Dynamic risk prediction models for different subtypes of hypertensive disorders in pregnancy

Xinyu Zhang¹, Qi Xu², Lin Yang¹*, Ge Sun¹, Guoli Liu²*, Cuiting Lian¹, Ziwei Li¹, Dongmei Hao¹, Yimin Yang¹ and Xuwen Li¹

¹Faculty of Environment and Life, Beijing University of Technology, Beijing, China, ²Department of Obstetrics, Peking University People’s Hospital, Beijing, China

Background: Hypertensive disorders in pregnancy (HDP) are diseases that coexist with pregnancy and hypertension. The pathogenesis of this disease is complex, and different physiological and pathological states can develop different subtypes of HDP.

Objective: To investigate the predictive effects of different variable selection and modeling methods on four HDP subtypes: gestational hypertension, early-onset preeclampsia, late-onset preeclampsia, and chronic hypertension complicated with preeclampsia.

Methods: This research was a retrospective study of pregnant women who attended antenatal care and labored at Beijing Maternity Hospital, Beijing Haidian District Maternal and Child Health Hospital, and Peking University People’s Hospital. We extracted maternal demographic data and clinical characteristics for risk factor analysis and included gestational week as a parameter in this study. Finally, we developed a dynamic prediction model for HDP subtypes by nonlinear regression, support vector machine, stepwise regression, and Lasso regression methods.

Results: The AUCs of the Lasso regression dynamic prediction model for each subtype were 0.910, 0.962, 0.859, and 0.955, respectively. The AUC of the Lasso regression dynamic prediction model was higher than those of the other three prediction models. The accuracy of the Lasso regression dynamic prediction model was above 85%, and the highest was close to 92%. For the four subgroups, the Lasso regression dynamic prediction model had the best comprehensive performance in clinical application. The placental growth factor was tested significant (P < 0.05) only in the stepwise regression dynamic prediction model for early-onset preeclampsia.

Conclusion: The Lasso regression dynamic prediction model could accurately predict the risk of four HDP subtypes, which provided the appropriate guidance and basis for targeted prevention of adverse outcomes and improved clinical care.

KEYWORDS
hypertensive disorders in pregnancy, subtype, risk factor analysis, modeling method, dynamic prediction model, lasso regression
Introduction

Hypertensive disorders in pregnancy (HDP) are diseases that coexist with pregnancy and hypertension, which are major causes of increased maternal morbidity and mortality (1–3). HDP includes gestational hypertension, preeclampsia, eclampsia, chronic hypertension complicated with preeclampsia, and gestational combined chronic hypertension (4, 5). PE can be divided into two subtypes according to the time of onset: early-onset preeclampsia and late-onset preeclampsia (6, 7). HDP can be predicted by relevant risk factors, leading to early treatment (8–11).

The pathogenesis of HDP is complex. Risk factors for HDP are related to clinical epidemiological factors (12, 13), hemodynamic factors (14, 15), basic biochemical factors (16), and biomarkers (17, 18). For vascular biomarkers, numerous studies confirmed that placental growth factor (PIGF) had the function of regulating placental trophoblast and endothelial cells, and had a good predictive value for preeclampsia (19–21). HDP has multiple risk factors, which cannot be accurately predicted by a single factor and requires a combined assessment of multiple risk factors (22, 23). To improve the accuracy of prediction, researchers carried out a variety of combinations of different risk factors. Stepan et al. (24) found that a combination of ultrasound, mean arterial pressure, clinical features, and PIGF improved the prediction of preeclampsia in the first trimester of pregnancy. Chen et al. (25) found that the combination of mean arterial pressure, PIGF, and pregnancy-associated plasma protein A was far superior to a single factor. Current studies on the prediction of HDP focused on static studies at specific gestational weeks (26, 27), while pregnancy is a dynamic process and various physiological factors are constantly changing during pregnancy (28). Therefore, it is necessary to conduct a continuous dynamic study of HDP.

Different HDP subtypes are based on different physiological and pathological conditions of pregnant women, and a single modeling approach is not effective in predicting HDP subtypes. Poon et al. (29) found that the early-onset preeclampsia prediction model had a high detection rate of 93.1% for early-onset preeclampsia, but only 35.7% and 18.3% for late-onset preeclampsia and gestational hypertension. Sun et al. (30) compared the prediction effects of different methods on HDP and found that the Lasso regression method had the best prediction effect.

In this paper, we integrated multiple risk factors and multiple modeling approaches to develop dynamic prediction models for HDP subtypes. The prediction effects of various models were compared to select the optimal prediction model for effective prediction of each subtype.

