<0.001
GGT （U/L）	12.00 [9.00, 17.10]	12.10 [8.55, 20.30]	0.612
APOb （g/L）	1.24±0.28[a]	1.20±0.33[a]	0.042
CHOL (mmol/L)	6.29±1.22[a]	5.95±1.58[a]	<0.001
TG (mmol/L)	4.05±1.66[a]	4.00±1.70[a]	0.598
LDL (mmol/L)	3.14±0.94[a]	2.96±1.02[a]	0.002
Glu (mmol/L)	4.88±1.26[a]	4.76±1.12[a]	0.09
CREm (umol/L)	50.77±11.65[a]	61.53±15.06[a]	<0.001
LDH (U/L)	205.70 [175.60, 255.70]	265.50[218.75,348.90]	<0.001
URIC (umol/L)	369.65±95.17[a]	462.57±117.44[a]	<0.001

PT (sec)	11.15±0.91[a]	11.14±0.92[a]	0.885
FDP (mg/L)	11.15 [7.71, 17.32]	14.80 [9.99, 25.14]	<0.001
TT (sec)	16.31±1.12[a]	16.75±1.14[a]	<0.001
D-dimer (mg/L FEU)	3.61 [2.37, 5.25]	4.33 [2.72, 7.22]	<0.001
Fib (g/L)	4.30±0.89[a]	3.85±1.09[a]	<0.001
INR	0.95±0.06[a]	0.95±0.07[a]	0.912
APTT (sec)	27.48±3.78[a]	28.58±4.04[a]	<0.001
PLT (×10^9/L)	197.09±57.70[a]	178.89±56.77[a]	<0.001
RBC (×10^12/L)	3.78±0.50[a]	3.69±0.52[a]	0.001
HCT (%)	33.21±4.32[a]	32.67±4.05[a]	0.033
PDW (fL)	12.92±2.55[a]	14.02±2.88[a]	<0.001
MPV (fL)	10.79±1.02[a]	11.30±1.03[a]	<0.001

[a]Mean and standard deviation;

BMI, body mass index; IVF-ET, in vitro fertilization- embryo transfer; GDM, gestational diabetes mellitus; PROM, premature rupture of membranes; HDL, high-density lipoprotein; AST, aspartame aminotransferase; ALT, alanine aminotransferase; GGT, transglutimase; APOb, apolipoprotein b; CHOL, cholesterol; TG, triglyceride; LDL, low-density lipoprotein; Glu, glucose; CREm, creatinine; LDH, lactate dehydrogenase; URIC, uric acid; PT, prothrombin time, FDP, fibrinogen degradation products, TT, thrombin time; Fib, fibrinogen; INR, international normalized ration, aPTT, activated partial thromboplastin time; PLT, platelets; RBC, red blood cell count; Hct, hematocrit; PDW, platelet distribution weight, MPV, mean platelet volume

Table 3: Multivariate logistic regression analysis of variables to identify factors predictive of preeclampsia in twin pregnancies

Co-variable	Odds ratio (OR)	95% CI of OR		*P*-value
		Lower Limit	Upper limit	
Primipara	1.343	1.024	1.762	0.033
Regular prenatal visits	0.626	0.466	0.842	0.002
Pre-pregnancy BMI	1.071	1.03	1.114	0.001
CREm	1.033	1.022	1.044	0.001
URIC	1.004	1.003	1.006	0.001
MPV	1.275	1.119	1.453	0.001
HDL	0.472	0.388	0.576	0.001
AST	1.006	0.996	1.017	0.256
LDH	1.004	1.002	1.005	0.001
Fib	0.794	0.688	0.916	0.002

CI, confidence intervals; BMI, body mass index; CREm, creatinine; URIC, uric acid; MPV, mean platelet volume; HDL, high-density lipoprotein; AST, aspartame aminotransferase; LDH, lactate dehydrogenase; Fib, fibrinogen

