Predicting hypertensive disorders in pregnancy using multiple methods: Models with the placental growth factor parameter

Ge Sun\textsuperscript{a,b}, Qi Xu\textsuperscript{c}, Song Zhang\textsuperscript{a,b}, Lin Yang\textsuperscript{a,b,*}, Guoli Liu\textsuperscript{c,*}, Yu Meng\textsuperscript{a,b}, Aiqing Chen\textsuperscript{d}, Yimin Yang\textsuperscript{a,b}, Xuwen Lin\textsuperscript{a,b}, Dongmei Hao\textsuperscript{a,b}, Xiaohong Liu\textsuperscript{d} and Jing Shao\textsuperscript{d}

\textsuperscript{a}Faculty of Environment and Life Sciences, Beijing University of Technology, Beijing 100124, China
\textsuperscript{b}Beijing International Science and Technology Cooperation Base for Intelligent Physiological Measurement and Clinical Transformation, Beijing 100124, China
\textsuperscript{c}Peking University People’s Hospital, Beijing 100044, China
\textsuperscript{d}Beijing Yes Medical Devices Co. Ltd., Beijing 100152, China

Abstract.

\textbf{BACKGROUND:} Placental growth factor (PlGF), one of the biomarkers, has a certain predictive effect on hypertensive disorders in pregnancy (HDP).

\textbf{OBJECTIVE:} To study the HDP prediction effect of different methods for variable selection and modeling for models containing PlGF.

\textbf{METHODS:} For the model containing PlGF, the appropriate range of PlGF parameters needed to be selected. Step-logistic regression and lasso were used to compare the model effect of twice range selection. The PlGF model with good predictive effect and appropriate detecting gestational age was selected for the final prediction.

\textbf{RESULTS:} The effect of the model containing PlGF tested at 15–16 weeks was better than the PlGF value without comprehensive screening. The sensitivity of both methods was over 92%. By comprehensive comparison, the final model of lasso method in this study was more effective.

\textbf{CONCLUSIONS:} In this study, a variety of methods were used to screen models containing PlGF parameters. According to clinical needs and model effects, the optimal HDP prediction model with PlGF parameters in the second trimester of 15–26 weeks of pregnancy was finally selected.

Keywords: Placental growth factor, model parameters, variable selection

1. Introduction

Hypertensive disorders in pregnancy (HDP) is an important risk factor for increasing neonatal and maternal morbidity and mortality [1–3]. Early prediction and treatment can be carried out through related risk factors [4]. Preeclampsia in HDP is one of the most serious pregnancy complications [5,6]. Studies
Table 1
Classification of risk factors for HDP

| Category                        | Risk factors                                      |
|---------------------------------|---------------------------------------------------|
| Basic situation                 | Age, Gravidity, Parity, Height, Pre-BMI           |
| Family history                  | Family history of hypertension                     |
| Diseases                        | GDM, Diabetes mellitus with pregnancy, Pregnancy with immune system disease |
| The situation of this pregnancy | SBP, DBP, MAP, GA-W                                |
| Biomarkers                      | PlGF                                              |

Notes: Pre-BMI: Pre-pregnancy body mass index; Diseases: Existing or potential underlying medical diseases and pathological conditions; GDM: Gestational diabetes mellitus; SBP, DBP, MAP: Systolic blood pressure, Diastolic blood pressure, and Mean arterial pressure all at 11–13 weeks of pregnancy; GA-W: Weight gain during pregnancy.

have shown that placental growth factor (PlGF) was related to the diagnosis of HDP [7]. Nguyen et al. studied the predictive value of Soluble fms-Like Tyrosine Kinase 1 (sFlt-1) and PlGF for women at high risk of preeclampsia [8]. Combining maternal risk factors, mean arterial pressure (MAP), PlGF, and uterine artery pulsatility index (UTPI) for related prediction accuracy was higher [9]. Bian et al. used sFlt-1/PlGF ratio to predict the risk of preeclampsia in Asian women [10]. PlGF combined with other angiogenesis markers, such as sFlt-1, also had a certain prognostic value for preeclampsia [11,12]. There are also some controversies in related prediction research. Cnossen et al. found that the predictive value of uterine artery Doppler studies alone for early and late onset preeclampsia was very low [13]. No test could reliably predict preeclampsia, and further prospective studies were needed to prove the clinical utility of predictors [14].