Materials and methods

Research object

We performed a retrospective study on pregnant women who attended antenatal checkups at Beijing Maternity Hospital from 2006 to 2008, at Beijing Haidian District Maternal and Child Health Hospital from 2015 to 2016, and at Peking University People’s Hospital from July 2015 to 2017. Our control group was healthy pregnant women without hypertensive disorders during pregnancy, not taking long-term medication, and without fetal malformations. A total of 1,267 women were recruited for this study, and the data were collected and analyzed. The study was approved by the ethical committee of Beijing Maternity Hospital. The clinical features of the study population are shown in Table 1.

| Group         | Number of people |
|---------------|------------------|
| GH            | 205              |
| EOPE          | 95               |
| LOPE          | 234              |
| CHCP          | 85               |
| Control       | 648              |

GH: gestational hypertension; EOPE: early-onset preeclampsia; LOPE: late-onset preeclampsia; CHCP: chronic hypertension complicated with preeclampsia; Control: normal pregnancy women.

Table 2 lists the static factors used in this study.

| Type               | Factors                                                                 |
|--------------------|-------------------------------------------------------------------------|
| Quantitative factors | Age, height, pre-BMI                                                    |
| Qualitative factors     | First birth, multiple pregnancy, history of spontaneous abort, history of HDP, history of diabetes, family history of hypertension, family history of diabetes, gestational diabetes, pregestational diabetes mellitus, pregnancy combined with immune system disorders, pregnancy combined with hematologic disorders, pregnancy combined with thyroid disorders |

Pre-BMI: pre-pregnancy body mass index.

Table 3 presents the dynamic factors used in this study.

| Type                  | Factors                                                                 |
|-----------------------|-------------------------------------------------------------------------|
| Clinical epidemiologic factors | BMI                                                                    |
| Hemodynamic factors    | SBP, DBP, PP, MAP, K, CO, CI, TPR                                       |
| Blood biochemical factors | HCT, MPV, PLT, ALT, AST, CRE, UA                                       |
| Biomarkers            | PIGF                                                                    |

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; K: pulse wave shape coefficient; CO: cardiac output; CI: cardiac index; TPR: total peripheral resistance; HCT: hematocrit; MPV: mean platelet volume; PLT: platelet count; ALT: aspartate aminotransferase; AST: alanine aminotransferase; CRE: creatinine; UA: uric acid; PIGF: placental growth factor.
Factors included in the analysis

The following data were collected from the maternal electronic medical records of the hospital: (1) the demographic data of pregnant women; (2) the clinical examination index. We classified the collected factors according to whether they changed with pregnancy: (a) static factors; (b) dynamic factors.

### Static factors

Static factors were divided into two categories (Table 2): (i) quantitative factors, included age, height, and pre-pregnancy body mass index; (ii) qualitative factors, included first birth, multiple pregnancy, maternal history of disease, maternal family history of disease and maternal complications.

### Dynamic factors

Dynamic factors were divided into four categories (Table 3): (i) clinical epidemiologic factors; (ii) hemodynamic factors; (iii) basic biochemical factors; (iii) biomarkers.

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### Tables

**Table 4**: Static factors analysis of gestational hypertension.

| Factor                              | GH     | Control | OR   |
|-------------------------------------|--------|---------|------|
| Qualitative factors                 |        |         |      |
| First birth                         | 145 (76.3%) | 515 (81.4%) | 0.738 |
| Multiple pregnancy                  | 5 (2.6%) | 4 (0.6%) | 4.250 |
| History of spontaneous abortion     | 47 (24.7%) | 141 (22.3%) | 1.147 |
| History of HDP                      | 1 (0.5%) | 1 (0.2%) | 3.344 |
| History of diabetes                 | 5 (2.6%) | 10 (1.6%) | 1.684 |
| Family history of hypertension      | 41 (21.6%) | 105 (16.6%) | 1.384 |
| Family history of diabetes          | 8 (4.2%) | 32 (5.1%) | 0.826 |
| Gestational diabetes                | 21 (11.1%) | 37 (5.8%) | 2.002 |
| Gestational diabetes mellitus       | 5 (2.6%) | 2 (0.3%) | 8.527 |
| Immune system disorders in pregnancy| 4 (2.1%) | 14 (2.2%) | 0.951 |
| Hematologic disorders in pregnancy  | 4 (2.1%) | 20 (3.2%) | 0.659 |
| Thyroid disease in pregnancy        | 14 (7.4%) | 30 (4.7%) | 1.599 |
| Quantitative factors                |        |         |      |
| Age (years)                         | 30.830 ± 3.908 | 30.220 ± 3.742 | – |
| Height (m)                          | 1.626 ± 0.049 | 1.624 ± 0.048 | – |
| Pre-BMI (kg/m²)                     | 23.926 ± 4.503 | 21.140 ± 3.101 | – |