Figures

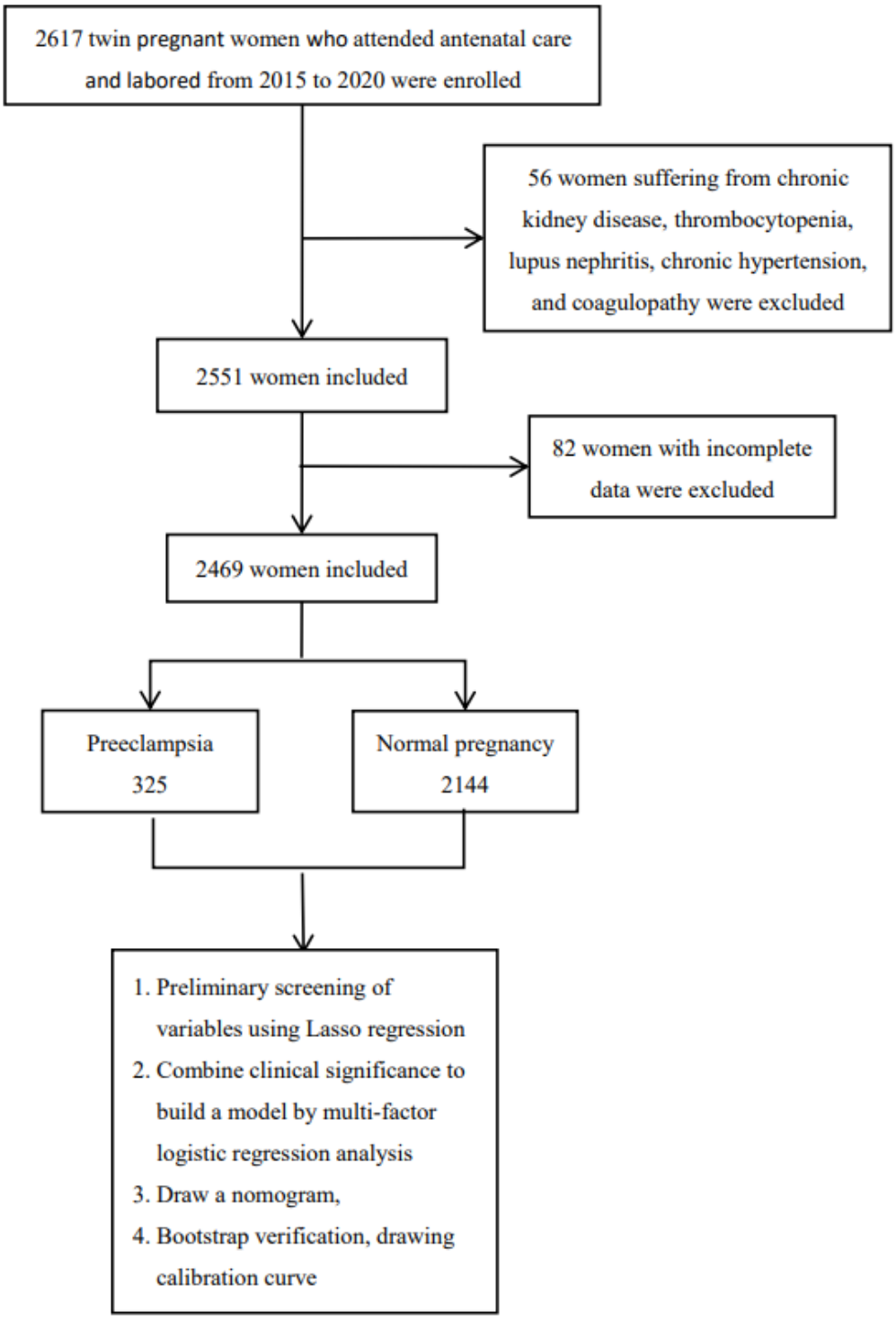

Figure 1

Flowchart of participant selection for the study cohort

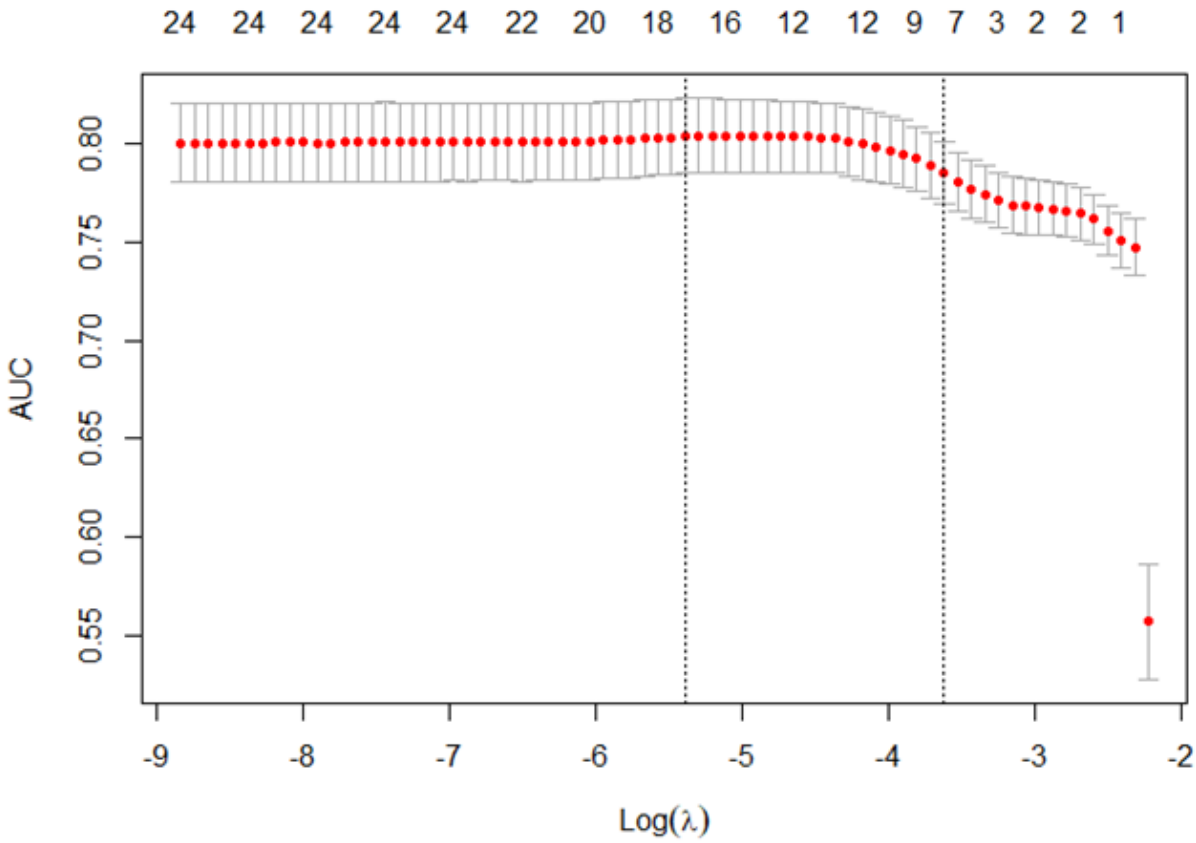

Figure 2

Tuning parameter (lambda) selection in the LASSO model used 10-fold cross-validation via 1se criteria for determining the risk of preeclampsia in twin pregnancies LASSO, Least absolute shrinkage and selection operator