A large number of foreign studies have confirmed the role of PlGF in predicting HDP. Such as using maternal factors plus biomarkers (PlGF, etc.) for prediction. But the associated clinical utility was unclear. For PlGF, one of biomarkers, the appropriate range of PlGF parameters included in the predictive model needed to be further selected. Moreover, variable screening methods were mostly based on the statistical indicator (P value), rather than comprehensive screening of risk factors. The data analysis method of this study mainly included two aspects: variable selection and model methods. Model parameters were screened based on the effects of various models containing PlGF, and several model methods were comprehensively selected to compare the prediction effects.

2. Materials and methods

2.1. Subjects

The data source of this study: 1368 cases collected from July 2015 to December 2016 provided by the Obstetrics Department of Peking University People’s Hospital. After the pregnant women gave birth, according to the doctor’s final diagnosis, the subjects were divided into 186 HDP group and 1182 control (normal pregnancy) group.

Exclusion criteria for overall data: pregnant women with chronic hypertension combined with pregnancy or eclampsia; cases with incomplete factors or data; singular values.

2.2. Classification of risk factors

The model parameters selected in this study were shown in Table 1.
| Gestational weeks | PI GF value (pg/ml) |
|-------------------|-------------------|
| 5–15 weeks        | 35                |
| 16–20 weeks       | 60                |
| > 20 weeks        | 100               |

Placental insufficiency raises the risk of preterm birth (< 35 weeks) High risk: < 12

2.3. For PI GF parametric model

2.3.1. Preliminary screening of PI GF parameters

In this study, we reviewed the cases where serum PI GF was mainly tested twice. The gestational week of the next test (mainly starting at 15 weeks) was greater than the previous one. Therefore, 211 cases of data were preliminarily selected. Among them, 37 cases were in the HDP group (pregnant women without chronic hypertension combined with pregnancy and eclampsia); 174 cases were in the control (normal pregnancy) group. The ratio of training set to test set was 7:3. In the training set, there were 28 cases in the HDP group and 119 cases in the control group. In the test set, there were 9 cases and 55 cases in the HDP group and control group, respectively.

About the parameters of PI GF: PI GF₁ for the first test, PI GF₂ for the second test, PI GF diag for PI GF₂ minus PI GF₁. This study included the risk factors (without PI GF) mentioned in Table 1 and three factors related to PI GF, using step-logistic regression and lasso model to screen variables and build models. Both methods automatically screen and leave PI GF₂ (mainly the PI GF value of the second test starting from 15 weeks). And in the step-logistic regression test, PI GF₂ was not statistically significant. \( P < 0.05 \) has significant difference. Therefore, it was necessary to further select PI GF parameters according to the physiological changes of PI GF and effect of the prediction model.

2.3.2. Selection of the appropriate model with PI GF parameter

The main biological function of PI GF is to promote the formation of placental blood vessels [10,11]. PI GF is a kind of biomarker. Changes in serum PI GF of healthy pregnant women during pregnancy: PI GF levels are low at 5–15 weeks of gestation, and PI GF increases rapidly at 15–26 weeks, reaching a peak at 28–30 weeks of gestation.

And the main distribution of PI GF measured twice was also concentrated in 15–26 weeks. Combined with the variable screening and model effect of 2.3.1, the appropriate model with PI GF parameter could be selected. Finally, this study selected the serum PI GF test data at 15–26 weeks. The PI GF test for this study was a dry fluorescence immunoassay analyzer from Hebei Twente Biotechnology Development Co., Ltd. Table 2 showed the normal range of PI GF value provided by the company that tested PI GF in this study.

According to Table 2, the data of serum PI GF in 15–26 weeks were specifically selected. When PI GF has multiple detection values at 15–26 weeks, it generally takes a relatively abnormal value. At 15 weeks, PI GF value ≤ 35 is abnormal. At 15–20 weeks (Not including 15 weeks), PI GF value ≤ 60 is abnormal. At 20–26 weeks (Not including 20 weeks), PI GF value ≤ 100 is abnormal. As long as the PI GF value is less than 12 pg/ml, it is preferred.

Finally, the results of this study selected data for a total of 922 cases. There were 85 cases in the HDP group (pregnant women without chronic hypertension combined with pregnancy and eclampsia) and 837 cases in the control (normal pregnancy) group. For the training set: 57 cases of HDF group, 588 cases of control group. For the test set: 28 cases of HDP group, 249 cases of control group. The ratio of the two data sets was 7:3.
Table 3

Comparison of the two models before screening

| Model-PiGF1, PiGF2, PiGF_{diag} | P     | AUC (95%CI) | Sensitivity | Specificity |
|---------------------------------|-------|-------------|-------------|-------------|
| Step-logistic regression        | 0.062 | 0.695 (0.526–0.864) | 0.789       | 0.573       |
| Lasso                           | 0.008 | 0.776 (0.649–0.903) | 0.883       | 0.581       |

Notes: $P < 0.05$ has significant difference. AUC: area under the curve; 95%CI: 95% confidence interval.