**Table 5**: Static factors analysis of early-onset preeclampsia.

| Factor                              | EOPE   | Control | OR   |
|-------------------------------------|--------|---------|------|
| Qualitative factors                 |        |         |      |
| First birth                         | 56 (70.0%) | 515 (81.4%) | 0.535 |
| Multiple pregnancy                  | 7 (8.8%) | 4 (0.6%) | 15.079 |
| History of spontaneous abortion     | 39 (48.6%) | 141 (22.3%) | 3.319 |
| History of HDP                      | 2 (2.5%) | 1 (0.2%) | 16.205 |
| History of diabetes                 | 2 (2.5%) | 10 (1.6%) | 1.597 |
| Family history of hypertension      | 15 (18.8%) | 105 (16.6%) | 1.160 |
| Family history of diabetes          | 2 (2.5%) | 32 (5.1%) | 0.482 |
| Gestational diabetes                | 2 (2.5%) | 37 (5.8%) | 0.413 |
| Gestational diabetes mellitus       | 0      | 2 (0.3%) | 0.997 |
| Immune system disorders in pregnancy| 2 (2.5%) | 14 (2.2%) | 1.134 |
| Hematologic disorders in pregnancy  | 2 (2.5%) | 20 (3.2%) | 0.786 |
| Thyroid disease in pregnancy        | 2 (2.5%) | 30 (4.7%) | 0.515 |
| Quantitative factors                |        |         |      |
| Age (years)                         | 30.650 ± 4.543 | 30.220 ± 3.742 | – |
| Height (m)                          | 1.618 ± 0.051 | 1.624 ± 0.048 | – |
| Pre-BMI (kg/m²)                     | 55.734 ± 8.588 | 21.140 ± 3.101 | – |

**Table 6**: Static factors analysis of late-onset preeclampsia.

| Factor                              | LOPE   | Control | OR   |
|-------------------------------------|--------|---------|------|
| Qualitative factors                 |        |         |      |
| First birth                         | 172 (78.5%) | 515 (81.4%) | 0.839 |
| Multiple pregnancy                  | 12 (5.5%) | 4 (0.6%) | 9.116 |
| History of spontaneous abortion     | 90 (41.1%) | 141 (22.3%) | 2.434 |
| History of HDP                      | 6 (2.7%) | 1 (0.2%) | 17.803 |
| History of diabetes                 | 7 (3.2%) | 10 (1.6%) | 2.057 |
| Family history of hypertension      | 51 (23.3%) | 105 (16.6%) | 1.527 |
| Family history of diabetes          | 24 (11.0%) | 32 (5.1%) | 2.312 |
| Gestational diabetes                | 12 (5.5%) | 37 (5.8%) | 0.934 |
| Gestational diabetes mellitus       | 1 (0.5%) | 2 (0.3%) | 1.447 |
| Immune system disorders in pregnancy| 9 (4.1%) | 14 (2.2%) | 1.895 |
| Hematologic disorders in pregnancy  | 2 (0.9%) | 20 (3.2%) | 0.282 |
| Thyroid disease in pregnancy        | 8 (3.7%) | 30 (4.7%) | 0.762 |
| Quantitative factors                |        |         |      |
| Age (years)                         | 30.350 ± 4.300 | 30.220 ± 3.742 | – |
| Height (m)                          | 1.619 ± 0.053 | 1.624 ± 0.048 | – |
| Pre-BMI (kg/m²)                     | 23.239 ± 3.916 | 21.140 ± 3.101 | – |

GH, gestational hypertension; Control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.

*Mean and standard deviation.

*P < 0.05 compared to Control.