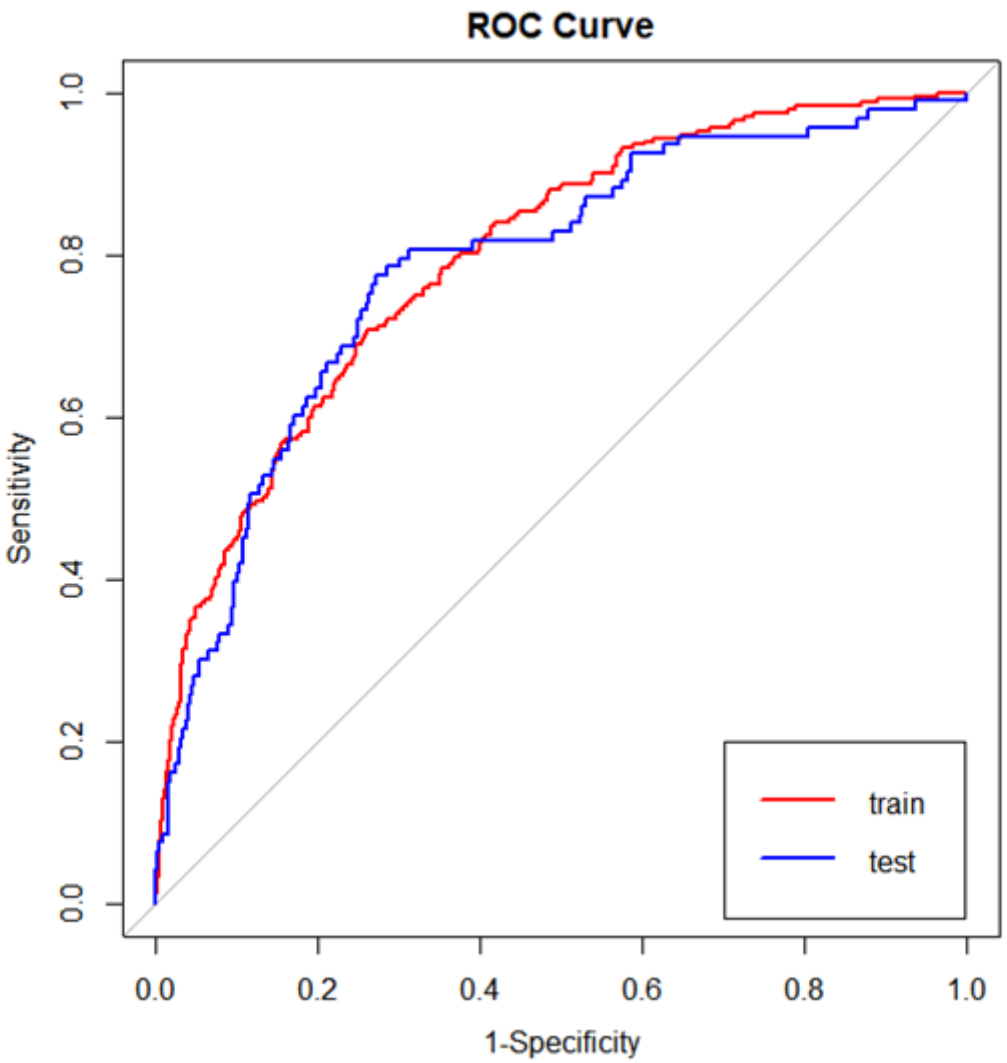

Figure 3

The ROC curve of the preliminary screened variables in the training set and the test set ROC, receiver operating curve