Table 4

Comparison of two models for detecting PiGF in 15–26 weeks

| Model-PiGF (15–26 w) | P     | AUC (95%CI) | Sensitivity | Specificity |
|----------------------|-------|-------------|-------------|-------------|
| Step-logistic regression | 0.000 | 0.798 (0.703–0.893) | 0.929       | 0.590       |
| Lasso                | 0.000 | 0.807 (0.721–0.893) | 0.929       | 0.643       |

Notes: $P < 0.05$ has significant difference. AUC: area under the curve; 95%CI: 95% confidence interval.

2.4. Data and statistical analysis

IBM SPSS statistics 23.0 software was used for data analysis. Step-logistic regression and lasso was used for model research in R studio (R version 4.0.1) Step-logistic regression and lasso are both regression methods in nature. Both of them have the function of automatic variable screening. The two regression methods are combined to carry out variable screening and modeling. The significance level alpha was set to 0.05. A 95% confidence interval was set in this study.

3. Results

In this study, the categories of predictive model parameters were derived from Table 1. For the model containing PiGF, the situation before the screening in 2.3.1 and after the screening in 2.3.2 was compared, as shown in Tables 3 and 4. Except for PiGF, all the other parameters (see Table 1) existed consistently before being included in the prediction model for automatic variable screening in 2.3.1 and 2.3.2.

For the models without PiGF screening in Table 3, the step-logistic regression test of PiGF2 mentioned in 2.3.1 showed no statistical difference. In Table 4, both methods put the relative outliers of PiGF at 15–26 weeks into account. Each model index has been improved, and it was statistically significant to test PiGF in the step-logistic regression ($P < 0.05$). Especially the sensitivity, both methods have reached more than 92%. The final model selected the lasso method in Table 4, as shown in Table 5.

4. Discussion

Some angiogenic factors (Soluble fms-Like Tyrosine Kinase 1 (sFlt-1), placental growth factor (PiGF), and Soluble endothelin) in the second trimester may be tools for predicting preeclampsia [14]. Numerous studies have demonstrated that sFlt-1 and PiGF can play a role in the prediction of early preeclampsia in the second trimester [15]. Knudsen et al. also affirmed the independent predictive effect of PiGF [16]. The levels of sFlt-1 and PiGF in pregnant women in Malaysia could be used as biochemical indicators of gestational hypertension [17]. As a predictive marker of preeclampsia, PiGF could simplify the clinical management of preeclampsia and reduced costs [18].

This study used maternal basic factors and PiGF, and also confirmed the predictive role of PiGF in the second trimester. Based on the quality and effect of the model, comprehensive variable screening and modeling analysis and prediction were carried out.
Table 5
Final model situation

| Model parameters                  | Coefficient |
|-----------------------------------|-------------|
| Pre-BMI                           | 0.07051     |
| Family history of hypertension    | 0.39227     |
| Diabetes mellitus with pregnancy  | 0.23397     |
| Pregnancy with immune system disease | 0.04001   |
| DBP                               | 0.00806     |
| MAP                               | 0.10351     |
| PlGF                              | -0.00071    |
| Constant                          | -13.90915   |

Notes: Pre-BMI: Pre-pregnancy body mass index; DBP, MAP: Diastolic blood pressure and Mean arterial pressure both at 11–13 weeks of pregnancy.

5. Conclusion

In addition to basic statistical analysis, this research had comprehensive advantages in variable selection and model building. Maternal factors and biomarker PlGF were combined to predict. Based on the model and clinical needs, a comprehensive screening analysis was carried out to select the optimal prediction model plan containing the PlGF parameter. Finally, the PlGF value of 15–26 weeks (the second trimester) was selected for model research containing the PlGF parameter. The PlGF test in step-logistic regression was statistically significant ($P < 0.05$). Moreover, the comprehensive indicators such as area under the curve (AUC), sensitivity, and specificity of the model have been improved. In particular, the sensitivity of the two methods reached about 93%. Finally, the model parameters of lasso method were comprehensively selected for final HDP prediction. Future studies will need to increase the number of PlGF tests at full gestational age and increase the variety of risk factors.

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Conflict of interest

None to report.

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