**P < 0.05 compared to Control.
TABLE 7 Static factors analysis of chronic hypertension complicated with preeclampsia.

| Factors                              | CHCP     | Control   | OR  |
|--------------------------------------|----------|-----------|-----|
| Qualitative factors                  |          |           |     |
| First birth                          | 52 (74.3%) | 515 (81.4%) | 0.662|
| Multiple pregnancy                   | 3 (4.3%)* | 4 (0.6%) | 7.041|
| History of spontaneous abortion      | 11 (15.7%) | 141 (22.3%) | 0.651|
| History of HDP                       | 1 (1.4%) | 1 (0.2%) | 9.159|
| History of diabetes                  | 0 | 10 (1.6%) | 0.984|
| Family history of hypertension       | 21 (30.0%)* | 105 (16.6%) | 2.155|
| Family history of diabetes           | 3 (4.3%) | 32 (5.1%) | 0.841|
| Gestational diabetes                 | 11 (15.7%)* | 37 (5.8%) | 3.003|
| Pre-gestational diabetes mellitus    | 6 (8.6%)** | 2 (0.3%) | 29.578|
| Immune system disorders in pregnancy | 7 (10.0%)** | 14 (2.2%) | 4.913|
| Hematologic disorders in pregnancy   | 1 (1.4%) | 20 (3.2%) | 0.444|
| Thyroid disease in pregnancy         | 8 (11.4%)* | 30 (4.7%) | 2.594|
| Quantitative factors                 |          |           |     |
| Age (years)                          | 31.930 ± 5.123** | 30.220 ± 3.742* | –    |
| Height (m)                           | 1.629 ± 0.055* | 1.624 ± 0.048* | –    |
| Pre-BMI (kg/m²)                      | 24.142 ± 5.157*** | 21.140 ± 3.101* | –    |

CHCP; chronic hypertension complicated with preeclampsia; Control, normal pregnancy women; Pre-BMI, pre-pregnancy body mass index.

*Mean and standard deviation.

**P < 0.01 compared to Control.

Dynamic prediction model

In this paper, the data were characterized by a large variety of parameters and the data volume was a small sample (in thousands), so we chose nonlinear regression, support vector machine (SVM), stepwise regression and Lasso regression to develop the prediction models. The advantages of these methods were that they were suitable for small samples and had good generalization ability. Among these methods, stepwise regression and Lasso regression had the function of automatic filtering variables.

Dynamic factors changed continuously during pregnancy, so we included the gestational week as a parameter in this research from both the formula and algorithm perspectives: we constructed a custom regression dynamic gestational week fitting formula by using nonlinear regression; we developed dynamic prediction models by using SVM, stepwise regression and Lasso regression. In model training for each subgroup, we selected 15 pregnant women in the subgroup and control group to form the validation set, and the rest pregnant women were divided into training set and test set at a ratio of 7:3.

TABLE 8 Dynamic factors analysis of gestational hypertension.

| Factor                | Group | 10–13 weeks | 14–20 weeks | 21–27 weeks | 28–34 weeks | 35–40 weeks |
|-----------------------|-------|-------------|-------------|-------------|-------------|-------------|
| SBP (mmHg)            | GH    | 122.450*   | 120.556*    | 122.513*    | 125.667*    | 128.714*    |
| Control               | 115.581 | 111.809    | 109.199     | 110.033     | 109.543     |             |
| DBP (mmHg)            | GH    | 80.150*    | 77.917*     | 78.897*     | 79.190*     | 82.286*     |
| Control               | 73.806 | 69.953     | 68.460      | 69.510      | 69.139      |             |
| PP (mmHg)             | GH    | 42.300     | 42.639      | 43.615*     | 46.476*     | 46.429*     |
| Control               | 41.775 | 41.856     | 40.738      | 40.523      | 40.404      |             |
| MAP (mmHg)            | GH    | 95.541*    | 92.776*     | 95.436*     | 96.776*     | 100.645*    |
| Control               | 90.372 | 85.705     | 83.575      | 84.479      | 85.083      |             |
| K                     | GH    | 0.375*     | 0.361*      | 0.386       | 0.379       | 0.398       |
| Control               | 0.402* | 0.381      | 0.375       | 0.397       | 0.396       |             |
| CO (L/min)            | GH    | 4.824*     | 4.987*      | 4.783       | 5.475*      | 5.038*      |
| Control               | 4.316 | 4.784      | 4.871       | 4.967       | 4.493       |             |
| CI ([L/(min m²)]      | GH    | 3.015      | 3.168*      | 2.884       | 3.147       | 2.867       |
| Control               | 2.778 | 3.043      | 3.096       | 3.000       | 2.633       |             |
| TPR (ml/L/s/m²)       | GH    | 1.203*     | 1.077*      | 1.294*      | 1.096       | 1.267*      |
| Control               | 1.313* | 1.193      | 1.098       | 1.080       | 1.231*      |             |
| HCT (%)               | GH    | 37.415     | 37.422*     | 36.793*     | 37.365*     | 37.368*     |
| Control               | 37.599 | 35.222     | 35.183      | 36.119      | 36.509      |             |
| MPV (FL)              | GH    | 9.578*     | 10.686*     | 9.839       | 9.571       | 9.671       |
| Control               | 8.974 | 9.254      | 9.624       | 9.666       | 9.415       |             |
| PLT (<10¹²/L)         | GH    | 211.523    | 223.564     | 224.368*    | 198.786     | 202.536     |
| Control               | 223.024 | 220.193    | 205.692     | 196.365     | 196.159     |             |
| ALT (U/L)             | GH    | 17.162*    | 16.007*     | 20.319*     | 22.716      | 23.054      |
| Control               | 23.891 | 21.525     | 22.736      | 20.809      | 22.921      |             |
| AST (U/L)             | GH    | 20.096*    | 18.537*     | 21.190*     | 23.286      | 23.714      |
| Control               | 23.752 | 22.655     | 23.204      | 22.731      | 23.656      |             |
| CRE (µmol/L)          | GH    | 47.295*    | 52.869*     | 64.183      | 63.336*     | 55.543      |
| Control               | 52.284 | 61.909     | 65.824      | 64.958      | 65.500      |             |
| UA (µmol/L)           | GH    | 206.329    | 235.860*    | 245.833     | 282.490*    | 301.645*    |
| Control               | 210.676 | 240.863    | 246.089     | 228.416     | 265.853     |             |