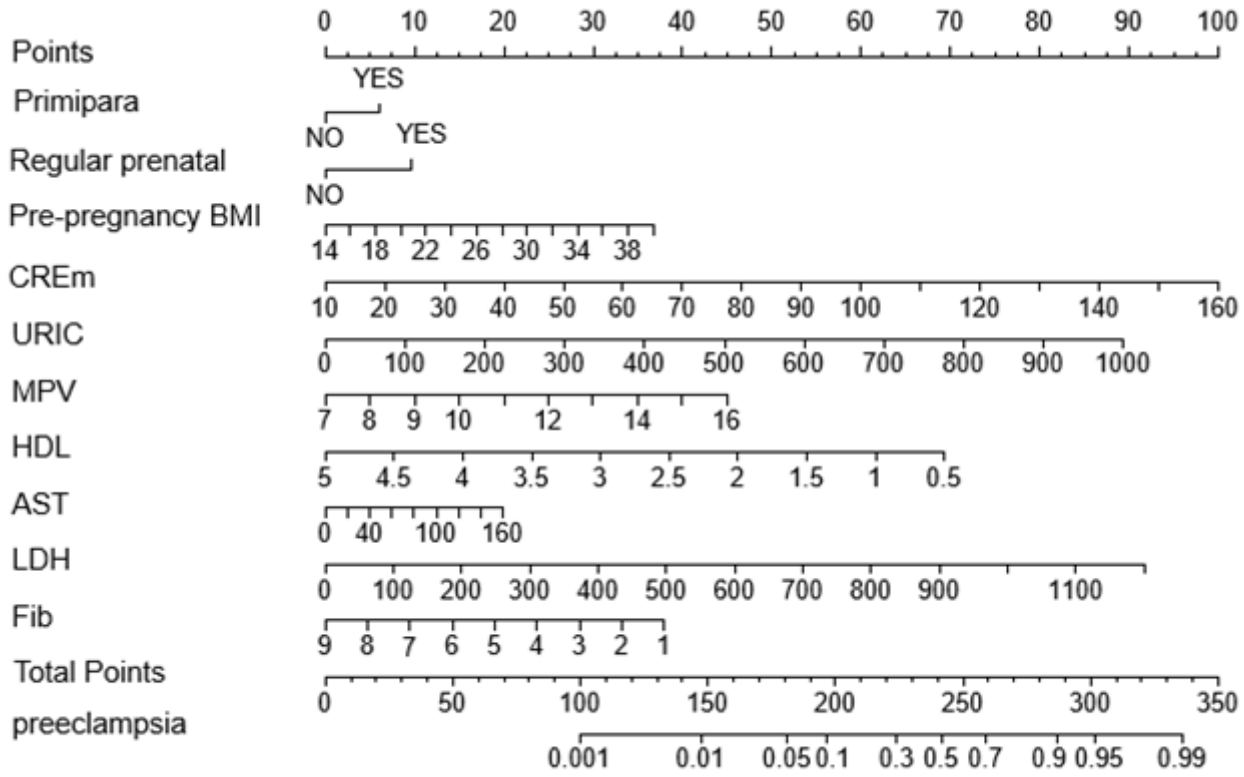

Figure 4

Nomogram for predicting the risk of preeclampsia in twin pregnancies

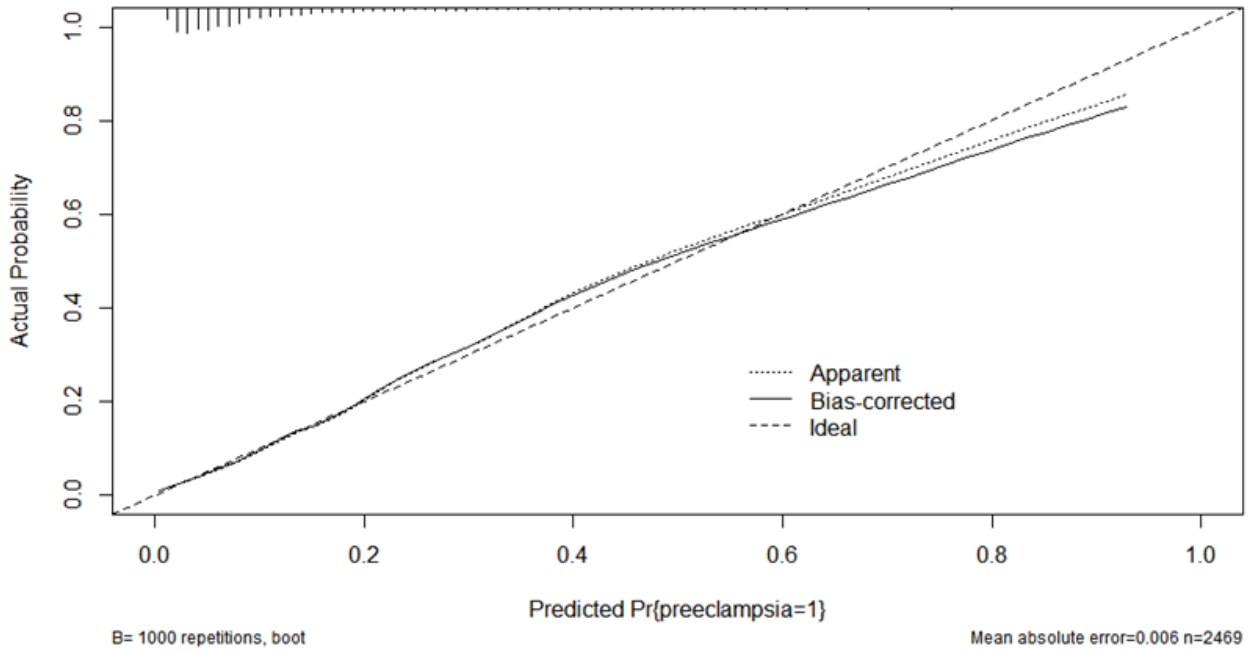

Figure 5

Calibration curves for predicting the risk of preeclampsia in twin pregnancies - nomogram construction (bootstrap = 1 000 repetitions)