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; K, pulse wave shape coefficient, dimensionless; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; HCT, hematocrit; MPV, mean platelet volume; PLT, platelet count; ALT, aspartate aminotransferase; AST, alanine aminotransferase; CRE, creatinine; UA, uric acid.

**P < 0.05 compared to Control.

*Value outside the normal range.

Statistical analysis

Quantitative factors are presented as X (mean) ± SD (standard deviation). Qualitative factors are presented as percentages (%). Risk factors were screened for each HDP subgroup. For static factors, we conducted independent sample T test for qualitative factors and selected factors with P < 0.05; we performed chi-square test for qualitative factors, and selected factors with OR > 1 and P < 0.05. For dynamic factors, the clinical epidemiological factors and biomarkers for this research were body mass index and PI GF. A large number of researches had confirmed that body mass index and PI GF were risk factors for HDP (31, 32), so we analyzed...
the hemodynamic and basic biochemical factors. We divided the pregnant woman's gestational weeks into five stages: 0–13, 14–20, 21–28, 29–34, 35–40 weeks. We performed independent sample t-tests for hemodynamic and basic biochemical factors at each stage, and selected factors with P < 0.05 and abnormal value (mean value outside the normal range).

We used IBM SPSS Statistics 26.0 to develop a custom dynamic gestational week fitting formula. Matlab 2019b was used for SVM model research. R software (v4.0.1) was used for stepwise regression and Lasso regression model researches. We compared model prediction effects by area under the ROC curve (AUC), accuracy, and the model was externally validated by the validation set.

### Results

#### Analysis of static risk factors

For gestational hypertension, we compared qualitative factors between the gestational hypertension group and the control group, and found there were statistically significant differences in multiple pregnancy, gestational diabetes and pregestational diabetes mellitus between the two groups (OR > 1 and P < 0.05). The pre-pregnancy body mass index of gestational hypertension group was significantly higher than that of control group (P < 0.05) (Table 4). For early-onset preeclampsia, the qualitative factors that met OR > 1 and P < 0.05 were multiple pregnancy, history of spontaneous abortion and history of HDP.

### Table 9 Dynamic factors analysis of early-onset preeclampsia.

| Factor          | Group 10–13 weeks | 14–20 weeks | 21–27 weeks | 28–34 weeks | 35–40 weeks |
|-----------------|------------------|-------------|-------------|-------------|-------------|
| MAP (mmHg) LOPE | 90.119* 92.526* | 91.526* 89.891* | 108.468* | 84.353* 84.453* | 84.519* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |

### Table 10 Dynamic factors analysis of late-onset preeclampsia.

| Factor          | Group 10–13 weeks | 14–20 weeks | 21–27 weeks | 28–34 weeks | 35–40 weeks |
|-----------------|------------------|-------------|-------------|-------------|-------------|
| MAP (mmHg) LOPE | 89.87* 92.85* 96.00 9.641 | 1.129* 1.149 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
| TPR (mmHg s/ml) LOPE | 1.347* | 1.149 | 1.118 1.152 | 1.339* | 1.134* 1.090 1.258* |
diabetes (OR > 1 and HDP, family history of hypertension and family history of pregnancy, history of spontaneous abortion, history of preeclampsia group and control group in multiple pregnancy, family history of diabetes morbidity, pregnancy combined with immune system disorders and pregnancy combined with thyroid disorders were risk factors of chronic hypertension complicated with preeclampsia (OR > 1 and P < 0.05). Pre-pregnancy body mass index among the quantitative factors was a risk factor for chronic hypertension combined with preeclampsia (P < 0.05) (Table 7).

### Analysis of dynamic risk factors

We analyzed all dynamic factors within the five gestational stages, and found dynamic factors were significantly different between the gestational hypertension group and the control group (Table 8). The difference in platelet count (PLT) between the early-onset preeclampsia group and the control group was not statistically significant, and the mean value did not exceed the normal range (Table 9). In this paper, we did not consider PLT as a risk factor for early-onset preeclampsia. We found there was no statistically significant differences in total peripheral resistance (TPR) between the late-onset preeclampsia group and the control group, but the TPR was outside the normal range at 10–13 and 35–40 weeks (Table 10). Therefore, we considered TPR as a risk factor for late-onset preeclampsia. The difference in pulse pressure (PP) between the chronic hypertension combined with preeclampsia group and the control group was not statistically significant, and the mean value did not exceed the normal range (Table 11). Therefore, we did not consider PP as a risk factor for chronic hypertension combined with preeclampsia.

### Model construction results

We used nonlinear regression, SVM, step regression and Lasso regression for each HDP subgroup to develop prediction models. The P-values of the models were all less than 0.001, which indicated that the models were stable. We compared the prediction results of the four models, the Lasso regression prediction model of the gestational hypertension was optimal: accuracy = 90.32%, AUC = 0.910, sensitivity = 75.86%, specificity = 93.32%; the Lasso regression prediction model of the early-onset preeclampsia was optimal: accuracy = 91.78%, AUC = 0.962, sensitivity = 86.21%, specificity = 92.18%; Lasso regression prediction model for late-onset preeclampsia was optimal: accuracy = 91.72%, AUC = 0.955, sensitivity = 93.10%, specificity = 91.63% (Figure 1 and Table 12). PlGF was tested significant (P < 0.05) only in the stepwise

### Table 11 Dynamic factors analysis of chronic hypertension complicated with preeclampsia.

| Factors | Group | 10–13 weeks | 14–20 weeks | 21–27 weeks | 28–34 weeks | 35–40 weeks |
|---------|-------|-------------|-------------|-------------|-------------|-------------|
| SBP (mmHg) | LOPE | 125.42* | 130.75* | 136.09* | 136.12* | 136.16* |
|          | Control | 115.54 | 112.21 | 109.36 | 110.16 | 112.21 |
| DBP (mmHg) | LOPE | 81.81* | 87.50* | 92.45* | 92.47* | 92.53* |
|          | Control | 75.79 | 70.25 | 68.20 | 69.95 | 70.56 |
| PP (mmHg) | LOPE | 43.61 | 43.25 | 43.63 | 42.13 | 44.83 |
|          | Control | 41.75 | 41.95 | 41.16 | 40.56 | 41.64 |
| MAP (mmHg) | LOPE | 96.57* | 101.91* | 107.24* | 95.18* | 108.87 |
|          | Control | 90.33 | 86.10 | 83.49 | 84.58 | 87.04 |
| K | LOPE | 0.40* | 0.35* | 0.36* | 0.37 | 0.39 |
|          | Control | 0.38 | 0.35 | 0.37 | 0.37 | 0.39 |
| CO (L/min) | LOPE | 4.84* | 4.81 | 4.78 | 4.77 | 4.66 |
|          | Control | 4.20 | 4.08 | 3.99 | 3.98 | 4.00 |
| CI (L/(min m2)) | LOPE | 3.23* | 3.25* | 3.12 | 3.09 | 3.01 |
|          | Control | 2.78 | 3.02 | 3.05 | 3.01 | 2.69 |
| TPR (mmHg s/ml) | LOPE | 1.06* | 1.05* | 1.12 | 1.17 | 1.34* |
|          | Control | 1.33* | 1.15 | 1.08 | 1.07 | 1.22* |
| HCT (%) | LOPE | 35.61* | 37.12* | 37.44* | 37.13 | 38.76 |
|          | Control | 37.58 | 35.25 | 35.20 | 36.31 | 36.34 |
| MPV (μm) | LOPE | 10.06* | 11.31* | 11.05* | 10.60* | 10.75* |
|          | Control | 8.98 | 9.22 | 9.59 | 9.72 | 9.52 |
| PLT (×109/L) | LOPE | 225.79* | 247.30* | 212.00 | 210.40 | 192.67 |
|          | Control | 222.40 | 223.21 | 204.59 | 195.33 | 195.49 |
| ALT (U/L) | LOPE | 14.90* | 28.18* | 22.67 | 19.76 | 22.65 |
|          | Control | 23.78 | 21.57 | 22.73 | 21.91 | 23.17 |
| AST (U/L) | LOPE | 24.14* | 50.11* | 22.45 | 21.33 | 22.40 |
|          | Control | 23.71 | 22.60 | 23.22 | 22.79 | 23.80 |
| CRE (μmol/L) | LOPE | 44.37* | 59.64* | 52.39* | 63.62* | 62.58* |
|          | Control | 52.22 | 61.68 | 66.18 | 49.83 | 55.70 |
| UA (μmol/L) | LOPE | 220.56* | 321.10* | 252.95 * | 302.11* | 344.23* |
|          | Control | 200.54 | 240.7 | 246.35 | 228.71 | 264.89 |

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; K: pulse wave shape coefficient; dimensionless; CO: cardiac output; CI: cardiac index; TPR: total peripheral resistance; HCT: hematocrit; MPV: mean platelet volume; PLT: platelet count; ALT: aspartate aminotransferase; AST: alanine aminotransferase; CRE: creatinine; UA: uric acid. *P < 0.05 compared to Control. **Value outside the normal range.
FIGURE 1
ROC curves of the models: (A–D) were the ROC curves of the four models of gestational hypertension; (E–H) were the ROC curves of the four models of early-onset preeclampsia; (I–L) were the ROC curves of the four models of early-onset preeclampsia; (M–P) were the ROC curves of the four models of chronic hypertension complicated with preeclampsia.
TABLE 12 Test results of the models.

| Group | Model  | P      | AC (%) | SE (%) | SP (%) | AUC (95% CI) |
|-------|--------|--------|--------|--------|--------|--------------|
| GH    | NLR    | <0.001 | 79.25  | 79.31  | 79.24  | 0.873 (0.828–0.918) |
| SVM   | <0.001 | 93.08  | 72.41  | 97.37  | 0.894 (0.844–0.944) |
| Step  | <0.001 | 89.13  | 74.71  | 92.12  | 0.910 (0.870–0.951) |
| Lasso | <0.001 | 90.32  | 75.86  | 93.32  | 0.910 (0.870–0.951) |
| EOPE  | NLR    | <0.001 | 77.40  | 75.86  | 77.51  | 0.884 (0.818–0.950) |
| SVM   | <0.001 | 95.66  | 75.86  | 97.07  | 0.940 (0.879–1.000) |
| Step  | <0.001 | 90.64  | 86.21  | 90.95  | 0.959 (0.929–0.989) |
| Lasso | <0.001 | 91.78  | 86.21  | 92.18  | 0.962 (0.934–0.991) |
| CHCP  | NLR    | <0.001 | 80.38  | 76.86  | 81.45  | 0.847 (0.803–0.891) |
| SVM   | <0.001 | 88.27  | 62.81  | 95.99  | 0.894 (0.857–0.931) |
| Step  | <0.001 | 85.19  | 71.90  | 89.22  | 0.863 (0.822–0.905) |
| Lasso | <0.001 | 85.58  | 72.73  | 89.47  | 0.859 (0.816–0.903) |
| CHCP  | NLR    | <0.001 | 83.91  | 89.66  | 83.50  | 0.921 (0.863–0.979) |
| SVM   | <0.001 | 97.70  | 75.86  | 99.26  | 0.952 (0.906–1.000) |
| Step  | <0.001 | 93.33  | 79.31  | 94.33  | 0.945 (0.893–0.998) |
| Lasso | <0.001 | 91.72  | 93.10  | 91.63  | 0.955 (0.906–1.000) |

NLR, nonlinear regression; SVM, support vector machine; Step, stepwise regression; Lasso, Lasso regression; AC, accuracy; SE, sensitivity; SP, specificity; AUC, area under the ROC curve.

**TABLE 13 Parameters of the stepwise regression dynamic prediction model for the early-onset preeclampsia.**

| Factor                   | Coefficient |
|--------------------------|-------------|
| Gestational weeks        | −1.12E−01*  |
| Multiple pregnancy       | 3.25E+00**  |
| History of spontaneous abortion | 8.03E−01* |
| BMI                      | 3.53E−02**  |
| MAP                      | 9.99E−02**  |
| CO                       | −6.23E−01   |
| CI                       | 1.22E+00*   |
| PGF                      | −1.47E−02*  |
| AST                      | −1.59E−01*  |
| UA                       | 1.66E−02**  |
| Constant term            | −1.79E+01** |

BMI, body mass index; MAP, mean arterial pressure; CO, cardiac output; CI, cardiac index; PGF, placental growth factor; AST, alanine aminotransferase; UA, uric acid. *P<0.05; **P<0.01.

regression dynamic prediction model for early-onset preeclampsia (Table 13), the predictive effect of PGF in gestational hypertension, late-onset preeclampsia, and chronic hypertension complicated with preeclampsia was not significant, with parameter term coefficients of −3.26E−03, −1.39E−04, and −6.11E−03, respectively.

The validation results showed that Lasso regression prediction model had the highest accuracy among the four prediction models in the chronic hypertension complicated with preeclampsia (Table 14).

**TABLE 14 Validation results of the prediction models.**

| Group | Model  | AC (%) | SE (%) | SP (%) | AUC (95% CI) |
|-------|--------|--------|--------|--------|--------------|
| GH    | NLR    | 93.33  | 100.00 | 86.67  |              |
| SVM   | 83.33  | 66.67  | 100.00 |
| Step  | 86.67  | 73.33  | 100.00 |
| Lasso | 86.67  | 73.33  | 100.00 |
| EOPE  | NLR    | 80.00  | 93.33  | 66.67  |              |
| SVM   | 73.33  | 46.67  | 100.00 |
| Step  | 96.67  | 93.33  | 100.00 |
| Lasso | 83.33  | 66.67  | 100.00 |
| CHCP  | NLR    | 80.00  | 100.00 | 66.67  |              |
| SVM   | 66.67  | 33.33  | 100.00 |
| Step  | 100.00 | 100.00 | 100.00 |
| Lasso | 100.00 | 100.00 | 100.00 |

NLR, nonlinear regression; SVM, support vector machine; Step, stepwise regression; Lasso, Lasso regression; AC, accuracy; SE, sensitivity; SP, specificity.

### Discussion

Hypertensive pregnancy in disorders are pregnancy-specific systematic disorders that globally affect 5%–10% of all pregnancies (33, 34). We performed a comprehensive screening of high-risk factors for gestational hypertension, early-onset preeclampsia, late-onset preeclampsia and chronic hypertension combined with preeclampsia, which through the acquisition of clinical medical records of patients. For each HDP subtype, we constructed dynamic prediction models using nonlinear regression, support vector machines, stepwise regression, and Lasso regression. The results showed that the Lasso regression dynamic prediction model had the best prediction effect for the four HDP subtypes, which could help clinicians accurately assess the risk of HDP.

We compared the AUC of the four prediction models for each HDP subgroup, and we found that the AUC of the Lasso regression prediction model was higher than the other three prediction models. The accuracy of Lasso regression prediction model was over 85% for each HDP subgroup, and 91.78% for EOPE subgroup was the highest (Table 12). External validation of the model through the validation set, we found that Lasso regression prediction model had a good identification effect, with the accuracy of 86.67%, 83.33%, 76.67% and 100.00% for each HDP subtype, respectively (Table 14). Lasso regression allows automatic filtering of model parameters, and the Lasso regression model simplifies the input parameters of the model and makes the model structure simpler (Table 13).

PGF is a member of the vascular endothelial growth factor family and has important functions in regulating placental trophoblast and endothelial cell function (35). Numerous studies have shown that PGF is a risk factor for HDP and has a predictive value for preeclampsia in particular (36, 37).
PlGF was tested significant only in the stepwise regression model for the early-onset preeclampsia, which indicated a significant predictive effect of PlGF on the early-onset preeclampsia (Table 13).

Finally, there were some limitations in this research. First, this research was carried out in China, and the medical records used for model construction were all from pregnant Chinese women. Due to differences among regions and races, the applicability of the model to other countries needs to be further verified. Second, we developed prediction models for the four HDP subtypes in this study and found that the lasso regression prediction model had the best prediction effect, so it was impossible to explore the predictive ability of other HDP subtype.

Conclusion

We investigated the predictive effect of different variable selection and modeling approaches on HDP subtypes, and found the Lasso regression prediction model performed well and accurately predicted the risk of HDP subtypes. The Lasso regression prediction model provided corresponding guidance and served as a basis for preventing adverse outcomes and improving clinical treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Science and Technology of Beijing University of Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ, LY, and GL: conception and design of the research. QX, GL, and GS: acquisition of data. XZ, GS, and QX: analysis and interpretation of the data and statistical analysis. LY, DH, YY and XL: funding acquisition. XZ: writing of the manuscript. LY, CL, ZL, and XZ: critical revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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